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December 28, 2016

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Drug Master File Staff
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: DMF #: 027320
Holder: McKesson Specialty Health (McKesson)
DMF Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program
Re: REMS Shared Program
DMF Type: V
DMF Submission Information: Clinical/Clinical Information
REMS Submission Identifier: Assessment
eCTD Sequence Number: 0027

Dear Drug Master File Staff:

This Type V DMF contains the Risk Evaluation and Mitigation Strategy (REMS) for Transmucosal Immediate Release Fentanyl for the Shared System REMS program.

McKesson herewith provides the REMS Assessment 6 at 5 years.

McKesson states that the information provided in this Master File is current and assure that the material furnished will meet the specifications described herein. McKesson also confirms that the Holder obligations are observed.

We request that all information in this file be treated as confidential commercial information by the Food and Drug Administration pursuant to 21 C.F.R. §20.61, and that no information from this file be provided to any unauthorized persons without the express written consent of the DMF holder.

If you have any questions or concerns, please do not hesitate to contact Debra Hackett, U.S. Agent for McKesson, at 610-407-1729 or alternatively via email at debra.hackett@accenture.com. Thank you.

Sincerely,

Debra Hackett, Senior Regulatory Project Manager, Regulatory Affairs
U.S. Agent, Accenture, LLP

Attachments: Table of Contents for the submission
Electronic Submission Specifications

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Assessment – 5 years

Module Section	Description
1.2 Cover Letter	Cover Letter w/ Attachments
1.16 – Risk Management Plans	REMS History REMS Assessment – 5 years

Electronic Submission Specifications

This submission is compliant with FDA's Guidelines for Industry and current eCTD specifications.

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway.

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Statement of Commitment: Attached, please find a signed statement of commitment. The statement certifies that the DMF 027320 is current and that McKesson will comply with the statements made in it.

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Modification No.	Date Approved	Documents Affected	Overview of Modification
1	June 5, 2012	• REMS • Prescriber Program Overview • Education Program • Prescriber Enrollment Form • Patient Provider Agreement Form • Patient and Caregiver Overview • Dear Healthcare Provider Letter • Outpatient Pharmacy Overview • Chain Pharmacy Overview • Inpatient Pharmacy Overview • Outpatient Pharmacy Enrollment Form • Chain Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Outpatient Pharmacy Letter • Inpatient Pharmacy Letter • Dear Distributor Letter • Distributor Enrollment Form • Supporting Document	**Sequence 0002**: Edits to Patient-Prescriber Agreement Form, the addition of the Closed System Pharmacy Enrollment Form*, the addition of the newly approved TIRF product, Subsys (fentanyl sublingual spray) and minor editorial changes. *The Closed System Pharmacy Enrollment Form was not formally submitted through the Gateway but was submitted via email on May 18, 2012 and included in the June 5, 2012 FDA approval letter.

Modification No.	Date Approved	Documents Affected	Overview of Modification
N/A	N/A	Assessment Report 1 at 6 months – due 06/28/2012	**Sequence 0003**: Assessment report covering 12/28/2011 to 04/27/2012
2	November 7, 2013	Draft Documents submitted on or before 09/28/2012 • Chain Pharmacy Enrollment Form • Outpatient Pharmacy Enrollment Form • Closed System Pharmacy Overview • Education Program • Frequently Asked Questions (FAQ) • Outpatient Pharmacy Letter • REMS • Supporting Document	**Sequence 0004**: Modification proposed to: • Incorporate closed system pharmacies into the TIRF REMS Access Program • Correct minor inconsistencies between the FDA provided versions and the current PDF versions of REMS materials
N/A	N/A	Assessment Report 2 at 1 year – due 12/28/2012	**Sequence 0005**: Assessment Report covering 04/28/2012 to 10/28/2012
2	November 7, 2013	Amendment to 09/28/2012 supplement: • Chain Outpatient Pharmacy Enrollment Form • Independent Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient	**Sequence 0006**: Modification proposed to: • Revised terminology, processes, and definitions for outpatient pharmacies • Revised attestations for physicians and patients to address concerns regarding patient access • Revised Program Overview and Frequently Asked Questions to improve clarity and content

Modification No.	Date Approved	Documents Affected	Overview of Modification
		Pharmacy Enrollment Form • Distributor Enrollment Form • Prescriber Enrollment Form	• Updated REMS materials to reflect the completion of the transition phase for the
		• Patient Provider Agreement Form • Chain Outpatient Pharmacy Overview • Independent Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Patient and Caregiver Overview • Prescriber Overview • Education Program • Knowledge Assessment • Frequently Asked Questions (FAQ) • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Healthcare Provide Letter • Dear Distributor Letter • REMS	TIRF REMS Access Program

Modification No.	Date Approved	Documents Affected	Overview of Modification
		• Supporting Document • Website Landing Page	
N/A	N/A	Assessment Report 3 at 2 years – due 12/28/2013	**Sequence 0007: Assessment Report covering 10/29/2012 to 10/28/2013**
N/A	N/A	Safety Surveillance Report #1 – due 03/31/2014	**Sequence 0008: Safety surveillance data covering Q4 2012 to Q3 2013**
3	December 24, 2014	• REMS • Prescriber Program Overview • Education Program • Prescriber Enrollment Form • Patient and Caregiver Overview • Independent Outpatient Pharmacy Overview • Chain Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Independent Outpatient Pharmacy Enrollment Form • Chain Outpatient	**Sequence 0009**: Modification proposed to: • Updated REMS materials to eliminate product specific information which does not impact the safe use of TIRF products • Updated REMS materials to reference the currently approved TIRF products list on the FDA Approved REMS website • Updated REMS materials to remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe • Incorporated revised assessment metrics into the Supporting Document • Revised Education Program to emphasize and strengthen appropriate conversion

Modification No.	Date Approved	Documents Affected	Overview of Modification
		Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Distributor Enrollment Form • FAQ	and patient counseling information • Updated REMS and Supporting Document to clarify deactivation of a patient PPAF as opposed to the patient record • Updated pharmacy overview documents and
		• Supporting Document • Website Prototype	• FAQ to call out cash claim requirement • Updated TIRF REMS Access website to incorporate items above and link respective Full Prescribing Information and Medication Guides to DailyMed
N/A	N/A	Cash Claim Information Request Response – due 05/30/2014	**Sequence 0010: Response to 5/16/2014 FDA Cash Claim Information Request**
N/A	N/A	DMF Annual Report – due 08/20/2014	**Sequence 0011: DMF Annual Report**
3	December 24, 2014	• REMS • Prescriber Program Overview • Education Program • Knowledge Assessment • Prescriber Enrollment Form • Patient and Caregiver Overview • Independent Outpatient	**Sequence 0012**: Modification proposed to: • Updated REMS materials to eliminate product specific information which does not impact the safe use of TIRF products • Updated REMS materials to reference the TIRF Products webpage on the TIRF REMS Access website • Updated REMS

Modification No.	Date Approved	Documents Affected	Overview of Modification
		Pharmacy Overview • Chain Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Independent Outpatient Pharmacy Enrollment Form • Chain Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Distributor Enrollment Form • FAQ • Supporting Document • Website Prototype	materials to remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe • Incorporated revised assessment metrics into the Supporting Document • Revised Education Program to emphasize and strengthen appropriate conversion and patient counseling information • Updated REMS and Supporting Document to clarify deactivation of a patient PPAF as opposed to the patient record • Updated pharmacy overview documents and FAQ to call out cash claim requirement • Updated TIRF REMS Access website to incorporate items above and link respective Full Prescribing Information and Medication Guides to DailyMed • Updated Education Program and Knowledge Assessment to incorporate approved labeling supplement

Modification No.	Date Approved	Documents Affected	Overview of Modification
3	December 24, 2014	Unchanged from Sequence 0012, plus: • Dear Healthcare Provider Letter • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Distributor Letter	**Sequence 0013**: Unchanged from Sequence 0012, plus: • Dear Healthcare Provider Letter • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Distributor Letter
N/A	N/A	Assessment Report 4 at 3 years – due 12/28/2014	**Sequence 00014: Assessment Report covering 10/29/2013 to 10/28/2014**
N/A	N/A	BioDelivery Sciences International – Letter of Authorization	**Sequence 0015: BioDelivery Sciences International – Letter of Authorization**
N/A	N/A	Actavis Laboratories Inc. – Letter of Authorization	**Sequence 0016: Actavis Laboratories Inc. – Letter of Authorization**
N/A	N/A	DMF Annual Report – due 08/20/2015	**Sequence 0017: DMF Annual Report**
N/A	N/A	36-Month Assessment – Consolidated Information Requests	**Sequence 0018: Response to FDA 36-Month Assessment Information Requests**
N/A	N/A	Assessment Report 5 at 4 years – due 12/28/2015	**Sequence 00019: Assessment Report covering 10/29/2014 to 10/28/2015**
N/A	N/A	Sentnyl Therapeutics, Inc. – Letter of Authorization	**Sequence 00020: Sentnyl Therapeutics, Inc. – Letter of Authorization**
N/A	N/A	Withdraw Authorization for Galena BioPharma, Inc.	**Sequence 00021: Letter of Authorization/Withdrawn Letter of Authorization**

Modification No.	Date Approved	Documents Affected	Overview of Modification
N/A	N/A	Administrative Change; Change in US Agent	**Sequence 00022: Administrative Change; Change in US Agent**
N/A	N/A	48-Month REMS Supplemental Assessment Report	**Sequence 00023: 48-Month REMS Supplemental Assessment Report**
N/A	N/A	DMF Annual Report – due 08/20/2016	**Sequence 0024: DMF Annual Report**
7N/A	N/A	Administrative Change; Change in US Agent	**Sequence 00025: Administrative Change; Change in US Agent**
NA	N/A	Assessment Report 6 at 5 years – due 12/28/2016	**Sequence 0027: Assessment Report covering 10/29/2015 to 10/28/2016**

Title:	Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program 60-Month FDA REMS Assessment Report
Reporting Timeframe:	29 OCT 2015 to 28 OCT 2016
Document Number:	Final 1.0
Product Name:	Transmucosal Immediate-Release Fentanyl
Sponsor:	TIRF REMS Industry Group (TRIG) of Companies: Actavis Laboratories FL, Inc. BioDelivery Sciences International, Inc. Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Insys Therapeutics, Inc. Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc. Sentynl Therapeutics, Inc.

Confidentiality Statement

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LIST OF ABBREVIATIONS

AE	Adverse Event
ANDA	Abbreviated New Drug Application
AR	Authorized Representative
BTP	Breakthrough Pain
CAP	Corrective Action Plan
CFR	Code of Federal Regulations
DEA	Drug Enforcement Administration
DMF	Drug Master File
DoD	Department of Defense
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HCP	Healthcare Provider
ID	Identification
IR	Immediate Release
KAB	Knowledge, Attitude, and Behavior
LTC	Long-Term Care
MedDRA	Medical Dictionary for Drug Regulatory Activities
NCPDP	National Council for Prescription Drug Program
NCRT	Non-Compliance Review Team
NDA	New Drug Application
NDC	National Drug Code
NPI	National Provider Identifier
OTP	Opioid Treatment Program
PMS	Pharmacy Management System
PPAF	Patient-Prescriber Agreement Form
PT	Preferred Terms
RADARS®	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk Evaluation and Mitigation Strategy
REMS edits	Checks conducted by the TIRF REMS Access Program to confirm that all safety requirements were met
SOP	Standard Operating Procedure

TIRF	Transmucosal Immediate-Release Fentanyl
TIRF Medicines	Transmucosal Immediate-Release Fentanyl product(s)
TIRF REMS Access	REMS program for TIRF medicines
TIRF Sponsors	The group of sponsors that are submitting this REMS
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
VA	Veteran's Association

OVERVIEW

The Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access program was approved by the Food and Drug Administration (FDA) on 28 December 2011 for ABSTRAL®, ACTIQ®, FENTORA®, LAZANDA®, ONSOLIS®, SUBSYS® and generic versions of these TIRF medicines. The TIRF REMS Access program was successfully launched on 12 March 2012, approximately 11 weeks after REMS approval. As of 12 March 2016, the TIRF REMS Access program has been fully implemented for 4 years.

The shared system REMS includes a Medication Guide; Elements to Assure Safe Use (ETASU) of prescriber and pharmacy certification, and dispensing to outpatients with evidence of safe use conditions; an Implementation System, and a Timetable for Submission of Assessments.

In the last 4 years, the TIRF REMS Access program assessment reports were submitted according to the following schedule:

Assessment Report	Reporting Period	Submission Date
6-Month	28 December 2011 - 27 April 2012	28 June 2012
12-Month	28 April 2012 - 28 October 2012	28 December 2012
24-Month	29 October 2012 - 28 October 2013	28 December 2013
36-Month	29 October 2013 – 28 October 2014	28 December 2014
48-Month	29 October 2014 – 28 October 2015	28 December 2015

This sixth REMS assessment report (60-Month) covers the timeframe from 29 October 2015 to 28 October 2016. As per agreement with FDA, safety surveillance analyses have slightly different time periods as noted in the relevant sections within the report.

In addition to the annual submission cycle, a Supplemental Report was submitted to FDA in May 2016. This report included responses to multiple new requests communicated in the 36-Month FDA Assessment Report Acknowledgement Letter that could not be included in the December 2015 submission based on timing of the feedback. The FDA agreed to this approach on 08 September 2015 and the report was submitted prior to the deadline of 04 May 2016. On 21 July 2016, FDA provided feedback on the patient, prescriber, and pharmacist surveys. After careful review of the requested changes, the TRIG notified FDA that in order to incorporate all changes, an extension for report submission would be required. As proposed by FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month KAB survey results will be submitted separately from the overall REMS assessment report on or before 17 February 2017. Additional requests included in the 48-Month FDA Assessment Report Acknowledgement Letter will also be included in the 17 February 2017 submission as requested by FDA and detailed in Section 4.

Prescriber Enrollment

At the end of this reporting period, 8,151 prescribers were enrolled in the TIRF REMS Access program. A total of 1,446 were newly enrolled in the TIRF REMS Access program and 2,631 prescribers successfully re-enrolled during the reporting period. A total of 3,635 prescribers became inactivated, with 3,616 (99.5%) due to expiration of their enrollment at some time during the reporting period. A few prescribers were inactivated because they opted out of the program or were deceased. Of these prescribers who became inactivated during the reporting period due to enrollment expiration, 76.4% had enrollment that remained expired at the end of the period with the remaining 23.6% re-enrolled prior to the end of the reporting period.

During this reporting period, 54 prescribers attempted enrollment but were still pending 3 to 6 months after initiating the enrollment process and 194 prescribers were pending enrollment for longer than 6 months since initiating the enrollment process. The most common reasons for pending enrollment were: training not complete, no attestation, the provided Drug Enforcement Administration (DEA) number did not have the correct schedule for prescribing TIRF medicines, knowledge assessment failure on the first attempt, and invalid DEA number.

Pharmacy Enrollment

At the end of this reporting period, 42,665 pharmacies were enrolled (had activity in this reporting period or remained enrolled from the previous reporting period) in the TIRF REMS Access program. A total of 1,537 pharmacies were newly enrolled in the TIRF REMS Access program during this reporting period. Of the newly enrolled dispensing pharmacies (e.g., excluding pharmacy headquarters), 1,026 were chain pharmacy stores, 387 were independent outpatient pharmacies, 114 were inpatient pharmacies, and 8 were closed system pharmacy locations. During this reporting period, a total of 4,723 dispensing (i.e., not chain pharmacy headquarters) pharmacies were inactivated, with 4,488 inactivations due to expiration of their enrollment. Of those dispensing pharmacies inactivated during the reporting period for enrollment expiration, 53.8% (n=2,416) remained expired at the end of the period, and the remaining 46.2% (n=2,072) re-enrolled prior to the end of the reporting period.

A total of 39 pharmacies attempted enrollment but were still pending 3 to 6 months after initiating the process and a total of 209 pharmacies were pending enrollment for longer than 6 months. The most common reasons for pending enrollment were no attestation, pending test transaction verification, and training not complete.

Distributors Enrollment

During the reporting period, there was 1 newly enrolled distributor and 20 distributors that re-enrolled. There were 5 distributors inactivated during the reporting period due to enrollment expiration; 2 of these distributors had re-enrolled by the end of the reporting period. Although there were 3 distributors whose enrollment expired during the reporting period and whose enrollment remained expired as of the end of the reporting period, access to TIRF medicines is unimpeded because these locations were acquired by other enrolled entities or were initially enrolled as the wrong stakeholder type.

Patients

As of the end of the reporting period, 42,164 patients have been enrolled cumulatively; of these, 4,255 were newly enrolled in the TIRF REMS Access program during this reporting period. Because patients are passively enrolled with their first prescription, they are not required to re-enroll at any point. Instead, prescribers must renew a patient's Patient-Prescriber Agreement Form (PPAF) every 2 years. By the design of the program, a patient's enrollment status will never change to inactivated.

Dispensing Activity

A total of 117,708 prescriptions were submitted to the TIRF REMS Access program for approval in the current reporting period, including 117,335 prescriptions from non-closed system pharmacies and 373 prescriptions from closed system pharmacies. Of the total prescriptions submitted for approval, 105,076 (89.3%) were approved for dispensing without encountering any REMS-related rejections. A total of 2,363 prescriptions encountered at least one REMS-related rejection prior to being authorized due to failure to meet REMS requirements for the prescriber and/or patient and/or pharmacy. An additional 10,269 prescriptions encountered at least one REMS-related rejection and were never authorized for dispensing. A single prescription may have been submitted and rejected multiple times.

The average time for a prescription that had at least one REMS-related rejection to become authorized was 6.3 days (median 2.0 days).

Non-Compliance

During the current reporting period, 62 confirmed instances of stakeholder non-compliance with the TIRF REMS Access program requirements were reviewed and investigated. This included 54 prescriber reports, 7 non-closed system pharmacy reports, and 1 wholesaler/distributor report. There were no spontaneous closed system pharmacy reports. A description of these cases including 58 activity reports and 4 narratives are included in Section 6.2, Table 24 and Table 25, respectively.

Closed System Pharmacy and Inpatient Pharmacy Audits

Audits of 6 closed system pharmacy entities were conducted during this reporting period. Four closed system entities (ID#CS7, ID#CS9, ID#CS10, and ID#CS12) were found to be non-compliant with the TIRF REMS Access program requirements. These pharmacies were re-educated and issued a Notice for Non-Compliance by the Non-Compliance Review Team (NCRT). All 4 non-compliance cases have since been closed. A description of the audits and details of these cases and actions taken are provided in Section 6.3.1.

Audits of 5 inpatient pharmacies were conducted during this reporting period and 1 inpatient pharmacy was identified as non-compliant. A description of the audit questionnaire and a summary of the audit findings is included in Section 6.3.2.

Safety Surveillance Data

Safety surveillance data for this 60-Month FDA REMS Assessment Report consists of data from the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System and aggregate adverse event (AE) data from all the TRIG sponsors.

RADARS System Data

Data from 5 RADARS System Programs that gather data from unique populations along the spectrum of drug abuse were used to monitor for the non-medical use (abuse and misuse) of TIRF products. Based on FDA request, the data included in this report compare event rates for a time period prior to full implementation of the TIRF REMS and a time period after REMS implementation.

Descriptively, population rates for the TIRF products across all outcome variables were low compared to rates for the 3 Schedule II opioid comparator arms; while prescription adjusted rates for the TIRF products were higher than the rates for the 3 Schedule II opioid comparator arms. Findings were similar in the sensitivity analysis including hydrocodone in the Schedule II opioids group. In the Poison Center Program, there were only 5 intentional abuse mentions of TIRF products in the pre period, leaving little room for a decrease in the post period, and making this comparison under powered. Pre to post decreases were seen for 7 of the 24 outcome-rate combinations examined for TIRF products, yet only 1 was statistically significant (population rates among individuals entering opioid treatment programs). Lack of significance for the mean decreases may be due to lack of power driven by small event counts.

A description of these data is included in Section 7.4 of this report, and the complete methods and results are included in the RADARS System Program Report Protocol and the RADARS System Program Report in Appendix 12.4 and Appendix 12.5, respectively.

Aggregate Spontaneous Adverse Event Data of Interest

Spontaneous AE data of interest including events of addiction, overdose, death, and pediatric exposures were provided by each sponsor and aggregated into one comprehensive line listing. A total of 353 unique case reports were identified as meeting the criteria for inclusion in the analysis based on case preferred terms and review of the case narrative information. Of the 353 cases, the highest proportion of reports had an outcome of death (344, 97.5%), and many reports had no cause of death provided. There were 6 (1.7%) reports of addiction, and 3 (0.8%) pediatric exposures. There were 4 (1.1%) reported overdoses to an identified TIRF product.

After a review of the associated MedWatch Forms or narratives for root cause analysis, no reports of inappropriate conversions between TIRF products were noted. Additionally, none of the narratives indicated unintentional exposures or use by non-opioid tolerant patients. There were 3 reports of pediatric exposure. In all 3 of the reports, the medication was intentionally prescribed to the pediatric patient.

When comparing the rate of AEs by prescription in the current reporting period (29 August 2015-28 August 2016) with the results in the 48-month report (29 August 2014-28 August 2015), the number of cases per 100,000 prescriptions decreased, respectively, for

addiction (6.8 vs. 10.7), overdose (4.5 vs. 5.3), and pediatric exposure (3.4 vs. 3.6). Conversely, the number of cases of death per 100,000 prescriptions increased in the current reporting period compared with the 48-month report period (389.4 vs. 261.3).

When comparing the rate of AEs by patient in the current reporting period (29 August 2015-28 August 2016) with the results in the 48-month report (29 August 2014-28 August 2015), the number of cases per 100,000 patients decreased, respectively, for addiction (54.0 vs. 75.4) and overdose (36.0 vs. 37.7). A rate increase was observed in pediatric exposure (27.0 vs. 25.1) and death (3,097.2 vs. 1,846.5).

Additional details are included in Section 7.2.

Knowledge, Attitudes, and Behavior (KAB) Surveys

As agreed to by FDA and the TRIG, the 60-month KAB survey results will be submitted separately from the overall REMS assessment report on or before 17 February 2017.

1 BACKGROUND

Opioids remain the mainstay of treatment of moderate to severe pain, but their safe use requires careful consideration of proper patient selection and treatment characteristics in order to mitigate any inherent health risks.

Opioids are formulated as both extended-release and immediate-release (IR) products. Extended-release or long acting opioid products are designed to provide extended analgesic activity to control persistent pain. TIRF medicines and short-acting opioid products have a rapid onset and short duration of action and are designed for the treatment of acute episodes of pain that 'break through' chronic pain control (breakthrough pain or 'BTP'). All the TIRF medicines are short-acting fentanyl products.

As with all high-potency opioid analgesics, there are significant potential risks associated with use and misuse of TIRF medicines, including acute respiratory depression, which may lead to death. With appropriate clinical use in opioid-tolerant patients these risks have been shown to be low. However, instances of diversion, overdose, and prescribing to opioid non-tolerant patients have led to serious and, on occasion, fatal AEs demonstrating that short-acting fentanyl products can pose a significant health risk if not used appropriately.

The FDA has determined that a REMS is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The group of Sponsors who are submitting this 60-Month FDA REMS Assessment Report (Actavis Laboratories FL, Inc., BioDelivery Sciences International, Inc., Cephalon, Inc. [a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.], Depomed, Inc., Insys Therapeutics, Inc., Mallinckrodt Pharmaceuticals, Mylan, Inc., Par Pharmaceutical, Inc., and Sentynl Therapeutics, Inc.) are herein referred to as TIRF Sponsors. One company joined the TRIG during the reporting period: Sentynl Therapeutics, Inc. replaced Galena Biopharma on 09 January 2016. The TIRF REMS Access program is administered by McKesson Specialty Health and RelayHealth. This report has been prepared by United BioSource Corporation (UBC).

The TIRF medicines subject to the TIRF REMS are itemized in Table 1 below.

Table 1 TIRF Medicines

Product Name (active ingredient)/formulation
NDA 22510, ABSTRAL (fentanyl) sublingual tablets
NDA 20747, ACTIQ (fentanyl citrate) oral transmucosal lozenge and its authorized generic
NDA 21947, FENTORA (fentanyl buccal tablet)
NDA 22569, LAZANDA (fentanyl) nasal spray
NDA 22266, ONSOLIS (fentanyl), buccal soluble film
NDA 202788, SUBSYS (fentanyl sublingual spray)
ANDA 77312, fentanyl citrate oral transmucosal lozenge
ANDA 78907, fentanyl citrate oral transmucosal lozenge
ANDA 79075, fentanyl buccal tablet

Abbreviations: ANDA=Abbreviated New Drug Application; NDA=New Drug Application

The TIRF REMS Access program addresses the current requirements set forth by the FDA and provided to TIRF Sponsors. The program will be monitored over time and modified when and where appropriate.

The initial REMS was approved on 28 December 2011 and went live on 12 March 2012. The FDA required 6-month and 12-month reports during the first year after approval, and then annually thereafter (Table 2). Reporting periods for each assessment report are described below. Data cut-off is 60 days prior to the submission date. Due to availability of data and the time needed to generate/analyze the data, safety surveillance reporting utilizes a modified data cut-off. The RADARS System reporting includes data from 3rd quarter 2012 through 2nd quarter 2016 and the aggregate spontaneous AE data of interest includes data from 29 August 2015 through 28 August 2016.

Table 2 Assessment Report Periods

Assessment Report	Reporting Period	Submission Date
6-Month	28 December 2011 – 27 April 2012	28 June 2012
12-Month	28 April 2012 – 28 October 2012	28 December 2012
24-Month	29 October 2012 – 28 October 2013	28 December 2013
36-Month	29 October 2013 – 28 October 2014	28 December 2014
48-Month	29 October 2014 – 28 October 2015	28 December 2015
60-Month	29 October 2015 – 28 October 2016	28 December 2016

In addition to the annual submission cycle, a Supplemental Report was submitted to FDA in May 2016. This report included responses multiple new requests that were communicated in the 36-Month FDA Assessment Report Acknowledgement Letter that could not be included in the

December 2015 submission based on timing of the feedback. The FDA agreed to this approach on 08 September 2015 and the report was submitted prior to the deadline of 04 May 2016.

On 21 July 2016, FDA provided feedback on the patient, prescriber, and pharmacist surveys. After careful review of the requested changes, the TRIG notified FDA that in order to incorporate all changes, an extension for report submission would be required. As proposed by FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month KAB survey results will be submitted separately from the overall REMS assessment report on or before 17 February 2017. Additional requests included in the 48-Month FDA Assessment Report Acknowledgement Letter will also be included in the 17 February 2017 submission as requested by FDA and detailed in Section 4.

2 REMS GOALS

The goals of the TIRF REMS Access program are to mitigate the risks of misuse, abuse, addiction, overdose and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

3 SUPPORTING INFORMATION ON PROPOSED REMS ELEMENTS

The TIRF Sponsors are executing the TIRF REMS Access program to ensure the appropriate use of TIRF medicines and proper patient selection. All stakeholders subject to the TIRF REMS Access program, including patients, prescribers, pharmacies and distributors, must be enrolled in the TIRF REMS Access program, educated on the requirements of the program and required to document that they understand and will abide by the ETASU.

Program materials are provided on the TIRF medicines in addition to product-specific materials. The Education Program and Knowledge Assessment components of the program contain both TIRF medicine class and product-specific components. All program tools, including enrollment forms, PPAFs, stakeholder letters, and overview documents containing program information specific to the TIRF REMS Access program, are available at www.TIRFREMSACCESS.com.

The program procedures are monitored for adherence and the TIRF Sponsors will continue to conduct ongoing and retrospective analyses as necessary to comply with all mandates and to maximize the safe use of the TIRF medicines.

3.1 Additional Elements

3.1.1 Medication Guide

The product-specific TIRF Medication Guide should be dispensed with each TIRF medicine prescription. Every TIRF medicine has a unique Medication Guide.

3.1.2 Letters to Healthcare Professionals

A Communication Plan for the TIRF REMS was not required. However, TIRF Sponsors sent materials to targeted stakeholders to support implementation of the TIRF REMS Access program at the time of program launch. These communications included Dear Healthcare Provider (HCP) and Dear Pharmacy letters, and informed prescribers and authorized pharmacists on the risks associated with the use of TIRF medicines, the procedures and requirements of the TIRF REMS Access program and means to report AEs.

3.2 Elements to Assure Safe Use

Because of the significant potential health risks associated with prescribing TIRF medicines to opioid non-tolerant patients, it is important that prescribers are aware of the procedures for appropriate patient selection and appropriate dosing and titration. This is achieved by each prescriber's enrollment through a review of the TIRF REMS Access Education program including the TIRF medicine's Full Prescribing Information, successful completion of the Knowledge Assessment, and completion of the Prescriber Enrollment Form.

TIRF medicines are only available through the TIRF REMS Access program to reduce the risks of inappropriate patient selection and ensure appropriate dosing and administration of TIRF medicines. To ensure that TIRF medicines are only dispensed to appropriate patients, pharmacies that dispense TIRF medicines must be enrolled in the TIRF REMS Access program. There are different enrollment requirements for outpatient pharmacies (e.g., retail, mail order, institutional outpatient pharmacies that dispense for outpatient use) and inpatient pharmacies (e.g., hospitals that dispense for inpatient use only). For Long-Term Care (LTC) and Hospice patients whose prescriptions were obtained through an outpatient pharmacy setting, the pharmacy, patient, and prescriber must be enrolled in the TIRF REMS Access program.

Outpatient pharmacy enrollment requires an authorized pharmacist at the pharmacy to review the TIRF REMS Access Education program, successfully complete the Knowledge Assessment, and submit a completed and signed TIRF REMS Access program enrollment form. The authorized pharmacist ensures that their Pharmacy Management System (PMS) is able to support communication with the TIRF REMS Access program using established telecommunication standards. This requires submitting standardized test transactions to validate the system enhancements. The authorized pharmacist is responsible for educating all pharmacy staff who participate in dispensing TIRF medicines on the risks associated with TIRF medicines and the requirements of the TIRF REMS Access program.

For chain pharmacies, an authorized chain pharmacy representative completes the enrollment process on behalf of all individual store locations associated with that chain. The authorized chain pharmacy representative acknowledges that training has been provided to all pharmacy

staff involved in the dispensing of TIRF medicines. Once the TIRF REMS Access Education program and Knowledge Assessment have been completed, the authorized chain pharmacy representative, on behalf of the chain, is required to acknowledge their understanding of the appropriate use of TIRF medicines and agree to adhere to the TIRF REMS Access program requirements by submitting a completed and signed enrollment form.

For inpatient pharmacy enrollment, the authorized pharmacist is required to review the TIRF REMS Access Education program, successfully complete the Knowledge Assessment, and submit a completed and signed enrollment form on behalf of the pharmacy. The authorized inpatient pharmacist is required to acknowledge that they understand that outpatient pharmacies within their facility must be enrolled separately.

Implementation of the TIRF REMS Access program for closed system outpatient pharmacies launched on 30 June 2012. Closed system outpatient pharmacies are integrated healthcare systems that dispense for outpatient use but their PMS is unable to support the process of electronically transmitting the validation and claim information. To enroll in the TIRF REMS Access program, the authorized pharmacist must review the TIRF REMS Access Education program, successfully complete the Knowledge Assessment, and submit a completed and signed enrollment form on behalf of the pharmacy. A list of closed system pharmacy locations that have been trained must be provided to the TIRF REMS Access program.

Patients are passively enrolled in the TIRF REMS Access program when their first prescription is processed by a pharmacy. A completed PPAF should be sent to the TIRF REMS Access program by the prescriber within 10 working days from the processing date of the patient's first prescription for a TIRF medicine. A maximum of 3 prescriptions are allowed within 10 working days from the date that the patient has their first prescription filled. No further prescriptions are to be dispensed after the 10-working-day window until a completed PPAF is received. A patient's HCP can submit a copy of the PPAF to the TIRF REMS Access program via the Web site, fax, or United States (US) mail.

3.2.1 Prescription Verification

Following initial patient enrollment, upon processing of a patient's first TIRF medicine prescription, pharmacies verify for all subsequent prescriptions that both the prescriber and patient are enrolled in the TIRF REMS Access program and that all REMS requirements are met prior to dispensing. Prescription verification is not required for inpatient use of TIRF medicines.

Non-Closed System Pharmacies

Prescription verification occurs through a model that uses a pharmacy billing claim and engages a switch provider in the validation process.

Upon receipt of a prescription for a TIRF medicine at an enrolled pharmacy, the prescription details are entered into their PMS and a transaction is sent to the TIRF REMS Access program via a switch provider. If the patient is not enrolled and this is their first prescription, the TIRF REMS Access program uses the transaction data to automatically transfer patient details into the TIRF REMS Access program database for passive enrollment.

For all subsequent prescriptions, the REMS database is then interrogated, via the switch provider, to validate the REMS edits (i.e., confirm that all TIRF REMS Access program requirements are met).

In the case where a prescription passes all REMS edits, a billing request is then sent to the payer by the switch provider. Once the payer authorizes payment, the switch provider then authorizes the pharmacy to dispense the TIRF medicine as with a normal prescription, returning an authorization number that is captured by the TIRF REMS Access program.

Specific reasons why a prescription would not meet a REMS edit are described in Table 14.

If the prescription does not pass all REMS edits (e.g., one of the stakeholders was not enrolled), the TIRF REMS Access program rejects the claim prior to the claim being forwarded to the payer and the pharmacy receives a rejection notice from the switch provider. This automated feedback indicates the reason for rejection, instructs the pharmacist not to dispense the TIRF medicine, and notifies the pharmacist to contact the TIRF REMS Access program Call Center for further information.

Closed System Outpatient Pharmacies

Upon receipt of a prescription for a TIRF medicine at an enrolled closed system outpatient pharmacy, a pharmacy staff member will contact the TIRF REMS Access program via phone or fax to provide prescription details for verification. The TIRF REMS Access program then validates the enrollment status for the patient, prescriber and pharmacy. If the patient is not enrolled, the TIRF REMS Access program will use this transaction information to automatically transfer patient details into the TIRF REMS Access database for passive enrollment. If all three stakeholders are enrolled (i.e., passes all REMS edits), the closed system outpatient pharmacy is given an authorization number which is captured by the TIRF REMS Access program. If the prescription does not pass all REMS edits (e.g., one of the stakeholders is not enrolled), the TIRF REMS Access program will not provide an authorization number and the closed system outpatient pharmacy will receive a rejection notice. This feedback is provided to the closed system outpatient pharmacy via phone or fax and includes the reason for rejection, information on how the rejection may be resolved and instructions to not dispense the TIRF prescription until resolution is reached.

3.3 Implementation System

The Implementation System and its components are described in the following sections.

3.3.1 Wholesaler/Distribution Enrollment and Fulfillment

Wholesalers/distributors who distribute TIRF medicines must be enrolled in the TIRF REMS Access program before they are allowed to distribute TIRF medicines.

For the purpose of the TIRF REMS Access program, the term distributor refers to a wholesaler, distributor, and/or chain pharmacy distributor. TIRF medicine distributors received a Dear Distributor Letter describing the TIRF REMS Access program and the requirements to purchase TIRF medicines from TIRF Sponsors and sell TIRF medicines to pharmacies upon FDA approval of the program. To enroll, the distributor's authorized representative (AR) must review

the distributor program materials, complete and sign the Distributor Enrollment Form and fax it to the TIRF REMS Access program. TIRF Sponsors have processes in place to prevent shipping TIRF medicines to any distributor who has not completed and signed the enrollment form.

3.3.2 The TIRF REMS Access Program Compliance [Metric 22]

The TIRF REMS Access program NCRT was created by the TRIG on 19 October 2012 and is tasked with reviewing reports of suspected non-compliance with the TIRF REMS Access program requirements. The NCRT is composed of membership from all the TRIG sponsors. There are currently 29 individuals across the 10 sponsors; the functional areas or specialties represented by the members include Regulatory, Medical Affairs, REMS Specialist, Legal, Quality, and Drug Safety.

TIRF Sponsors monitor prescriber, pharmacy, and wholesaler/distributor activities for compliance with TIRF REMS Access program requirements. Corrective actions (e.g., re-education, additional monitoring, process revision, and stakeholder inactivation) are instituted by the TIRF Sponsors if non-compliance is confirmed, as appropriate. The Non-Compliance Plan is described in Section 4.1.4 and results of non-compliance investigations are included in Section 6 of this report. The full Non-Compliance Protocol is included in Appendix 12.1.

3.3.3 TIRF REMS Access Program Call Center

The TIRF REMS Access program maintains a Call Center component. The Call Center is staffed by qualified and trained specialists, who provide TIRF REMS Access program support to patients, prescribers, pharmacies, and distributors.

4 REMS ASSESSMENT PLAN METHODS

The aim of the TIRF REMS Access program's evaluation is to assess the effectiveness of the mitigation strategies in meeting the goals of the TIRF REMS Access program to ensure safe use, proper prescribing, and appropriate distribution of TIRF medicines. Findings from these evaluations are used to identify ways to improve the processes, as needed.

The 48-Month FDA Assessment Report Acknowledgement Letter included multiple new requests to be incorporated into the 60-Month FDA REMS Assessment Report or the planned 17 February 2017 submission. Table 3 provides the TRIG's response to each item communicated in the 48-Month FDA Assessment Report Acknowledgment Letter.

Table 3 48-Month FDA Assessment Report Acknowledgement Letter Requests

Request Number*	FDA Request	Response Location
2a.	Regarding the assessment of opioid tolerance submitted in the 48-Month FDA REMS Assessment Report, approximately 42% of patients prescribed TIRF products were not opioid tolerant. The TRIG needs to further investigate this concerning finding. A timeline for a plan to further evaluate this finding should be submitted with the 17 February 2017, submission of the 60-month REMS assessment survey results. At a minimum, further evaluation of this finding will include product-specific assessment of opioid tolerance that each member sponsor will submit only to their NDA or ANDA. Additional details regarding this evaluation will be communicated in a separate letter.	The timeline for further evaluation of findings from the IMS Study submitted in the Supplemental Report will be included in the 17 February 2017 submission pending timing of the receipt of the separate letter from FDA.
2b.	Regarding the persistency analysis submitted by the TRIG, these data indicate that the number of patients who may be exposed to "inappropriate conversion between TIRF medicines" is not insignificant. Thus these TIRF product switches need to be further assessed by the TRIG and a protocol developed to assess the starting doses of the TIRF products that existing TIRF patients switch to in order to ascertain what proportion of these switches are conducted as per products' labeling. In addition, if the data system used has outcome data, this would be informative as to whether or not any switch marked as "inappropriate" resulted in any adverse sequelae. Limitations of the databases and/or approaches used are to be included in the protocol. Please submit this protocol with the 17 February 2017, submission of the 60-month REMS assessment survey results; if additional time for protocol development is needed, please request an extension.	A protocol for phase II of the Persistency Analysis is planned to be included in the 17 February 2017 submission.
2c.	We would like to schedule a meeting to discuss opportunities for obtaining additional data on accidental exposure to children and others for whom TIRF products are not prescribed, as well as to discuss possible ways to address the low awareness of the need to prescribe and dispense TIRF medicines to appropriate patients.	A teleconference between FDA and the TRIG is scheduled for 22 February 2016 at 3 PM Eastern Standard Time.

Request Number*	FDA Request	Response Location
3a.	In the FDA's 36-Month FDA Assessment Report Acknowledgement Letter (date 03 August 2015), the TRIG was asked to "Conduct outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons and report the results in your next Assessment Report. We are concerned about potential patient access issues." In the 48-Month FDA REMS Assessment Report, the TRIG responded that: "Based on…analysis, there is no barrier to patient access and further outreach is unwarranted." The TRIG states that 516 prescribers (8.6%) chose to not re-enroll and that these prescribers had an average of no more than four prescriptions total over the course of the reporting period. However, the reasons why these prescribers withdrew from the program are unknown as are the reasons why 1,134 prescribers had their enrollment expire this reporting period and remain expired. Additionally, the reasons why 412 pharmacies chose not to re-enroll are not presented. It is therefore important that the TRIG proceed with conducting an "…outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons… we are concerned about potential patient access issues." Submit a timeline for the plan to conduct this outreach in the 17 February 2017, submission of the 60-month REMS assessment survey results.	A timeline for outreach to a representative sample of health professionals and pharmacies who did not re-enroll to ascertain their reasons for not re-enrolling will be provided in the 17 February 2017 submission.
3b.	There continues to be a steady increase in mean and median prescription processing times during this reporting period versus the previous periods. The TRIG was previously asked to investigate this finding, but did not do so, instead stating that this finding may be due to a lower number of prescriptions with at least one initial REMS-related rejection this reporting (1,735) period as compared to the 36-month report (3,738). These differences cited by the TRIG do not appear to be so large as to account for some sort of number skewing induced by a small sample size. The TRIG needs to investigate and identify the causes of these increasing delays in prescription processing as these are potential indicators of access barriers.	At the current time it is not possible to distinguish between prescriptions that encounter at least one REMS-related rejection that are quickly resolved and those that are not. However, the TRIG has determined that of all the prescriptions that do encounter at least one REMS-related rejection over 80% are resolved within the first 10 days (See Section 5.1.5.3).

Request Number*	FDA Request	Response Location
3c.	The TRIG Protocol for Corrective Actions for Instances of Non-Compliance contains few concrete criteria or decision trees as to how to deal with episodes of non-compliance. Thus it is unclear to us what types of non-compliance actions would reliably lead to suspension or deactivation. The TRIG should add increased specificity to the NCRT protocol as well as to the Supporting Document of the REMS. In addition, it is concerning that the TRIG's criteria for an incident of an individual prescriber non-compliance with Patient-Prescriber Agreement Form (PPAF) requirements needs to involve at least "5 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from initial enrollment date." These criteria would appear to potentially lead to an under-reporting of PPAF noncompliance. The TRIG should explore mechanisms to capture lower levels of non-compliance.	The TRIG will consider updates to the Non-Compliance Protocol and the Supporting Document to add increased specificity around how non-compliance actions may lead to suspension or deactivation. A response pertaining to the criteria for an incident of individual non-compliance with PPAF requirements is provided in Section 6.1.
3d.	Regarding the three instances where a non-closed system pharmacy dispensed a TIRF product after a TIRF REMS rejection, all 3 reports were brought to the attention of the TRIG only after the pharmacy contacted the REMS. The TRIG should develop a more active mechanism by which to identify and prevent such occurrences.	The TRIG is looking into a more active mechanism to identify and prevent instances where a non-closed system pharmacy dispenses a TIRF product after a TIRF REMS rejection is received.
3e.	Although results for both governmental (Veteran's Health Administration and Department of Defense) and closed-pharmacy systems appear to have improved from the 36-month audit, they continue to be unsatisfactory. The 36-Month FDA Assessment Report Acknowledgement Letter requested that the TRIG "Re-evaluate whether a novel authorization process is warranted or technically feasible at this time for the closed system pharmacies and report your conclusions with your next Assessment Report." The TRIG has issued the following response: "The TRIG has determined that the current prescription authorization volume for closed system pharmacies is less than 1% of all TIRF prescriptions and due to the absence of complaints with the current process, no changes are warranted at this time." An absence of complaints does not necessarily mean that a closed pharmacy system process is functioning optimally. These audits are likely one of the best sources of information regarding the performance of these closed-system pharmacies in meeting the REMS requirements. If the TRIG does not favor a novel authorization process for all of the closed-system pharmacies solely due to the poor performance of the governmental entities, the TRIG should propose an outreach to these programs to improve compliance. In addition, the TRIG should be sure to include both governmental entities in the 60-month audit so that their performance in the REMS can	Response is included in Section 5.1.5.4 and supporting information is also referenced in the CSP audit information in Section 6.3.1 The TRIG is discussing incorporating an assessment of prescription processing times for prescriptions that do not experience any REMS-related rejections.

Request Number*	FDA Request	Response Location
	continue to be monitored. Lastly, the TRIG presents the process times for prescriptions that have experienced at least one REMS-related rejection. However, data on the overall processing time of a prescription that does not meet with any rejections is unclear. Given that one of the pieces of information solicited during the closed-system audits is "Date and time of each prescription transaction," this is an excellent opportunity for the TRIG to assess prescription processing times for prescriptions that do not experience any REMS-related rejections. The TRIG should add this component to their closed-system audits	
3f.	For the Inpatient Pharmacy audits, 6 inpatient pharmacies either did not respond to the audit request or decided not to participate. In the current inpatient pharmacy enrollment form, the pharmacy only agrees to have their training audited. We are considering revisions to this enrollment form to allow for process audits so as to increase the potential pool of inpatient pharmacies in the audit and will communicate any required modifications during the review of the next REMS assessment.	The TRIG looks forward to further communication from FDA on this item.
3g.	The TRIG reports a number of instances where prescribers were either unaware of requirements to submit a PPAF or chose not to do so. It is important that the TRIG investigate mechanisms to reinforce to prescribers the necessity of timely completion of PPAFs.	The TRIG will further query non-compliant prescribers to determine more specific reasons of why they were not compliant with the REMS requirements. The TRIG will assess these responses to determine appropriate actions.
3h.	For subsequent submissions of RADARS data that contain CII opioid comparators, expand the CII immediate-release opioid category to include oxycodone/acetaminophen, oxycodone/aspirin, and oxycodone/ibuprofen.	The TRIG confirms that the CII immediate-release opioid category currently includes these products in the analysis.
3i.	The Agency has increasing concerns about the use of RADARS data to assess some of the outcomes outlined in the TIRF REMS. Given the limitations of RADARS, the Agency believes that additional data sources that can track adverse outcomes of interest associated with the TIRF products are necessary, and the TRIG must study intermediate objectives more closely related to the REMS intervention. The FDA proposes a meeting with the TRIG to discuss and explore new approaches to assessing this REMS with the goal of gathering useful information to better understand the impact of the REMS and to improve the program going forward.	The TRIG plans to discuss this further during the scheduled 22 February 2016 teleconference.

*Numbering is aligned with the numbering of the FDA requests communicated in the 48-Month FDA Assessment Report Acknowledgement Letter.

4.1 Data Sources for REMS Assessments

Data were collected from the following main sources as described in detail below: a) TIRF REMS Access program utilization statistics (Section 4.1.1), b) dispensing activity for enrolled pharmacies (Section 4.1.2), c) program infrastructure and performance, d) TIRF REMS Access non-compliance plan, e) safety surveillance, and f) periodic surveys of patients, HCPs, and pharmacies. All programmed source tables and figures, as well as source data are on file at UBC and available upon request.

Note: Every metric number shown in the following tables is used to identify the respective metric in the headers and text of the results.

4.1.1 The TIRF REMS Access Program and Product Utilization Statistics

For the assessment of enrollment, utilization, and discontinuation statistics for prescribers, pharmacies, patients, and distributors, the following metrics were tabulated for the current reporting period and cumulatively.

Metric Number*	Metric
a.	**Patient Enrollment**
1.	Number of unique patients enrolled
2.	Number of patients inactivated
b.	**Prescriber Enrollment**
3.	Number of prescribers enrolled
4.	Number of prescribers that attempted enrollment but whose enrollment is pending for >3 months and >6 months along with the specific reasons why their enrollment is pending
5.	Number of prescribers inactivated
c.	**Pharmacy Enrollment**
6	Number of pharmacies enrolled by type (inpatient, chain, independent, closed system; provide identity of closed system entities)
7.	Number of pharmacies that attempted enrollment but whose enrollment is pending >3 months and >6 months along with the specific reasons why their enrollment is pending (stratified by type)
8.	Number of pharmacies inactivated by type (inpatient, chain, independent, closed system)
d.	**Distributor Enrollment**
9.	Number of distributors enrolled
10.	Number of distributors inactivated

*Numbering corresponds with the current TIRF REMS Access program Supporting Document (approved on 24 December 2014).

4.1.2 Dispensing Activity for Enrolled Pharmacies

For the assessment of dispensing activity, the following metrics were tabulated and stratified by pharmacy type for the current reporting period and cumulatively.

Metric Number*	Metric
11.	Number of prescriptions/transactions authorized; for closed systems, provide the number of prescription/transactions per closed system entity
12.	Number of prescriptions/transactions denied/rejected and the reasons for denial/rejection. Include the number of prescriptions/transactions rejected for safety issues (provide description of safety issues and any interventions or corrective actions taken)
13.	The mean and median amount of time it takes for a prescription that experienced at least one initial REMS-related rejection to be authorized
14.	Number of patients with more than three prescriptions dispensed during the first ten days after patient passive enrollment without a PPAF
15.	Number of prescriptions dispensed after ten days without a PPAF in place

*Numbering corresponds with the current TIRF REMS Access program Supporting Document (approved on 24 December 2014).

4.1.3 Program Infrastructure and Performance

The following metrics on program infrastructure performance were collected and summarized for the current reporting period.

Metric Number*	Metric
16.	Number of times a backup system was used to validate a prescription, with reason(s) for each instance (for example, pharmacy level problem, switch problem, or REMS database problem) clearly defined and described
17.	Number of times unintended system interruptions occurred for each reporting period. Describe the number of stakeholders affected, how the issue was resolved, and steps put into place to minimize the impact of future interruptions
18.	Call center report with • Overall number of contacts • Summary of frequently asked questions • Summary of REMS-related problems reported
19.	Description of corrective actions taken to address program/system problems

*Numbering corresponds with the current TIRF REMS Access program Supporting Document (approved on 24 December 2014).

4.1.4 TIRF REMS Access Program Non-Compliance Plan

The TIRF sponsors provide the following data regarding non-compliance in each assessment report (per reporting period).

Metric Number*	Metric
20.	Report the results of yearly audits of at least 3 randomly selected closed pharmacy systems to assess the performance of the system(s) developed to assure REMS compliance. These reports are to include: • Verification of training for all pharmacists dispensing TIRF products • Numbers of prescription authorizations per closed system • Reconciliation of data describing TIRF product prescriptions received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS Access program. Data to include the 12-month period preceding the audit date. Include details on how the reconciliation is conducted (e.g., electronic versus manual process). • Describe any corrective actions taken for any non-compliance identified during the audit and corrective actions taken to address non-compliance
21.	Report the results of yearly audits of at least 5 randomly selected inpatient hospital pharmacies to assess the performance of the system(s) developed to assure REMS compliance starting in the 48-Month FDA REMS Assessment Report. Provide the number of units of use of TIRFs ordered per inpatient hospital pharmacy audited per 12-month period. These reports are to include: • Verification of training for all pharmacists dispensing TIRF products • Verification that processes such as order sets/protocols are in place to assure compliance with the REMS program • Describe any corrective actions taken for any non-compliance identified during the audit, as well as preventative measures that were developed as a result of uncovering these non-compliance events
22.	Description of number, specialties, and affiliations of the personnel that constitute the NCRT as well as: • Description of how the NCRT defines a non-compliance event • Description of how non-compliance information is collected and tracked • Criteria and processes the Team uses to make decisions • Summary of decisions the Team has made during the reporting period • How the Team determines when the compliance plan should be modified
23.	Describe each non-compliance event and the corrective action measure taken, as well as the outcome of the corrective action
24.	Number of TIRF prescriptions dispensed that were written by non-enrolled prescribers and include steps taken to prevent future occurrences
25.	Number of prescriptions dispensed by non-enrolled pharmacies and include steps taken to prevent future occurrences

Metric Number*	Metric
26.	Number of times a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits and if any such events occurred, describe how these events were identified
27.	Number of times a TIRF was prescribed to an opioid non-tolerant individual. Include what was done to minimize such instances; if any such events occurred, describe how these events were identified
28.	Number of instances of inappropriate conversions between TIRF products, as well as any outcome of such an event. If any such events occurred, describe how these events were identified

*Numbering corresponds with the current TIRF REMS Access program Supporting Document (approved on 24 December 2014).

4.1.4.1 Non-Compliance Monitoring

The goal of the Non-Compliance Plan is to help the TRIG identify and investigate deviations from and non-compliance with TIRF REMS requirements to ensure patient safety and continuously improve the program. A confirmed non-compliance event is one for which the information collected through investigation of the potential non-compliance event clearly indicates that a program deviation has occurred and/or evidence of the program goals not being met through stakeholder actions is identified.

The TIRF REMS Access program routinely monitors stakeholder activity to identify potential incidents of non-compliance events with program requirements and investigates all reports of suspected non-compliance. Non-compliance information is collected through standard program reports, spontaneous reports identified via the program's Call Center, vendor/sponsor reported events, outreach to relevant stakeholders to validate data/information and solicit further information, and investigation of the TIRF REMS Access database. The data are tracked through a non-compliance case that is opened on the stakeholder record in the TIRF REMS Access database.

If a non-compliance event is confirmed, additional investigation is conducted to determine the scope, impact, and root cause of the event. Stakeholders are notified of the investigation via a formal letter from the TIRF REMS Access program and may also be requested to develop a Corrective Action Plan (CAP). All CAPs are reviewed and approved by the NCRT.

The NCRT will determine if the Non-Compliance Protocol should be modified as the program evolves. Any changes to the plan proposed by the NCRT will be voted upon by the TRIG.

The full Non-Compliance Protocol is included in Appendix 12.1.

4.1.5 Safety Surveillance

The following safety surveillance data were collected. Reporting periods for each type of data were modified based on timing of availability of data.

Metric Number*	Metric
29.	TIRF Sponsors will process AE reports related to their specific products and report to the FDA according to current regulations outlined in 21 Code of Federal Regulations (CFR) 314.80 and the sponsors' respective Standard Operating Procedures.
30.	TIRF Sponsors will produce one comprehensive report that presents spontaneous AE data from all sponsors of the TIRF REMS Access program, as well as data from other databases (characteristics of which are described below). This report will focus on four categories of AEs of interest: addiction, overdose, death, and pediatric exposures. This report should include the following: • Line listings under each category of AEs of interest as listed above • Line listings should provide at a minimum the following information: o Identifying case number o Age and Gender of the patient o Date of the event as well as of the report o The Preferred Terms o Indication of TIRF use o Duration of TIRF therapy o Concomitant medications o Event Outcome • Other metrics of interest include: o Number of event reports in each event category of interest o Counts of AEs related to inappropriate conversions between TIRF products o Counts of AEs related to accidental and unintentional exposures o Counts of AEs that are associated with use of TIRF medicines in non-opioid tolerant patients • Duplicate cases are identified and eliminated • Case reports with AEs in multiple categories will be listed in each category of interest, and will be noted as such • For each AE category, an overall summary analysis of the cases will be provided addressing the root cause(s) of the events • Rate of each AE of interest will be calculated using two distinct denominators: the number of prescriptions for TIRF products and the number of patients receiving a TIRF product throughout the reporting interval. Trends and changes in the rates of these events will be compared year-to-year

Metric Number*	Metric
31.	Surveillance data focusing on events of addiction, overdose, death, and pediatric cases should also be drawn from the databases that are listed below. Conclusions regarding these data should be included in and inform the overall conclusions in the summary report referred to in Metric 30 directly above: • Non-medical use of prescription drugs • Surveys conducted at substance abuse treatment programs • College surveys • Poison control center data • Impaired health care workers • Drug-related hospital emergency department visits • Drug-related deaths • Other databases as relevant

*Numbering corresponds with the current TIRF REMS Access program Supporting Document (approved on 24 December 2014).

4.1.6 Periodic Surveys of Patients, Prescribers, and Pharmacies

Prescribers', pharmacists', and patients' understanding regarding the appropriate use of TIRF medicines and TIRF REMS Access program requirements are evaluated through Knowledge, Attitude, and Behavior (KAB) surveys. The surveys are administered to selected prescribers, pharmacies, and patients.

5 RESULTS

5.1 REMS Program Utilization

Described in this section are the total numbers of all enrolled stakeholders (prescribers, patients, pharmacies, and distributors), as well as stakeholder inactivations, dispensing activities, and barriers or delays in patient access.

5.1.1 Patient Enrollment [Metric 1 and 2]

During the current reporting period, there were 4,255 newly enrolled patients (Table 4). Because patients are passively enrolled with their first prescription there is no patient re-enrollment, but prescribers are required to renew PPAFs with patients every 2 years. By design, a patient's enrollment status will never change to inactivated.

Table 4 Patient Enrollment

Parameter	Current Reporting Period[a] 29OCT2015 to 28OCT2016 Number of Newly Enrolled Patients N	Cumulative[a,b,c] 28DEC2011 to 28OCT2016 Total Number of Enrolled Patients N
Total Number of Enrolled Patients	4,255	42,164

[a] An enrolled patient is a patient who has received at least one prescription for a TIRF medication.
[b] Includes patients that transitioned into the TIRF REMS Access program from other individual REMS programs.
[c] Cumulative is defined as the sum of all reporting periods. Cumulative patients from the end of prior period may differ from last period's report due to reconciliation of duplicate patients.

5.1.2 Prescriber Enrollment and Inactivations [Metric 3, 4, 5]

Cumulatively there have been 16,549 prescribers who have successfully completed enrollment in the program. At the end of this reporting period there are 8,151 prescribers who are currently enrolled. This includes 1,446 newly enrolled prescribers, 2,631 prescribers who re-enrolled and 4,074 who remain active from a previous period (Table 5). Table 6 shows those prescribers who have been inactivated.

Table 5 Prescriber Enrollment

Parameter	Current Reporting Period[a] 29OCT2015 to 28OCT2016 N (%)
Total Number of Prescribers with Enrollment Activity In This Reporting Period	4,077
Number of Newly Enrolled Prescribers	1,446 (35.5%)
Number of Re-Enrolled Prescribers	2,631 (64.5%)
Number of Prescribers Who Remain Enrolled from Previous Reporting Periods	4,074
Total Number of Prescribers Enrolled as of the End of This Reporting Period	8,151
Cumulative Number of Prescribers Ever Enrolled[b,c]	16,549

[a] Percentages are based on the total number (N) of enrolled prescribers.
[b] Cumulative is defined as the sum of all reporting periods.
[c] Number includes prescribers who transitioned into the TIRF REMS Access program from other individual REMS programs.

A total of 3,635 prescribers were inactivated at some point during the current reporting period, and the majority of these (3,616, 99.5%) were due to expiration of enrollment. It should be noted that a prescriber is required to enroll every 2 years within the TIRF REMS Access program. Of those 3,616 prescribers whose enrollment expired at some point during the current reporting period, 2,763 (76.4%) remained expired at the end of the reporting period (Table 6). In total, there were 8,401 prescribers who remained inactivated at the end of the reporting period.

Table 6 Prescriber Inactivations

Parameter	Current Reporting Period[a] 29OCT2015 to 28OCT2016 N (%)
Number of Prescribers Who Became Inactivated During this Reporting Period	3,635
Reason(s) For Inactivation[b]	
Deceased	2 (0.1%)
Program Opt-Out	16 (0.4%)
Non Compliant[c]	0[d]
Suspended	1 (<0.1%)
Enrollment Expired[e]	3,616 (99.5%)
Enrollment remained expired at end of period	2,763 (76.4%)
Number of Prescribers Inactivated in This Time Period who Remain Inactivated as of the End of this Reporting Period	2,781
Number of Prescribers Who Were Inactivated in a Previous Reporting Period and Remain Inactive as of the End of This Reporting Period	5,620
Total Number of Prescribers Inactivated as of the End of this Reporting Period	8,401
Cumulative Number of Prescribers Who Have Ever Been Inactivated[f]	12,365

[a] Prescribers whose status is 'inactive' at least once during the reporting period.
[b] Percentages are based on the total number (N) of inactivated prescribers. A prescriber may have more than one reason for inactivation.
[c] Prescribers may be included as both "non-compliant" and "suspended" since before becoming inactivated for non-compliance, prescribers go through a suspension period.
[d] No prescriber inactivations occurred during this reporting period due to non-compliance. There was a significant event of non-compliance reported after the reporting period, which is described in narrative ID#445.
[e] Prescribers whose status is 'Inactive-Expired' at any time during the reporting period.
[f] Cumulative is defined as the sum of all reporting periods.

During the current reporting period, there were 54 prescribers who attempted enrollment but whose enrollment was pending 3 to 6 months later. A total of 194 prescribers were pending enrollment for more than 6 months within the current reporting period. Prescribers may have attempted enrollment and became pending in another reporting period.

For prescribers pending enrollment for 3 to 6 months, the most frequent reasons were training not complete (83.3%), no attestation (81.5%), provided DEA number does not have correct schedule for this drug (11.1%), invalid DEA number (7.4%), and knowledge assessment failure on the first attempt (7.4%). For prescribers pending enrollment for more than 6 months, the most frequent reasons were similar and included no attestation (74.7%), training not complete (62.4%), knowledge assessment failure on the first attempt (13.9%), and provided DEA does not have correct schedule for this drug (12.4%).

The number of prescribers who attempted enrollment but are still pending enrollment for 3 to 6 months or more than 6 months, and the reasons for pending enrollment are shown in Table 7.

Table 7 Prescribers Pending Enrollment

Parameter	Current Reporting Period[a] 29OCT2015 to 28OCT2016	
	Prescribers Pending Enrollment ≥3 – 6 Months[b] N (%)	**Prescribers Pending Enrollment >6 Months[b] N (%)**
Prescribers Who Attempted Enrollment but are Still Pending Enrollment[c]	54	194
Reasons for Pending Enrollment		
Invalid DEA	4 (7.4%)	20 (10.3%)
Invalid NPI	2 (3.7%)	8 (4.1%)
Knowledge Assessment Failure - First Attempt	4 (7.4%)	27 (13.9%)
Knowledge Assessment Failure - Second Attempt	0	6 (3.1%)
Knowledge Assessment Failure - Third Attempt	1 (1.9%)	1 (0.5%)
Missing DEA Number	0	4 (2.1%)
Missing Email	0	2 (1.0%)
Missing NPI Number	1 (1.9%)	4 (2.1%)
Missing Phone Number	1 (1.9%)	1 (0.5%)
Missing Physician Signature Date	3 (5.6%)	4 (2.1%)
Missing Signature	3 (5.6%)	4 (2.1%)
Missing State License Number	0	5 (2.6%)
No Attestation	44 (81.5%)	145 (74.7%)

Parameter	Current Reporting Period[a] 29OCT2015 to 28OCT2016	
	Prescribers Pending Enrollment ≥3 – 6 Months[b] N (%)	Prescribers Pending Enrollment >6 Months[b] N (%)
Pending Enrollment Intake	2 (3.7%)	7 (3.6%)
Provided DEA does not have Correct Schedule for this Drug	6 (11.1%)	24 (12.4%)
Training Not Complete	45 (83.3%)	121 (62.4%)

[a] Reflects the total number of prescribers pending enrollment in the current reporting period. Prescribers may have attempted enrollment and become pending in another reporting period.
[b] Percentages are based on the total number (N) of prescribers attempting enrollment. Percentages may not add up to 100% because a single prescriber may be pending enrollment for more than one reason.
[c] Prescribers may be pending enrollment for more than one reason.

5.1.3 Pharmacy Enrollment, Inactivation, and Education [Metric 6, 7, 8]

There were a total of 26,543 pharmacies newly enrolled or re-enrolled in this reporting period. Of the 1,537 (5.8%) pharmacies that newly enrolled in the TIRF REMS Access program, 1,026 were chain pharmacy stores, 387 were independent outpatient pharmacies, 114 were inpatient pharmacies, and 8 were closed system pharmacy locations. The 8 closed system pharmacies are represented by 6 closed system entities (See Section 5.1.5.4). A total of 25,006 (94.2%) pharmacies re-enrolled: 22,043 were chain pharmacy stores, 2,260 were independent outpatient pharmacies, 439 were inpatient pharmacies, and 214 were closed system pharmacy locations (Table 8).

Table 8 Pharmacy Enrollment

Parameter	Current Reporting Period[a] 29OCT2015 to 28OCT2016		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)
Total Number of Pharmacies with Enrollment Activity in this Reporting Period[b]	26,316	227	26,543
Total Number of Newly Enrolled Pharmacies	1,529 (5.8%)	8 (3.5%)	1,537 (5.8%)
Inpatient Pharmacies	114 (7.5%)	N/A	114 (7.4%)
Chain Pharmacy Headquarters[c]	2 (0.1%)	N/A	2 (0.1%)
Chain Pharmacy Stores	1,026 (67.1%)	N/A	1,026 (66.8%)
Independent Outpatient Pharmacies	387 (25.3%)	N/A	387 (25.2%)
Closed System Headquarters[c]	N/A	0	0
Closed System Pharmacies	N/A	8 (100.0%)	8 (0.5%)

Parameter	Current Reporting Period[a] 29OCT2015 to 28OCT2016		
	Non-Closed System Pharmacies N (%)	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Total Number of Re-Enrolled Pharmacies	24,787 (94.2%)	219 (96.5%)	25,006 (94.2%)
Inpatient Pharmacies	439 (1.8%)	N/A	439 (1.8%)
Chain Pharmacy Headquarters[c]	45 (0.2%)	N/A	45 (0.2%)
Chain Pharmacy Stores	22,043 (88.9%)	N/A	22,043 (88.2%)
Independent Outpatient Pharmacies	2,260 (9.1%)	N/A	2,260 (9.0%)
Closed System Headquarters[c]	N/A	5 (2.3%)	5 (<0.1%)
Closed System Pharmacies	N/A	214 (97.7%)	214 (0.9%)
Number of Pharmacies that Remain Enrolled from a Previous Reporting Period	16,118	5	16,123
Inpatient Pharmacies	207 (1.3%)	N/A	207 (1.3%)
Chain Pharmacy Headquarters[c]	31 (0.2%)	N/A	31 (0.2%)
Chain Pharmacy Stores	14,466 (89.8%)	N/A	14,466 (89.7%)
Independent Outpatient Pharmacies	1,414 (8.8%)	N/A	1,414 (8.8%)
Closed System Headquarters[c]	N/A	1 (20.0%)	1 (<0.1%)
Closed System Pharmacies	N/A	4 (80.0%)	4 (<0.1%)
Total Number of Pharmacies Enrolled as of the End of this Reporting Period	42,433	232	42,665
Inpatient Pharmacies	760 (1.8%)	N/A	760 (1.8%)
Chain Pharmacy Headquarters[c]	78 (0.2%)	N/A	78 (0.2%)
Chain Pharmacy Stores	37,535 (88.5%)	N/A	37,535 (88.0%)
Independent Outpatient Pharmacies	4,060 (9.6%)	N/A	4,060 (9.5%)
Closed System Headquarters[c]	N/A	6 (2.6%)	6 (<0.1%)
Closed System Pharmacies	N/A	226 (97.4%)	226 (0.5%)
Cumulative Number of Pharmacies Ever Enrolled[d]	48,882	372	49,254
Inpatient Pharmacies	1,244 (2.5%)	N/A	1,244 (2.5%)
Chain Pharmacy Headquarters[c]	94 (0.2%)	N/A	94 (0.2%)
Chain Pharmacy Stores	41,039 (84.0%)	N/A	41,039 (83.3%)

Parameter	Current Reporting Period[a] 29OCT2015 to 28OCT2016		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)
Independent Outpatient Pharmacies[c]	6,505 (13.3%)	N/A	6,505 (13.2%)
Closed System Headquarters	N/A	7 (1.9%)	7 (<0.1%)
Closed System Pharmacies	N/A	365 (98.1%)	365 (0.7%)

[a] Percentages are based on the total number (N) of pharmacies for the reporting period.
[b] Pharmacies that are enrolled within this reporting period and were still enrolled at the end of the reporting period.
[c] Chain Pharmacy Stores or Closed System Pharmacy Stores may be associated with a Chain Pharmacy Headquarter or Closed System Headquarter enrolled in a previous reporting period.
[d] Cumulative number of pharmacies from the end of prior period may differ from last period's report due to reconciliation of duplicate records.

As shown in Table 9, there were 4,736 total pharmacies inactivated at least once during the current reporting period including 4,530 non-closed system pharmacies and 206 closed system pharmacy. The non-closed system pharmacies included 3,043 (67.2%) chain pharmacy stores, 1,222 (27.0%) independent outpatient pharmacies, and 252 (5.6%) inpatient pharmacies. The reason for most dispensing pharmacy inactivations was expired enrollment (95.0%, 4,488/4,723).

Table 9 Pharmacy Inactivations

Parameter	Current Reporting Period[a] 29OCT2015 to 28OCT2016		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)
Number of Pharmacies that Became Inactivated During this Reporting Period	4,530	206	4,736
Inpatient Pharmacies	252 (5.6%)	N/A	252 (5.3%)
Chain Pharmacy Headquarters	13 (0.3%)	N/A	13 (0.3%)
Chain Pharmacy Stores	3,043 (67.2%)	N/A	3,043 (64.3%)
Independent Outpatient Pharmacies	1,222 (27.0%)	N/A	1,222 (25.8%)
Closed System Pharmacies	N/A	206 (100.0%)	206 (4.3%)
Reason(s) for Inpatient Pharmacy Inactivation[b]			
Program Opt-Out	3 (1.2%)	N/A	3 (1.2%)
Enrollment Expired[c]	249 (98.8%)	N/A	249 (98.8%)
Enrollment remained expired at end of period	201 (80.7%)	N/A	201 (80.7%)
Reason(s) for Chain Pharmacy Headquarters Inactivation[d]			

	Current Reporting Period[a] 29OCT2015 to 28OCT2016		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Program Opt-Out	1 (7.7%)	N/A	1 (7.7%)
Enrollment Expired[c]	12 (92.3%)	N/A	12 (92.3%)
Enrollment remained expired at end of period	4 (33.3%)	N/A	4 (33.3%)
Reason(s) for Chain Pharmacy Store Inactivation[d]			
Program Opt-Out	224 (7.4%)	N/A	224 (7.4%)
Enrollment Expired[c]	2,819 (92.6%)	N/A	2,819 (92.6%)
Enrollment remained expired at end of period	1,242 (44.1%)	N/A	1,242 (44.1%)
Reason(s) for Independent Outpatient Pharmacy Inactivation[e]			
Program Opt-Out	8 (0.7%)	N/A	8 (0.7%)
Enrollment Expired[c]	1,214 (99.3%)	N/A	1,214 (99.3%)
Enrollment remained expired at end of period	934 (76.9%)	N/A	934 (76.9%)
Reason(s) For Closed System Pharmacy Inactivation[f]			
Enrollment Expired[c]	N/A	206 (100.0%)	206 (100.0%)
Enrollment remained expired at end of period	N/A	39 (18.9%)	39 (18.9%)
Numbers of Pharmacies Inactivated in This Time Period that Remain Inactivated as of the End of this Reporting Period	2,610	39	2,649
Inpatient Pharmacies	204 (7.8%)	N/A	204 (7.7%)
Chain Pharmacy Headquarters	5 (0.2%)	N/A	5 (0.2%)
Chain Pharmacy Stores	1,459 (55.9%)	N/A	1,459 (55.1%)
Independent Outpatient Pharmacies	942 (36.1%)	N/A	942 (35.6%)
Closed System Pharmacies	N/A	39 (100.0%)	39 (1.5%)
Total Number of Pharmacies Inactivated as of the End of This Reporting Period	6,444	137	6,581
Inpatient Pharmacies	484 (7.5%)	N/A	484 (7.4%)
Chain Pharmacy Headquarters	17 (0.3%)	N/A	17 (0.3%)
Chain Pharmacy Stores	3,500 (54.3%)	N/A	3,500 (53.2%)
Independent Outpatient Pharmacies	2,443 (37.9%)	N/A	2,443 (37.1%)
Closed System Pharmacies	N/A	137 (100.0%)	137 (2.1%)
Cumulative Number of Pharmacies Ever Inactivated[g]	16,763	360	17,123

	Current Reporting Period[a] 29OCT2015 to 28OCT2016		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Total Pharmacies N (%)**
Inpatient Pharmacies	696 (4.2%)	N/A	696 (4.1%)
Chain Pharmacy Headquarters	36 (0.2%)	N/A	36 (0.2%)
Chain Pharmacy Stores	12,514 (74.7%)	N/A	12,514 (73.1%)
Independent Outpatient Pharmacies	3,517 (21.0%)	N/A	3,517 (20.5%)
Closed System Pharmacies	N/A	360 (100.0%)	360 (2.1%)

[a] Pharmacies with 'inactive' status at least once during the reporting period.
[b] Percentages are based on the total number (N) of inactivated inpatient pharmacies. An inpatient pharmacy may have more than one reason for inactivation.
[c] Pharmacies whose status is 'Inactive-Expired' at any time during the enrollment period.
[d] Percentages are based on the total number (N) of inactivated chain pharmacy headquarters or chain pharmacy stores. A chain pharmacy headquarters or chain pharmacy store may have more than one reason for inactivation.
[e] Percentages are based on the total number (N) of inactivated independent outpatient pharmacy stores. An independent outpatient pharmacy store may have more than one reason for inactivation.
[f] Percentages are based on the total number (N) of inactivated closed system pharmacies. A closed system pharmacy may have more than one reason for inactivation.
[g] Cumulative is defined as the sum of all reporting periods.

During the current reporting period, there were 39 pharmacies that attempted enrollment but enrollment was pending 3 to 6 months later. As of the end of the reporting period, there were a total of 209 pharmacies pending enrollment for 6 months or longer. Pharmacies may have attempted enrollment and become pending in another reporting period.

For pharmacies pending enrollment for 3 to 6 months, the most frequent reasons were no attestation (46.2%), pending test transaction verification (46.2%), and training not complete (30.8%).

For pharmacies pending enrollment for 6 months or longer, the most frequent reasons were similar and included pending test transaction verification (54.1%), no attestation (40.2%), and training not complete (34.9%).

The number of pharmacies that attempted enrollment but are still pending enrollment for 3 to 6 months or longer than 6 months, and the reasons for pending enrollment are shown in Table 10.

Table 10 Pharmacies Pending Enrollment

Parameter	Current Reporting Period[a] 29OCT2015 to 28OCT2016					
	Pharmacies Pending Enrollment ≥3 - 6Months[b]			Pharmacies Pending Enrollment: >6 Months[b]		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	Total Pharmacies N (%)
Pharmacies that Attempted Enrollment but are Still Pending Enrollment	39	0	39	209	0	209
Reasons for Pending Enrollment						
Invalid DEA	1 (2.6%)	0	1 (2.6%)	3 (1.4%)	0	3 (1.4%)
Invalid NCPDP	0	0	0	6 (2.9%)	0	6 (2.9%)
Invalid NPI	1 (2.6%)	0	1 (2.6%)	3 (1.4%)	0	3 (1.4%)
Knowledge Assessment Failure - First Attempt	2 (5.1%)	0	2 (5.1%)	3 (1.4%)	0	3 (1.4%)
Knowledge Assessment Failure - Second Attempt	1 (2.6%)	0	1 (2.6%)	2 (1.0%)	0	2 (1.0%)
Knowledge Assessment Failure - Third Attempt	1 (2.6%)	0	1 (2.6%)	4 (1.9%)	0	4 (1.9%)
Missing Pharmacist Signature Date	0	0	0	2 (1.0%)	0	2 (1.0%)
Missing Signature	0	0	0	2 (1.0%)	0	2 (1.0%)
No Attestation	18 (46.2%)	0	18 (46.2%)	84 (40.2%)	0	84 (40.2%)
Pending Enrollment Intake	0	0	0	10 (4.8%)	0	10 (4.8%)
Pending Test Transaction Verification	18 (46.2%)	0	18 (46.2%)	113 (54.1%)	0	113 (54.1%)
Training Not Complete	12 (30.8%)	0	12 (30.8%)	73 (34.9%)	0	73 (34.9%)

[a] Reflects the total number of pharmacies pending enrollment in the current reporting period. Pharmacies may have attempted enrollment and became pending in another reporting period.

[b] Percentages are based on the total number (N) of pharmacies attempting enrollment. Percentages may not add up to 100% because a single pharmacy may be pending enrollment for more than one reason.

5.1.4 Wholesaler/Distributor Enrollment [Metric 9 and 10]

During the current reporting period, 1 (4.8%) wholesaler/distributor was newly enrolled in the REMS program and 20 (95.2%) re-enrolled (Table 11).

There were 5 wholesalers/distributors inactivated during the current reporting period due to enrollment expiration and 3 had not re-enrolled by the end of the reporting period (Table 12). The 3 distributors who became inactivated during this reporting period and remained inactivated at the end of the reporting period were acquired by other enrolled entities or were initially enrolled as the wrong stakeholder type.

Table 11 Distributor Enrollment

	Current Reporting Period[a] 29OCT2015 to 28OCT2016
Parameter	**N (%)**
Number of Distributors with Enrollment Activity in This Reporting Period	21
Number of Newly Enrolled Distributors	1 (4.8%)
Number of Re-Enrolled Distributors	20 (95.2%)
Number of Distributors that Remain Enrolled from Previous Reporting Periods	14
Total Number of Distributors Enrolled as of the End of the Reporting Period	35
Cumulative Number of Distributors Ever Enrolled[b,c]	49

[a] Percentages are based on the total number (N) for the relevant distributors for the period.
[b] Includes distributors that transitioned into the TIRF REMS Access program from other individual REMS programs.
[c] Cumulative distributors from the end of prior period may differ from last period's report due to reconciliation of duplicate distributors.

Table 12 Distributor Inactivations

	Current Reporting Period[a] 29OCT2015 to 28OCT2016
Parameter	**N (%)**
Number of Distributors that Became Inactivated in This Reporting Period[b]	5
Reason(s) for Distributor Inactivation	
Enrollment Expired[c]	5 (100.0%)
Enrollment remained expired at end of period	3 (60.0%)
Number of Distributors that Remain Inactivated From Previous Reporting Periods	11
Total Number of Distributors Inactivated as of the End of the Reporting Period	14
Cumulative Number of Distributors Ever Inactivated[d]	22

[a] Percentages are based on the total number (N) for the relevant inactivated distributors for the period.
[b] Distributors with 'inactive' status at least once during the reporting period.
[c] Distributors whose status is 'Inactive-Expired' at any time during the enrollment period.
[d] Cumulative is defined as the sum of all reporting periods.

5.1.5 Dispensing Activity [Metric 11, 12, 13]

5.1.5.1 Prescriptions Authorized [Metric 11]

A total of 117,708 prescriptions were adjudicated for safety by the TIRF REMS Access program in the current reporting period including 117,335 prescriptions from non-closed system pharmacies and 373 from closed system pharmacies (Table 13). Of the total prescriptions, 89.3% were subsequently approved for dispensing without encountering any REMS-related rejections (i.e., were authorized for dispensing by insurance or cash bin).

Table 13 Prescriptions from Outpatient Pharmacies That Did Not Encounter Any REMS-Related Rejections Prior to Being Authorized for Dispensing

	Current Reporting Period[b] 29OCT2015 to 28OCT2016			Cumulative[b,c] 28DEC2011 to 28OCT2016		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Number of Unique Prescriptions Submitted for Authorization	117,335	373	117,708	675,373	3,408	678,781
Total Number of Unique Prescriptions That Did Not Encounter Any REMS-Related Rejections Prior to Being Authorized for Dispensing[a]	104,748 (89.3%)	328 (87.9%)	105,076 (89.3%)	602,101 (89.2%)	2,741 (80.4%)	604,842 (89.1%)
Independent Pharmacies	67,353 (57.4%)	N/A	67,353 (57.2%)	396,356 (58.7%)	N/A	396,356 (58.4%)
Chain Pharmacy Stores	37,395 (31.9%)	N/A	37,395 (31.8%)	205,745 (30.5%)	N/A	205,745 (30.3%)
Closed System Pharmacies	N/A	328 (87.9%)	328 (0.3%)	N/A	2,741 (80.4%)	2,741 (0.4%)

[a] Prescriptions successfully adjudicated for safety (i.e., successful REMS edit) and authorized for dispensing by insurance or cash bin (bin number).
[b] Percentages are based on the total number (N) of unique prescriptions that never encountered a REMS-related rejection for the reporting period.
[c] Includes authorizations from all pharmacies that were enrolled in the TIRF REMS Access program at any time from inception of the program.

5.1.5.2 Prescriptions Encountering REMS-related Rejections [Metric 12]

When a prescription is presented it must meet the REMS edit requirements before it may be authorized for dispensing, or it is rejected. The reasons why a prescription will not meet a REMS edit requirement are included in Table 14.

If a prescription is rejected, the pharmacy must contact the TIRF REMS Access program to rectify the rejected transaction. Upon receiving an inbound call from a pharmacy provider, the TIRF REMS Access program Call Center Associate works to resolve the rejected transaction and to provide instructions on the corrective action needed to successfully process the transaction. Corrective action includes outreach and education to remedy rejected transaction processing. Of the 117,708 unique prescriptions submitted for approval during the current reporting period, 2,363 (2.0%) prescriptions encountered at least one REMS-related rejection prior to being authorized for dispensing from outpatient pharmacies (Table 15). There were a total of 10,269 prescriptions that encountered at least one REMS-related rejection and were never authorized for dispensing (Table 16).

Table 14 Reasons for Prescriptions Not Meeting REMS Edit Requirements

Reason	Description
Prescriber Identification (ID) Not Enrolled/Not Found	Found the prescriber last name but not the NPI, DEA or State License Number or both prescriber last name and ID are not found
PPAF Incomplete	Patient's PPAF is in an incomplete status; the PPAF is missing information
Patient Zip Code Missing	Patient's zip code was not submitted on the transaction
Prescriber Last Name Did Not Match Name Registered	Prescriber last name on the transaction did not match the prescriber last name associated with the Prescriber ID
Pharmacy Not Enrolled	Pharmacy is not enrolled; the pharmacy has not completed the enrollment or re-enrollment process
Prescriber ID Not Registered	Found the prescriber last name but the NPI, DEA or State License Number does not match prescriber.
PPAF Expired	Patient's PPAF expired due to 2 year PPAF expiration
PPAF No Activity	Patient's PPAF has expired due to no transaction activity within past 6 months
PPAF Terminated	Patient's PPAF terminated due to 2 year PPAF expiration (status was replaced with PPAF Expired effective 17 March 2015)
Prescriber Terminated	Prescriber enrollment terminated
Pharmacy Terminated	Pharmacy enrollment terminated

Table 15 presents the results for the prescriptions that encountered at least one REMS-related rejection prior to being authorized for dispensing from outpatient pharmacies. The most

frequent rejection reasons for independent pharmacies (n=1,212) were PPAF expired (34.9%), PPAF incomplete (26.3%), prescriber ID not registered (11.5%), and zip code missing (10.3%).

The most frequent rejection reasons for chain pharmacies (n=1,150) were prescriber last name did not match a registered prescriber (37.0%), PPAF expired (22.8%), zip code missing (15.7%), PPAF incomplete (15.5%), and prescriber ID not registered (9.0%).

One prescription from a closed system pharmacy encountered a REMS-related rejection prior to being authorized for dispensing in the current reporting period because of PPAF no activity (e.g., no transaction activity within the past 6 months).

Table 16 presents the results for the prescriptions that encountered at least one REMS-related rejection and were never authorized for dispensing from outpatient pharmacies. As stated previously, of the 117,708 unique prescriptions submitted for approval during the current reporting period there were a total of 10,269 prescriptions that encountered at least one REMS-related rejection and were never authorized for dispensing.

The most frequent rejection reasons for independent pharmacies (n=3,386) were prescriber ID not registered (32.6%), prescriber is terminated (23.0%), zip code missing (18.6%), and prescriber last name did not match a registered prescriber (12.8%).

The most frequent rejection reasons for chain pharmacies (n=6,839) were prescriber last name did not match a registered prescriber (54.3%), zip code missing (20.4%), prescriber ID not registered (19.0%), and prescriber is terminated (8.7%).

The most frequent rejection reasons for closed system pharmacies (n=44) were prescriber ID not registered (52.3%), prescriber last name did not match a registered prescriber (18.2%), pharmacy terminated (13.6%), and prescriber is terminated (9.1%).

Table 15 Prescriptions from Outpatient Pharmacies That Encountered at Least One REMS-Related Rejection Prior to Being Authorized for Dispensing

Parameter	Current Reporting Period[b] 29OCT2015 to 28OCT2016			Cumulative[b,c] 28DEC2011 to 28OCT2016		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)
Number of Unique Prescriptions Submitted for Authorization	117,335	373	117,708	675,373	3,408	678,781
Total Number of Unique Prescriptions that Encountered At Least One Initial REMS-Related Rejection Prior to being Authorized for Dispensing[a]	2,362 (2.0%)	1 (0.3%)	2,363 (2.0%)	21,733 (3.2%)	58 (1.7%)	21,791 (3.2%)
Independent Pharmacies	1,212 (1.0%)	N/A	1,212 (1.0%)	15,274 (2.3%)	N/A	15,274 (2.3%)
Chain Pharmacy Stores	1,150 (1.0%)	N/A	1,150 (1.0%)	6,459 (1.0%)	N/A	6,459 (1.0%)
Closed System Pharmacies	N/A	1 (0.3%)	1 (<0.1%)	N/A	58 (1.7%)	58 (<0.1%)
Independent Pharmacies						
Reason(s) for Rejection[d]						
Zip Code Missing	125 (10.3%)	N/A		6,689 (43.8%)	N/A	
PPAF Incomplete	319 (26.3%)	N/A		4,416 (28.9%)	N/A	
Prescriber last name did not match name registered	79 (6.5%)	N/A		1,925 (12.6%)	N/A	
Prescriber ID not registered	139 (11.5%)	N/A		1,768 (11.6%)	N/A	
PPAF Expired	423 (34.9%)	N/A		1,102 (7.2%)	N/A	
PPAF terminated	0	N/A		884 (5.8%)	N/A	
Prescriber is terminated	64 (5.3%)	N/A		343 (2.2%)	N/A	
Last Name and DOB Missing	13 (1.1%)	N/A		220 (1.4%)	N/A	
PPAF No Activity	90 (7.4%)	N/A		173 (1.1%)	N/A	

Parameter	Current Reporting Period[b] 29OCT2015 to 28OCT2016			Cumulative[b,c] 28DEC2011 to 28OCT2016		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)
Prescriber ID not submitted	19 (1.6%)	N/A		146 (1.0%)	N/A	
Pharmacy terminated	8 (0.7%)	N/A		123 (0.8%)	N/A	
First Name Missing	6 (0.5%)	N/A		73 (0.5%)	N/A	
Prescriber Terminated and Last Name Mismatch	7 (0.6%)	N/A		33 (0.2%)	N/A	
DOB Missing	0	N/A		24 (0.2%)	N/A	
First Name, Last Name, and Zip Code Missing	0	N/A		24 (0.2%)	N/A	
Zip Code and Last Name	0	N/A		13 (0.1%)	N/A	
First Name and Last Name Missing	0	N/A		10 (0.1%)	N/A	
DOB and Zip Code Missing	0	N/A		9 (0.1%)	N/A	
Last Name Missing	0	N/A		2 (<0.1%)	N/A	
Database Failure - System Unavailable due to maintenance	0	N/A		1 (<0.1%)	N/A	
First Name, Last Name and DOB Missing	0	N/A		1 (<0.1%)	N/A	
First Name, Last Name, Zip Code, and DOB Missing	0	N/A		1 (<0.1%)	N/A	
Multi-Match - two or more patient match on same criteria	0	N/A		1 (<0.1%)	N/A	
Chain Pharmacy Stores						
Reason(s) for Rejection[d]						
PPAF Incomplete	178 (15.5%)	N/A		2,492 (38.6%)	N/A	
Prescriber ID not registered	104 (9.0%)	N/A		1,190 (18.4%)	N/A	
Zip Code Missing	181 (15.7%)	N/A		1,043 (16.1%)	N/A	
Prescriber last name did not match registered	425 (37.0%)	N/A		931 (14.4%)	N/A	

Parameter	Current Reporting Period[b] 29OCT2015 to 28OCT2016			Cumulative[b,c] 28DEC2011 to 28OCT2016		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)
PPAF Expired	262 (22.8%)	N/A		656 (10.2%)	N/A	
PPAF terminated	0	N/A		518 (8.0%)	N/A	
Prescriber is terminated	51 (4.4%)	N/A		163 (2.5%)	N/A	
First Name Missing	50 (4.3%)	N/A		106 (1.6%)	N/A	
PPAF No Activity	68 (5.9%)	N/A		100 (1.5%)	N/A	
Last Name and DOB Missing	50 (4.3%)	N/A		90 (1.4%)	N/A	
Pharmacy terminated	1 (0.1%)	N/A		27 (0.4%)	N/A	
Prescriber ID not submitted	1 (0.1%)	N/A		20 (0.3%)	N/A	
Prescriber Terminated and Last Name Mismatch	7 (0.6%)	N/A		10 (0.2%)	N/A	
DOB Missing	1 (0.1%)	N/A		7 (0.1%)	N/A	
First Name and Last Name Missing	0	N/A		7 (0.1%)	N/A	
First Name, Last Name, and Zip Code Missing	0	N/A		6 (0.1%)	N/A	
First Name, Last Name and DOB Missing	2 (0.2%)	N/A		4 (0.1%)	N/A	
First Name, Last Name, Zip Code, and DOB Missing	1 (0.1%)	N/A		3 (<0.1%)	N/A	
Multi-Match - two or more patient match on same criteria	0	N/A		3 (<0.1%)	N/A	
First Name and DOB Missing	1 (0.1%)	N/A		2 (<0.1%)	N/A	
Pharmacy not Registered	0	N/A		2 (<0.1%)	N/A	
DOB and Zip Code Missing	0	N/A		1 (<0.1%)	N/A	
Database Failure - System unavailable due to system maintenance	0	N/A		1 (<0.1%)	N/A	
Last Name Missing	0	N/A		1 (<0.1%)	N/A	
Re-register	0	N/A		1 (<0.1%)	N/A	

Parameter	Current Reporting Period[b] 29OCT2015 to 28OCT2016			Cumulative[b,c] 28DEC2011 to 28OCT2016		
	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)	Non-Closed System Pharmacies N (%)	Closed System Pharmacies N (%)	All Pharmacies (Non-Closed and Closed) N (%)
Closed System Pharmacies						
Reason(s) for Rejection[d]						
Zip Code Missing	N/A	0		N/A	33 (56.9%)	
PPA Incomplete	N/A	0		N/A	10 (17.2%)	
Prescriber ID not registered	N/A	0		N/A	9 (15.5%)	
PPAF terminated	N/A	0		N/A	6 (10.3%)	
Prescriber last name did not match registered	N/A	0		N/A	6 (10.3%)	
PPAF Expired	N/A	0		N/A	3 (5.2%)	
PPAF No Activity	N/A	1 (100.0%)		N/A	1 (1.7%)	

[a] Prescription successfully adjudicated for safety (i.e., successful REMS edit) and authorized for dispensing by insurance or cash bin (bin number).
[b] Percentages are based on the total number (N) of number of unique prescriptions that encountered at least one initial REMS-related rejection prior to being authorized for dispensing for the reporting period.
[c] Includes authorizations from pharmacies that transitioned into the TIRF REMS Access program from other individual REMS programs.
[d] Prescriptions can be rejected for more than one reason.

Table 16 Prescriptions That Encountered at Least One REMS-Related Rejection and Never Authorized for Dispensing from Outpatient Pharmacies

	Current Reporting Period[a] 29OCT2015 to 28OCT2016			Cumulative[a] 28DEC2011 to 28OCT2016		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Number of Unique Prescriptions Submitted for Authorization	117,335	373	117,708	675,373	3,408	678,781
Total Number of Unique Prescriptions that Encountered At Least One Initial REMS-Related Rejection and Never Authorized for Dispensing	10,225 (8.7%)	44 (11.8%)	10,269 (8.7%)	51,539 (7.6%)	609 (17.9%)	52,148 (7.7%)
Independent Pharmacies	3,386 (2.9%)	N/A	3,386 (2.9%)	23,849 (3.5%)	N/A	23,849 (3.5%)
Chain Pharmacy Stores	6,839 (5.8%)	N/A	6,839 (5.8%)	27,690 (4.1%)	N/A	27,690 (4.1%)
Closed System Pharmacies	N/A	44 (11.8%)	44 (<0.1%)	N/A	609 (17.9%)	609 (0.1%)
Independent Pharmacies						
Reason(s) for Rejection[b]						
Prescriber ID not registered	1,105 (32.6%)	N/A		10,770 (45.2%)	N/A	
Prescriber last name did not match registered	432 (12.8%)	N/A		4,328 (18.1%)	N/A	
Zip Code Missing	631 (18.6%)	N/A		2,985 (12.5%)	N/A	
Prescriber is terminated	778 (23.0%)	N/A		2,468 (10.3%)	N/A	
PPAF Incomplete	168 (5.0%)	N/A		2,459 (10.3%)	N/A	
Pharmacy terminated	167 (4.9%)	N/A		827 (3.5%)	N/A	
Prescriber ID not submitted	80 (2.4%)	N/A		490 (2.1%)	N/A	
PPAF terminated	0	N/A		413 (1.7%)	N/A	

	Current Reporting Period[a] 29OCT2015 to 28OCT2016			Cumulative[a] 28DEC2011 to 28OCT2016		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
PPAF Expired	98 (2.9%)	N/A		346 (1.5%)	N/A	
PPAF No Activity	75 (2.2%)	N/A		138 (0.6%)	N/A	
Last Name and DOB Missing	19 (0.6%)	N/A		120 (0.5%)	N/A	
Prescriber Terminated and Last Name Mismatch	13 (0.4%)	N/A		108 (0.5%)	N/A	
First Name Missing	8 (0.2%)	N/A		54 (0.2%)	N/A	
First Name, Last Name, and Zip Code Missing	1 (<0.1%)	N/A		8 (<0.1%)	N/A	
Multi-Match - two or more patient match on same criteria	0	N/A		8 (<0.1%)	N/A	
DOB Missing	1 (<0.1%)	N/A		4 (<0.1%)	N/A	
First Name and Last Name Missing	1 (<0.1%)	N/A		4 (<0.1%)	N/A	
First Name, Last Name, Zip Code, and DOB Missing	0	N/A		2 (<0.1%)	N/A	
DOB and Zip Code Missing	1 (<0.1%)	N/A		1 (<0.1%)	N/A	
Last Name Missing	0	N/A		1 (<0.1%)	N/A	
Zip Code and Last Name	0	N/A		1 (<0.1%)	N/A	
Chain Pharmacy Stores						
Reason(s) for Rejection[b]						
Prescriber ID not registered	1,298 (19.0%)	N/A		14,870 (53.7%)	N/A	
Prescriber last name did not match registered	3,711 (54.3%)	N/A		6,163 (22.3%)	N/A	
PPAF Incomplete	139 (2.0%)	N/A		2,482 (9.0%)	N/A	
Prescriber is terminated	592 (8.7%)	N/A		2,019 (7.3%)	N/A	
Zip Code Missing	1,393 (20.4%)	N/A		1,759 (6.4%)	N/A	
Pharmacy terminated	148 (2.2%)	N/A		557 (2.0%)	N/A	

	Current Reporting Period[a] 29OCT2015 to 28OCT2016			Cumulative[a] 28DEC2011 to 28OCT2016		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
PPAF terminated	0	N/A		378 (1.4%)	N/A	
Last Name and DOB Missing	314 (4.6%)	N/A		377 (1.4%)	N/A	
PPAF Expired	115 (1.7%)	N/A		345 (1.2%)	N/A	
First Name Missing	248 (3.6%)	N/A		308 (1.1%)	N/A	
Prescriber ID not submitted	27 (0.4%)	N/A		264 (1.0%)	N/A	
Prescriber Terminated and Last Name Mismatch	48 (0.7%)	N/A		75 (0.3%)	N/A	
PPAF No Activity	43 (0.6%)	N/A		72 (0.3%)	N/A	
Multi-Match - two or more patient match on same criteria	1 (<0.1%)	N/A		12 (<0.1%)	N/A	
First Name and Last Name Missing	0	N/A		10 (<0.1%)	N/A	
Pharmacy not Registered	0	N/A		10 (<0.1%)	N/A	
Last Name Missing	0	N/A		4 (<0.1%)	N/A	
DOB Missing	1 (<0.1%)	N/A		1 (<0.1%)	N/A	
DOB and Zip Code Missing	0	N/A		1 (<0.1%)	N/A	
Database Failure - System unavailable due to system maintenance	0	N/A		1 (<0.1%)	N/A	
First Name, Last Name, Zip Code, and DOB Missing	1 (<0.1%)	N/A		1 (<0.1%)	N/A	
Closed System Pharmacies						
Reason(s) for Rejection[b]						
Prescriber ID not registered	N/A	23 (52.3%)		N/A	330 (54.2%)	
Prescriber last name did not match registered	N/A	8 (18.2%)		N/A	111 (18.2%)	
PPAF Incomplete	N/A	0		N/A	55 (9.0%)	

	Current Reporting Period[a] 29OCT2015 to 28OCT2016			Cumulative[a] 28DEC2011 to 28OCT2016		
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**All Pharmacies (Non-Closed and Closed) N (%)**
Pharmacy terminated	N/A	6 (13.6%)		N/A	47 (7.7%)	
Prescriber is terminated	N/A	4 (9.1%)		N/A	38 (6.2%)	
Zip Code Missing	N/A	3 (6.8%)		N/A	31 (5.1%)	
PPAF Expired	N/A	3 (6.8%)		N/A	5 (0.8%)	
PPAF terminated	N/A	0		N/A	4 (0.7%)	
Prescriber Terminated and Last Name Mismatch	N/A	1 (2.3%)		N/A	2 (0.3%)	
Multi-Match - two or more patient match on same criteria	N/A	0		N/A	1 (0.2%)	
Prescriber ID not submitted	N/A	0		N/A	1 (0.2%)	

[a] Percentages are based on the total number (N) of number of unique prescriptions for the period.
[b] Prescriptions can be rejected for more than one reason.

5.1.5.3 Time to Authorization [Metric 13]

In the 48-Month FDA Assessment Report Acknowledgement Letter, the FDA remarked that there continues to be a steady increase in mean and median prescription processing times as observed in the 48-month reporting period data versus the previous reporting period. The FDA requested that the TRIG investigate the cause of increasing delays in prescription processing as these are potential indicators of access barriers.

As previously described, a total of 2,363 prescriptions (representing 2.0% of all unique prescriptions submitted for authorization during the reporting period) encountered at least one initial REMS-related rejection prior to being authorized for dispensing. For all pharmacies, the mean time to authorization for a prescription that experienced at least one initial REMS-related rejection was 6.3 days while the median time was 2.0 days (Table 17). For chain pharmacy stores, it took a mean of 7.1 days (median 2.8 days) compared with independent outpatient pharmacies that took a mean of 5.5 days (median 1.7 day). For 1 closed system pharmacy prescription, it took 56.9 days. The TRIG has determined that of all the prescriptions that encounter at least one REMS-related rejection over 80% are resolved within the first 10 days (Table 18; Figure 1).

Table 17 Time to Authorization for a Prescription that Experienced at Least One Initial REMS-Related Rejection

	Current Reporting Period 29OCT2015 to 28OCT2016	Cumulative 28DEC2011 to 28OCT2016
Total Mean Time For Prescription to be Authorized[a] (Days)[b]	6.298	4.020
Inpatient Pharmacies	--	--
Chain Pharmacy Stores	7.136	4.934
Independent Outpatient Pharmacies	5.460	3.621
Closed System Pharmacies	56.859[c]	7.162
Total Median Time For Prescription to be Authorized[a] (Days)[b]	2.028	0.703
Inpatient Pharmacies	--	--
Chain Pharmacy Stores	2.798	1.171
Independent Outpatient Pharmacies	1.676	0.148
Closed System Pharmacies	56.859[c]	1.158

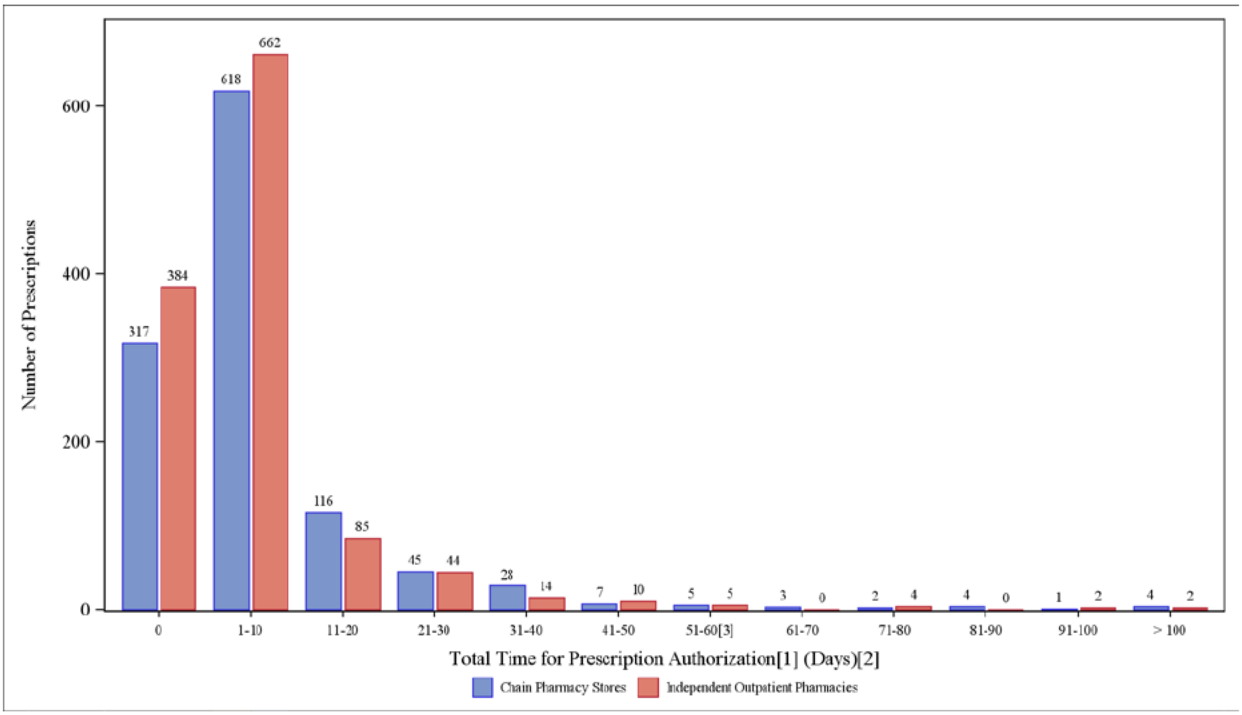
[a] Prescriptions included were resolved in the current reporting period. Prescriptions may have been initially rejected in a previous reporting period.
[b] Time to authorization for a prescription that experienced at least one initial REMS-related rejection excludes prescriptions processed through the inpatient pharmacy process.
[c] The mean and median data represent the actual time to authorization for 1 closed system pharmacy prescription.

Table 18 Distribution of Time to Authorization for a Prescription that Experienced at Least One Initial REMS-Related Rejection by Pharmacy Type and Overall for the Current Reporting Period

Total Time For Prescription to be Authorized[a] (Days)[b]	Chain Pharmacy Stores (N=1,150)	Independent Outpatient Pharmacies (N=1)	Closed System Pharmacies (N=1,212)	All Pharmacy Types (N=2,363)
0	317 (27.6)	0	384 (31.7)	701 (29.7)
1-10	618 (53.7)	0	662 (54.6)	1,280 (54.2)
11-20	116 (10.1)	0	85 (7.0)	201 (8.5)
21-30	45 (3.9)	0	44 (3.6)	89 (3.8)
31-40	28 (2.4)	0	14 (1.2)	42 (1.8)
41-50	7 (0.6)	0	10 (0.8)	17 (0.7)
51-60	5 (0.4)	1 (100.0)	5 (0.4)	11 (0.5)
61-70	3 (0.3)	0	0	3 (0.1)
71-80	2 (0.2)	0	4 (0.3)	6 (0.3)
81-90	4 (0.3)	0	0	4 (0.2)
91-100	1 (0.1)	0	2 (0.2)	3 (0.1)
> 100	4 (0.3)	0	2 (0.2)	6 (0.3)

[a] Prescriptions included were resolved in the current reporting period. Prescriptions may have been initially rejected in a previous reporting period.
[b] Time to authorization for a prescription that experienced at least one initial REMS-related rejection excludes prescriptions processed through the inpatient pharmacy process. Time was rounded to full days for categorization where values up to and including 0.5 days are categorized to the lower category.

Figure 1 Distribution of Time to Authorization for a Prescription that Experienced at Least One Initial REMS-Related Rejection for the Current Reporting Period



5.1.5.4 Prescription Authorizations for Closed-system Pharmacy Entities [Metric 11]

As described in Section 5.1.3, a total of 6 closed-system pharmacy entities were enrolled in the TIRF REMS Access program during this reporting period. These entities include:

- (b) (4) (b) (4)
- National Institutes of Health Clinical Center Pharmacy
- U.S. Department of Veterans Affairs
- (b) (4) (b) (4) (b) (4) (b) (4)
- DLA Troop Support
- (b) (4) (b) (4)

During the current reporting period, a total of 329 prescription authorizations were provided through these closed system pharmacy locations (Table 19). During the last reporting period on 18 May 2015, (b) (4) transitioned from being a closed-system pharmacy to a non-closed system pharmacy due to the pharmacy obtaining the ability to electronically adjudicate claims. Therefore, the prescription authorizations described

in Table 19 for (b) (4) are only included in the cumulative count and only represent prescriptions processed prior to this transition.

Table 19 Number of Prescription Authorizations per Closed System Pharmacy

	Current Reporting Period 29OCT2015 to 28OCT2016	Cumulative 28DEC2011 to 28OCT2016
Total Number of Closed System Pharmacy Prescription Authorizations	329	2,799

(b) (4) (b) (4) (b) (4) (b) (4) (b) (4)

	Current Reporting Period 29OCT2015 to	Cumulative 28DEC2011 to
(b) (4)		

[a] During the last reporting period on 18 May 2015, (b) (4) changed from a closed system pharmacy to a non-closed system pharmacy.

In the 48-Month FDA Assessment Report Acknowledgement Letter, the FDA requested that the TRIG propose an outreach to CSPs to improve compliance, if the TRIG does not favor a novel authorization process for all of the CSPs solely due to the poor performance of the governmental entities. Additionally, the FDA requested that the TRIG add the assessment of prescription processing times for prescriptions that do not experience any REMS-related rejections.

As reported in the 48-Month FDA REMS Assessment Report, the TRIG has determined that the current prescription authorization volume for CSPs is <1% (329/117,708) of all TIRF prescriptions and CSPs only account for <1% (232/42,665) of all pharmacies enrolled as of the end of this reporting period. To date, no complaints have been received from CSPs on the process; however, the TRIG acknowledges that there have been non-compliance events identified through the CSP audits where REMS processes have been bypassed. One challenge in updating the REMS authorization process to include a web-based modality in order to minimize non-compliance events (as described in many of the CSP audit CAPs), is the transient nature of pharmacy staff at these locations. Regardless of adding a modality to the authorization process, there is still turnover at the pharmacy level that leads to education gaps. A novel authorization process would provide another modality to minimize the risk to bypass REMS edits but still would require education on the process. Additionally, through anecdotal information, the TRIG is aware that some CSP locations are unable to access outside websites and may not be able to utilize a novel authorization process. The TRIG will continue to monitor and assess the need for an alternate solution as appropriate. One potential process the TRIG is evaluating is quarterly review of CSP data rather than an annual review in the current audit process. In addition to this potential process change, the TRIG is discussing incorporating an assessment of prescription processing times for prescriptions that do not experience any REMS-related rejections.

5.1.6 Barriers or Delays in Patient Access [Metric 14 and 15]

Prescriptions Dispensed Within First 10 Days after Patient Enrollment

Across all pharmacies, a total of 3,270 prescriptions were dispensed to 2,828 patients within the first 10 days after patient enrollment (Table 20). The majority of patients (n=2,817) were dispensed prescriptions by non-closed system pharmacies (3,259 prescriptions). A total of 982 patients received prescriptions without a PPAF from any pharmacy type and the majority received only 1 fill without a PPAF. A total of 3 patients received 3 prescriptions within 10 days without a PPAF on file. All 3 patients had their prescriptions filled through non-closed system pharmacies. No patient received more than 3 fills within 10 days without a PPAF on file.

48-Month FDA REMS Assessment Report Update

During the 48-month assessment period, 1 patient was reported as potentially receiving more than 3 fills within the 10-day period after enrollment without a PPAF on file from a non-closed system pharmacy. This occurred when an independent outpatient pharmacy submitted 4 prescriptions. Two prescriptions were batched billed from the pharmacy's PMS simultaneously, causing the prescriptions to pass through the REMS edits sub-seconds apart. Since a patient record was not found, the patient was passively enrolled in the TIRF REMS Access program twice. Ultimately, it was confirmed that the patient received only 3 unique prescriptions within the 10-day period.

Table 20 Prescriptions Dispensed During the First 10 Days after Passive Patient Enrollment

	Current Reporting Period 29OCT2015 to 28OCT2016				Cumulative[a] 28DEC2011 to 28OCT2016			
Parameter	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Combined Pharmacies[d] N (%)**	**Total Pharmacies N (%)**	**Non-Closed System Pharmacies N (%)**	**Closed System Pharmacies N (%)**	**Combined Pharmacies[d] N (%)**	**Total Pharmacies N (%)**
Number of prescriptions dispensed during the first 10 days after patient enrollment	3,259	11	0	3,270	40,727	222	11	40,960
Number of patients dispensed a prescription during the first 10 days after enrollment	2,817	11	0	2,828	34,061	185	5	34,251
With PPAF[b]								
1 Fill	1,597 (56.7%)	4 (36.4%)	0	1,601 (56.6%)	14,978 (44.0%)	57 (30.8%)	1 (20.0%)	15,036 (43.9%)
2 Fills	246 (8.7%)	0	0	246 (8.7%)	2,872 (8.4%)	9 (4.9%)	0	2,881 (8.4%)
3 Fills	38 (1.3%)	0	0	38 (1.3%)	423 (1.2%)	1 (0.5%)	0	424 (1.2%)
>3 Fills	6 (0.2%)	0	0	6 (0.2%)	86 (0.3%)	2 (1.1%)	0	88 (0.3%)
Without PPAF[b,c]								
1 Fill	922 (32.7%)	7 (63.6%)	0	929 (32.9%)	14,855 (43.6%)	107 (57.8%)	1 (20.0%)	14,963 (43.7%)
2 Fills	50 (1.8%)	0	0	50 (1.8%)	1,384 (4.1%)	5 (2.7%)	3 (60.0%)	1,392 (4.1%)
3 Fills	3 (0.1%)	0	0	3 (0.1%)	225 (0.7%)	4 (2.2%)	1 (20.0%)	230 (0.7%)
>3 Fills	0	0	0	0	10 (<0.1%)	0	0	10 (<0.1%)

[a] Cumulative data from the end of prior period may differ from the last period's report due to reconciliation of duplicate stakeholders.
[b] Percentages are based on the total number of patients for the period. Sum of percentages may be greater than 100% due to patients receiving prescriptions with and without a PPAF during the grace period.
[c] A patient may receive up to 3 fills in the first 10 days after enrollment without a PPAF.
[d] Patients who have filled a prescription at both a closed system pharmacy and a non-closed system pharmacy.

Prescriptions Dispensed Beyond 10 Days after Patient Enrollment

The TIRF REMS Access program requires that each patient have a PPAF submitted to the TIRF REMS Access program by their prescriber within 10 days of their passive enrollment in order to continue to receive a TIRF medicine. Table 21 below shows the number of prescriptions dispensed beyond the first 10 days without a PPAF on file. From the inception of the TIRF REMS through the current reporting period, 786 prescriptions have been dispensed beyond the first 10 days without a PPAF; no prescriptions dispensed beyond 10 days after enrollment without a PPAF were reported in the current reporting period.

48-Month FDA REMS Assessment Report Update

During the 48-month assessment period, 1 patient was reported as potentially receiving a fill that was dispensed beyond the 10 days after enrollment without a PPAF on file. This occurred when an independent outpatient pharmacy submitted 2 prescriptions for the same patient with variation in the spelling of the patient's last name. The variation caused the patient to become passively enrolled in the TIRF REMS Access program twice. A PPAF was received for the patient and processed on 1 of the 2 enrollment files. The enrollment files were identified to be duplicates and merged into one patient file, with a complete PPAF. Ultimately, it was confirmed that all prescriptions received outside of the 10 days after enrollment were received with a PPAF on file for the patient.

Table 21 Prescriptions Dispensed Beyond the First 10 Days after Passive Patient Enrollment Without a PPAF

	Current Reporting Period 29OCT2015 to 28OCT2016				Cumulative[a] 28DEC2011 to 28OCT2016			
Parameter	**Filled at Non-Closed System Pharmacies N**	**Filled at Closed System Pharmacies N**	**Filled at Combined Pharmacies[b] N**	**Filled at All Pharmacies N**	**Filled at Non-Closed System Pharmacies N**	**Filled at Closed System Pharmacies N**	**Filled at Combined Pharmacies[b] N**	**Filled at All Pharmacies N**
Fills beyond the first 10 days Without PPAF	0	0	0	0	751	32	3	786

[a] Cumulative data from the end of prior period may differ from the last period's report due to reconciliation of duplicate stakeholders.
[b] A patient who has filled a prescription at both a closed system pharmacy and a non-closed system pharmacy.

5.2 Program Infrastructure and Performance [Metrics 16, 17, 18, 19]

5.2.1 Backup System for Prescription Validation [Metric 16]

During this reporting period there were no instances in which a backup system was used to validate a prescription due to pharmacy level problems, switch problems, or REMS database problems.

5.2.2 System Interruptions/Errors and Corrective Actions [Metric 17, 19]

There were no unintended system interruptions during this reporting period [Metric 17].

There were no reports of program/system problems that occurred in this reporting period [Metric 19].

5.2.3 REMS Call Center [Metric 18]

A total of 124,796 calls to the TIRF REMS Access program were received during the reporting period. Table 22 below shows reasons for contacting the REMS Call Center by frequency (%). For presentation in the report, this table includes at least 80% of the total cumulative frequency. The most frequent reasons classified under the call reason were enrollment status inquiry (17.1%), pharmacy: pharmacy claim rejection (16.4%), PPAF inquiry (10.4%), and general program questions (6.1%). The call reasons listed below in Table 22 represent 81.9% of calls to the Call Center for the current reporting period.

Table 22 Current Assessment Period Contact Reasons

Reason	Count	Percent[a]
Enrollment Status Inquiry	21,285	17.1%
Pharmacy: Pharmacy Claim Rejection	20,451	16.4%
PPAF Inquiry	12,962	10.4%
General Program Questions	7,667	6.1%
Enrollment Follow Up	6,812	5.5%
Web Portal Logon Assistance	6,757	5.4%
Prescriber: Pharmacy Claim Rejection	6,514	5.2%
Enrollment Form	5,728	4.6%
Other/Miscellaneous	5,259	4.2%
PPAF Follow Up	4,569	3.7%
Identifier Issues	4,121	3.3%

[a] The total percentage presented in the table account for 81.9% of all reasons for contacting the Call Center.

There were no REMS-related barriers reported to the REMS Call Center during this reporting period.

6 TIRF REMS ACCESS PROGRAM NON-COMPLIANCE

Non-compliance is reported via four methods within this assessment report.

1. Stakeholder Non-Compliance Table: Non-compliance cases that have been identified during this reporting period by any stakeholder are counted in Section 6.1, Table 24.
2. Stakeholder Non-Compliance Narratives: Stakeholders who are associated with instances of non-compliance resulting from an NCRT "Warning" or any assessment monitoring are described via non-compliance narrative in Section 6.1, Table 25.
3. CSP Audit Results: Non-compliance cases identified through the CSP audits are described via audit summary in Section 6.3.1.
4. Inpatient Hospital Pharmacy Audit Results: Non-compliance cases identified through the inpatient audits are described via audit summary in Section 6.3.2.

These 4 methods of reporting non-compliance are additive in nature. Non-compliance cases discussed within the audit sections or the non-compliance narratives are not counted within the non-compliance table. Prescribers or pharmacies represented in the table are not described in the audit sections or the non-compliance narrative table.

6.1 Non-Compliance Feedback from the 48-Month FDA Acknowledgement Letter

The 48-Month FDA Acknowledgement Letter stated that FDA is concerning that the TRIG's criteria for an incident of an individual prescriber non-compliance with PPAF requirements needs to involve at least 5 or more patients enrolled by the prescriber without a complete PPAF on file (with each patient having greater than 10 working days lapse from the initial enrollment date). The FDA stated that these criteria would appear to potentially lead to an under-reporting of PPAF non-compliance and that the TRIG should explore mechanisms to capture lower levels of non-compliance.

Scenarios triggering a non-compliance case under the Non-compliance Protocol were designed to monitor for non-compliance with REMS requirements, while mitigating burden on prescribers and barriers for patients. Since the initiation of the Non-compliance Protocol, the NCRT has monitored instances where a prescriber has failed to have a complete PPAF on file in a timely manner. Upon identification that a prescriber has 5 or more patients enrolled without a complete PPAF on file and each patient is 10 working days past the initial enrollment date, a non-compliance case is opened for investigation ("Prescriber 2 Scenario" identified in the Non-compliance Protocol). Considerations that were taken into account when establishing this non-compliance scenario was the allowance of a patient receiving up to 3 prescriptions within the first 10 days without a PPAF under the approved REMS, the anticipated volume of prescribers writing one-time prescriptions for patients, and the anticipated amount of communication being sent to the prescriber. The TRIG has evaluated the occurrences of this non-compliance scenario over time by calculating rates of these events using the following denominators: prescribers enrolled as of the end of the reporting period, total number of prescriptions submitted for authorization, and the total number of prescriptions that were authorized by the TIRF REMS Access program. The rates of the Prescriber 2 Scenario across all denominators have gradually

decreased from the 36-month reporting period to the current reporting period. Based on this notable decrease, the TRIG has determined that this established non-compliance mechanism is working. However, the TRIG will continue to explore mechanisms to capture lower instances of non-compliance.

Table 23 Rates of Prescriber 2 Scenario Cases Over Time

	36-Month FDA REMS Assessment Report (N=120 reports)	48-Month FDA REMS Assessment Report (N=82 reports)	60-Month FDA REMS Assessment Report (N=50 reports)
Per 1,000 prescribers[a]	15.02	9.01	6.13
Per 10,000 submitted prescriptions[b]	7.52	5.37	4.25
Per 10,000 authorized prescriptions[c]	8.06	5.64	4.65

[a] The prescriber rates were based on reported number of prescribers enrolled as of the end of the reporting period. The denominators used for the 36-Month, 48-Month, and 60-Month REMS Assessment Report calculations were 7,992; 9,096; 8,151.

[b] The submitted prescription rates were based on the total number of prescriptions submitted for authorization. The denominators used for the 36-Month, 48-Month, and 60-Month REMS Assessment Report calculations were 159,560; 152,686; 117,708.

[c] The authorized prescription rates were based on the number of prescriptions that did not encounter any REMS-related rejections and was dispensed and the prescriptions that encountered at least one REMS-related rejection, but were eventually authorized and dispensed. The denominators used for the 36-Month, 48-Month, and 60-Month REMS Assessment Report calculations were 148,822; 145,498; 107,439.

6.2 Stakeholder Non-Compliance [Metric 23, 24, 25, 26, 27, 28]

Each unique stakeholder non-compliance case is investigated and non-compliance activity is generally reported 2 ways during a reporting period, either as a confirmed non-compliance activity report as in Table 24 or it is described in a narrative as in Table 25. If single non-compliance cases are reported over time and appear, for example, in Table 24 for 2 consecutive assessment reports, the Stakeholder's third offense will warrant a CAP and then all offenses are reported in a narrative only, and not in Table 24. Any confirmed non-compliance event that results in an NCRT "Warning" or is a result of any assessment monitoring (includes closed system monitoring and inpatient pharmacy audits) will be reported in a narrative.

During the current reporting period, 62 instances of potential stakeholder non-compliance with the TIRF REMS Access program were reviewed and investigated. A summary of the non-compliance activity is presented in Table 24 and Table 25.

Table 24 Non-Compliance Activity Reports by Stakeholder in the Current Reporting Period: 29 October 2015 to 28 October 2016

Stakeholder[a]	Non-Compliance Activity	Non-Compliant Reason (categorized as reported by the stakeholder)	No. of events	No. of stakeholders
Non-Closed System Pharmacy	Submission of a claim that did not go through the REMS edits. A TIRF medicine was dispensed without verifying through the TIRF PMS that the prescriber is enrolled and active, and that the patient is enrolled or has not been inactivated in the program.	Not aware of requirement to process cash claims	3	No. w/1 report: 3
		Received reject but dispensed drug	2	No. w/1 report: 2
		Dispensed drug without obtaining an authorization	2	No. w/1 report: 2
		Total Non-Closed System Pharmacy Cases	**7**	
Wholesaler/Distributor	Wholesaler/Distributor fills an order for TIRF medicines for a non-enrolled stakeholder.	No reason provided	1	No. w/1 report: 1
		Total Wholesaler/Distributor Cases	**1**	
Prescriber	Prescriber failure to have a complete PPAF on file in a timely manner (5 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from the initial enrollment date).	Not aware of PPAF requirement	9	No. w/1 report: 9
		Completed PPAF with patient but failed to send PPAF to TIRF REMS	18	No. w/1 report: 18
		Aware of PPAF requirements but failed to complete PPAF	8	No. w/1 report: 8
		No reason provided	15	No. w/1 report: 15
		Total Prescriber Reports	**50**	
		Total Number of Reports During This Reporting Period	**58**	

[a] There were no spontaneous reports of non-compliance from closed-system pharmacies.

During the reporting period, there was 1 instance where a TIRF prescription was dispensed by a non-closed system pharmacy that was written by non-enrolled prescribers after receiving a rejection from the TIRF REMS Access program [Metric 24] as described below.

> On 17 February 2016, the closed system authorization process was not followed, resulting in a pharmacy receiving manual authorization to dispense drug from a Call Center Associate when all safe use conditions were not met. The prescriber who wrote the TIRF prescription was not enrolled, therefore the authorization to dispense should not have been provided to the pharmacy. On 17 February 2016, the TIRF REMS Access program contacted the pharmacy to advise drug should not be dispensed. During the interaction the pharmacy confirmed it had already dispensed drug. TIRF REMS Access program contacted the prescriber, who was advised of enrollment requirements and provided assistance to complete enrollment into the program. Re-training on TIRF REMS Access program requirements and work instructions was provided to both the Call Center Associate who authorized the dispense and all other Call Center Associates.

There was 1 instance where a prescription was dispensed by a non-enrolled pharmacy [Metric 25] as described below.

> The TIRF REMS Access program was notified of a distributor that shipped TIRF medicine(s) to a non-enrolled pharmacy when the non-enrolled pharmacy contacted the TIRF REMS Access program regarding a prescription rejection for reason of pharmacy not enrolled. Upon notification of REMS requirements, the non-enrolled pharmacy shipped the TIRF medicine(s) back to the distributor. The AR for the distributor was re-educated on the REMS requirements and stated that the non-compliant shipment was due to a change in a National Drug Code (NDC) number that was not updated in their system. The NCRT issued a first Notice for Non-Compliance on 23 February 2016 requiring submission of a CAP on 15 March 2016. The distributor provided a CAP stating that programming changes would occur to the system to update all product NDCs that require a system flag that they are restrictions on the TIRF REMS Access program. The NCRT approved the CAP on 28 March 2016.

As shown in Table 24, there were 7 instances in which a TIRF prescription was dispensed because a pharmacy (closed or open system) was able to bypass REMS edits [Metric 26]. A total of 4 of these 7 instances were due to not using the cash BIN to process a claim. In all 4 of these instances the pharmacy was re-educated and a Notice for Non-Compliance was issued. The remaining 3 instances are described below.

1. The TIRF REMS Access program received a call for assistance with a REMS rejection due to a PPAF not on file on 02 May 2016. After confirming that the PPAF expired on 28 March 2016 and that the patient would need to complete a new PPAF with the prescriber before medication can be dispensed, the pharmacy confirmed the medication was already dispensed the week before. The pharmacy was re-educated on the REMS requirements and a Notice for Non-Compliance was issued. The TIRF REMS Access program has since confirmed that the patient has a new PPAF on file as of 03 May 2016.

2. The TIRF REMS Access program received a call for assistance with a REMS rejection due to a lapse in prescriber recertification on 18 May 2016. The pharmacy confirmed that medication was already dispensed to the patient even though a rejection was received on 26 April 2016. The prescriber has since completed re-enrollment as of 18 May 2016. The pharmacy was re-educated on the REMS requirements and a Notice for Non-compliance was issued.
3. The TIRF REMS Access program received a call for assistance with a REMS rejection due to a lapse in prescriber recertification on 05 October 2016. The pharmacy confirmed that the medication was dispensed on 05 September 2016. The prescriber has since completed re-enrollment as of 14 September 2016. The pharmacy was re-educated on the REMS requirements and a Notice for Non-Compliance was issued.

No reports of TIRF medicines being prescribed to an opioid non-tolerant individual [Metric 27] or cases of inappropriate conversions between TIRF products [Metric 28] were received by sponsor companies during this reporting period.

Table 25 summarizes in narrative form all resolved non-compliance cases (n=4); there were no non-compliance event narratives that remain open as of the end of the reporting interval.

Table 25 Non-Compliance Reports in the Current Reporting Period: 29 October 2015 to 28 October 2016

Report Description (N=3)	Report Status	Mitigating Action
ID#380 (Case # 25444573, 26320577) **[48-Month FDA REMS Assessment Report Non-Compliance]** On 22 June 2015 the prescriber was identified as not submitting PPAFs for 6 patients. On 06 July 2015, a request for contact correspondence was sent to the prescriber after multiple unsuccessful contact attempts between 22 June and 04 July 2015. The TIRF REMS Access program made an additional 6 outreach attempts following the issuance of the request for contact correspondence. On 03 August 2015 a formal Notice for Non-Compliance was issued to the prescriber, and the prescriber was re-educated. The 6 outstanding PPAFs will not be submitted as they were for patients identified as not continuing therapy. On 03 August 2015 the prescriber was again identified as not submitting PPAFs for 6 patients.	**Closed**	On 18 September 2015, a request for contact correspondence was sent with a Prescriber Overview after multiple unsuccessful outreach attempts between 26 August 2015 and 11 September 2015. The prescriber failed to contact the TIRF REMS Access program for re-education by the deadline of 10 October 2015. The 6 outstanding PPAFs will not be submitted as they were for patients identified as not continuing therapy. A first Warning letter was issued on 26 October 2015 with a request for a CAP. On 02 November 2015, a CAP was received from the prescriber; however, on 12 November 2015, the NCRT did not approve the plan as it did not align with the re-education received by the prescriber. **[60-Month FDA REMS Assessment Report Update]** Multiple unsuccessful attempts to reach the prescriber for a valid CAP were made from 12 November 2015 to 16 December 2015. Due to non-response, the prescriber was suspended from the TIRF REMS Access program on 16 December 2015 and required to submit a revised CAP by 04 January 2016. A CAP was received on 17 December 2015. The prescriber stated that the office had implemented a second fax line specific to PPAF submissions and the prescriber also received an overview on how to use the website to submit PPAFs. The NCRT approved the CAP on 18 December 2015. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.

Report Description (N=3)	Report Status	Mitigating Action
ID#413 (Case # 19987682, 22657145, 103199529) *This prescriber has not been described in a non-compliance narrative in previous assessment reports; however, he had non-compliant activity prior to this reporting period. Information pertaining to previous non-compliance outside of this reporting period has been included for reference.* On 27 May 2014 the prescriber was identified as not submitting PPAFs for 5 patients. The prescriber submitted 3 of the 5 PPAFs, as the remaining 2 PPAFs were identified as not continuing therapy. A formal Notice for Non-Compliance was issued to the prescriber on 03 July 2014. On 08 December 2014 the prescriber was identified as not submitting PPAFs for 6 patients. None of the outstanding 6 PPAFs were submitted as all patients were identified as not continuing therapy. A second formal Notice for Non-Compliance was issued to the prescriber on 12 February 2015. On 05 February 2016 the prescriber was identified as not submitting PPAFs for 6 patients who were at least 10 days past enrollment.	**Closed**	The prescriber was contacted and re-educated on 10 February 2016. The prescriber stated that his office is very busy and the PPAFs may have been lost or misplaced. The TIRF REMS Access program educated the prescriber about the website as the prescriber mentioned that he prefers to do things electronically. The prescriber submitted all 6 PPAFs. A Warning letter was issued to the prescriber requiring that a CAP is submitted by 15 March 2016. A CAP was received on 10 March 2016. The NCRT did not approve the CAP as it did not include a preventative action plan to ensure future adherence to PPAF requirements. A revised CAP was received on 23 March 2016, which stated that the prescriber will make sure that a PPAF will be faxed for every patient that receives a prescription and the portal will be checked to confirm documentation is complete. The revised CAP was approved by the NCRT on 14 April 2016. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.
ID#422 (Case # 12482456, 18919365, 20277540, 22269972 & 131991271) *This prescriber was previously included in non-compliance narratives presented in the 36-Month FDA*	**Closed**	The TIRF REMS Access program attempted to contact the prescriber multiple times between 17 March 2016 and 07 April 2016 for re-education. A request for contact, along with the Prescriber Overview, was issued to the prescriber after multiple unsuccessful attempts. The prescriber failed to contact the TIRF REMS Access

Report Description (N=3)	Report Status	Mitigating Action
REMS Assessment Report (ID #179: Case #12482456, 18919365 & 20277540). **[24-Month Assessment Report Non-Compliance]** Prescriber was issued a first formal Notice for Non-Compliance on 18 March 2013 for not submitting PPAFs. **[36-Month FDA REMS Assessment Report Non-Compliance]** Prescriber was issued a second formal Notice for Non-Compliance on 11 April 2014 for not submitting PPAFs and then a Warning on 11 July 2014 requiring submission of a CAP after the prescriber was again identified as not submitting PPAFs for patients at least 10 days past enrollment. The prescriber submitted a CAP on 14 July 2014 that was denied by the NCRT as it did not align with the re-education that it was the prescriber's responsibility to submit PPAFs for each patient. A revised CAP was received on 24 July 2014 which stated that the prescriber would take personal responsibility to make sure patients are educated and PPAFs are signed. The CAP was approved by the NCRT on 07 August 2014. A second Warning for Non-Compliance was issued to the prescriber on 13 November 2014 requiring submission of a CAP after the prescriber was again identified as not submitting PPAFs for patients at least		program by the 28 April 2016 deadline. Additional attempts to contact the prescriber were made and re-education was performed on 04 May 2016. The prescriber was issued a Warning with request for a CAP to be submitted by 26 May 2016. A CAP was received on 25 May 2016. The CAP was not approved by the NCRT as it was signed by an office nurse, not the prescriber. A revised CAP was received on 03 June 2016. The CAP was not approved by the NCRT as it did not describe a corrective action to be implemented to ensure the non-compliance was not repeated. A third revised CAP was received on 15 June 2016. The CAP stated that staff would be trained on the TIRF REMS Access website to submit PPAFs and handing out prescription information on TIRF medicines with each PPAF. The CAP was approved by the NCRT on 16 June 2016. Since closing the non-compliance case, no additional non-compliance cases for this prescriber have been identified.

Report Description (N=3)	Report Status	Mitigating Action
10 days past enrollment. The prescriber submitted a CAP on 01 December 2014 stating that he has met with all of his current staff members to ensure that they understand the importance of the TIRF REMS Program and thoroughly understand the protocol for the completion and submission of PPAFs. Additionally, the prescriber has made several changes within his office, including having TIRF REMS forms readily available to be signed in every patient room and personally reviewing his schedule daily to confirm that every patient who was prescribed a TIRF medicine has been REMS enrolled. The CAP was approved by the NCRT on 03 December 2014. **[60-Month FDA REMS Assessment Report Non-Compliance]** On 17 March 2016 the prescriber was again identified as not submitting PPAFs for 5 patients.		
ID#445 (Case # 190342508) The TIRF REMS Access program was notified by a sponsor of a prescriber with a DEA set to be deactivated 31 October 2016.	**Closed**	The TIRF REMS Access program confirmed that the prescriber signed an agreement with the state Board of Medical Examiners on 21 October 2016 stating that the prescriber would no longer accept new patients and would stop writing prescriptions for controlled substances immediately. The prescriber's DEA would then officially be deactivated on 31 October 2016. The TIRF REMS Access program reviewed prescription transaction data and confirmed that the prescriber had no prescription activity between 21 October 2016 and 31 October 2016. On 01 November 2016, the TIRF REMS Access program confirmed

Report Description (N=3)	Report Status	Mitigating Action
		that the prescribers DEA was no longer active. The TIRF REMS Access program notified the prescriber's office that the prescriber would be deactivated from the TIRF REMS Access program based on no longer having a valid, Schedule II DEA.

[a] No prescriber inactivations occurred during this reporting period due to non-compliance; however, there was a significant event of non-compliance reported after the reporting period ended on 28 October 2016.

6.3 Audits

As part of non-compliance monitoring, the TIRF REMS Access program pharmacies may be subject to periodic data requests and/or audits. Such activities may occur for suspected non-compliance with program requirements based on program monitoring activities.

6.3.1 Closed System Pharmacy Audits [Metric 20]

The REMS Assessment Plan includes the following components for closed system pharmacy audits:

(1) Verification of training for all pharmacists dispensing TIRF products

(2) Numbers of prescription authorizations per closed system

(3) Reconciliation of data describing TIRF product prescriptions received by the closed system pharmacy with TIRF product dispensed to patients with a valid enrollment in the TIRF REMS Access program.

The first component of the closed system pharmacy audit requirement is accomplished through the enrollment process for CSPs. To become enrolled the authorized representatives must attest that all pharmacy staff that participate in dispensing TIRF products will be trained on the TIRF REMS Access program requirements. The second component is done through the closed system pharmacy prescription authorization process. Closed system pharmacists are required to validate the enrollment status of the prescriber and patient prior to dispensing a TIRF product by calling or faxing the prescription details to the TIRF REMS Access program. The TIRF REMS Access program maintains records of prescription details and the associated REMS authorization. Table 19 provides information on all prescription authorizations by closed system pharmacy.

The third and final component includes reconciliation between the closed system pharmacy's dispensing data and the TIRF REMS Access program's REMS authorizations. To conduct this reconciliation, the TIRF REMS Access program requests dispensing records from the CSPs and compares the dispensing records to REMS authorization data from the TIRF REMS Access program. After confirmation that the closed system pharmacy agrees to participate in the reconciliation, a formal written request for data is issued upon request to the AR detailing the data to be provided and the deadline for submission. Specific data requested include:

- RX number for each prescription dispensed
- DEA number or National Provider Identifier (NPI) number of the facility that dispensed each prescription
- DEA number or NPI number of the prescriber that issued each prescription
- Date and time of each prescription transaction
- TIRF REMS Authorization code obtained for each prescription dispensed
- Due to the structure of some closed system pharmacy networks, the headquarters may be unable to provide data for all pharmacy locations as no central data repository is in existence; each pharmacy location maintains their own data. In these cases, a random sample of pharmacy locations is selected by the TIRF REMS Access program for participation.

- Findings from each investigation are reviewed with the NCRT and actions are taken in accordance with the Non-Compliance Protocol.

The CSP assessment metric required auditing of at least 3 randomly selected CSPs. The TRIG proactively included all CSPs in the audit with a request to provide dispensing records from 01 May 2015 through 30 April 2016. As a result, there were 6 audits conducted during this 60-month monitoring reporting period and 4 CSPs (ID#CS7, ID#CS9, ID#CS10 and ID#CS12) were found to be non-compliant with the TIRF REMS Access program requirements. Based on the identification of non-compliance, a non-compliance case was opened for each of these 4 CSPs.

Below are the details of these 6 closed-system pharmacy audits. Table 26 summarizes the reconciliation of the dispensing data from each CSP and the authorizations received from the TIRF REMS Access program during the course of the 6 audits.

Table 26 Closed System Pharmacy Audits

Audit ID Number	Date Closed System Monitoring Request for Data Sent	Date Dispensing Records Received[1]	Total Dispenses/Total Dispenses Not Authorized by the REMS	Non-Compliance Identified?
1 (ID#CS7)	26 May 2016	08 July 2016	164/1	Y
2 (ID#CS8)	26 May 2016	15 June 2016[2]	0/0	N
3 (ID#CS9)	26 May 2016	07 September 2016	40/7	Y
4 (ID#CS10)	26 May 2016	02 September 2016	27/1[3]	Y
5 (ID#CS11)	26 May 2016	20 June 2016[2]	0/0	N
6 (ID#CS12)	26 May 2016	02 September 2016	99/59	Y

[1] The date range for dispensing records received was 01 May 2015 through 30 April 2016.
[2] Pharmacy provided confirmation that no TIRF medicines were dispensed during the reporting period (01 April 2014-30 April 2015).
[3] Initial data showed that there was one location with three instances of dispensing TIRF medications without an authorization. However, after issuance of a Notice for Non-Compliance, additional information was received from the pharmacy confirming that the one location only had one instance of dispensing TIRF medications without an authorization.

Additional details on the 4 CSP audits that identified non-compliance are identified below.

Closed System Pharmacy Audit 1: ID#CS7 (Case #177904062)

Request for Data

On 26 May 2016, the TIRF REMS Access program initiated outreach to request data pertaining to all instances where TIRF medicines were dispensed from the pharmacy for reconciliation purposes to ensure that the manual closed system process is meeting the goals of the REMS.

On 02 June 2016, a formal closed system monitoring request for data was sent via fax to the AR, with a response requested by 24 June 2016.

Investigation

On 24 June 2016, the AR requested an extension until 08 July 2016 to submit the data. Dispensing records were provided on 08 July 2016, and the TIRF REMS Access program began to reconcile the data. The dispensing records contained data from 01 May 2015 through 30 April 2016 and included 164 instances where a TIRF product had been dispensed during the monitoring period. The dispensing records provided were compared to authorization data from the TIRF REMS Access program. To complete the reconciliation, additional data were requested from (b) (4) (b) (4) on 22 August 2016. The additional data were provided on 09 September 2016.

Findings

Data discrepancies were found during reconciliation and showed that in 1 of the 164 occurrences drug was dispensed without obtaining an authorization.

Outcome

A second formal Notice for Non-Compliance was issued on 21 September 2016 requiring a CAP be submitted by 21 October 2016. A CAP was received on 20 October 2016 stating that the non-compliant instance occurred because the Pharmacy Technician mistakenly took the patient insurance number written on the script as the REMS authorization number. The pharmacy has a process in place where a hard stop prompt displays in the system when a TIRF is to be dispensed notifying the Pharmacy Technician that the TIRF REMS must be called to obtain an authorization number. The authorization number is then documented before dispensing the medication. The Pharmacy Technician and the Pharmacist have been counseled on the error and the REMS requirements and process have been reinforced. The TRIG approved the CAP on 01 December 2016.

Closed System Pharmacy Audit 3: ID#CS9 (Case #177372348)

Request for Data

On 26 May 2016, the TIRF REMS Access program initiated outreach to request data pertaining to all instances where TIRF medicines were dispensed from the pharmacy for reconciliation purposes to ensure that the manual closed system process is meeting the goals of the REMS.

A formal request for data correspondence was issued via email to the Veteran's Administration (VA) on 26 May 2016.

Investigation

In the request for data in February 2014, the VA AR had advised that each VA site stores their own dispensing records (there is no central data storage) and they requested that the TIRF REMS Access program select a sample of sites to provide dispensing records. Therefore, on 04 August 2016, the TIRF REMS Access program provided 8 randomly selected and enrolled VA closed-system dispensing locations (accounting for 10% of the enrolled population for VA) to the VA for reconciliation. A response with the data was requested by 16 September 2016.

The requested dispensing data were received from the VA on 07 September 2016 and reconciled with authorization data from the TIRF REMS Access program. The dispensing records contained

data from 01 May 2015 through 30 April 2016 and included 40 instances where a TIRF product had been dispensed during the monitoring period.

Findings

The closed system pharmacy dispensing data showed that 1 location had 7 instances of dispensing TIRF medications without authorization.

Outcome

A third formal Notice for Non-Compliance was issued to the headquarters on 21 September 2016. A CAP was initiated on 26 September 2016 stating that prior to November 2015, the pharmacy staff were unaware of the requirement to obtain authorization prior to dispensing due to changes in personnel and limited dispensing of TIRF REMS products. The pharmacy is now requiring that all pharmacy clinical staff complete the TIRF REMS Access Education Program. Training will be documented and reviewed bi-annually to ensure compliance. Additionally, the system used at the pharmacies was updated to add a reminder for each TIRF NDC that authorization was required for dispensing and a Standard Operation Procedure (SOP) was developed to define the need for prior authorization and the steps to take to acquire prior authorization. This CAP was approved by the NCRT on 03 November 2016, after the TRIG confirmed with the pharmacy that all non-compliant dispenses identified in the 2015-2016 audit data, were prior to the initiation of this CAP.

Closed System Pharmacy Audit 4: ID#CS10 (Case #177920269)

Request for Data

On 26 May 2016, the TIRF REMS Access program initiated outreach to request data pertaining to all instances where TIRF medicines were dispensed from the pharmacy for reconciliation purposes to ensure that the manual closed system process is meeting the goals of the REMS.

A formal request for data correspondence was issued to the (b) (4) (b) (4) on 03 June 2016.

Investigation

In the request for data in February 2014, the (b) (4) (b) (4) AR had proposed that the TIRF REMS Access program provide REMS authorization data for randomly selected sites and provide the information to (b) (4) would then reconcile their own pharmacy's data to identify any non-compliance. This process has been used by (b) (4) to conduct audits for other REMS programs. Therefore, on 04 August 2016, the TIRF REMS Access program provided data for 8 randomly selected and enrolled (b) (4) (b) (4) closed-system dispensing locations (accounting for 20% of the enrolled population for (b) (4) (b) (4) to (b) (4) (b) (4) for reconciliation. A response with the data was requested by 16 September 2016.

The requested data were received from (b) (4) (b) (4) on 02 September 2016 and reconciled with authorization data from the TIRF REMS Access program. The dispensing records contained data from 01 May 2015 through 30 April 2016 and included 27 instances where a TIRF product had been dispensed during the monitoring period.

Findings

The closed system pharmacy dispensing data showed that 1 location had 3 instances of dispensing TIRF medications without authorization.

Outcome

A second formal Notice for Non-Compliance for was issued on 21 September 2016 requiring a CAP by 12 October 2016. Upon receipt of the notice, research was conducted by (b) (4) and additional information was provided to the TIRF REMS Access program. The additional data showed that the 1 non-compliant location only had 1 instance of dispensing TIRF medications without authorization from the TIRF REMS Access program. A revised second formal Notice for Non-Compliance was issued on 26 September 2016. A CAP was received on 26 September 2016, stating that the issue that occurred was due to the pharmacy's transition to a new pharmacy system and that as of 15 December 2016, all licensed pharmacists will be required to review the REMS guidelines and attest they are aware of all processes. Reminders will also be placed near the TIRF medication storage area to remind pharmacists to obtain authorization prior to dispensing. The NCRT approved the CAP on 17 November 2016.

Closed System Pharmacy Audit 5: ID#CS12 (Case #145003267)

Request for Data

On 26 May 2016, the TIRF REMS Access program initiated outreach to request data pertaining to all instances where TIRF medicines were dispensed from the pharmacy for reconciliation purposes to ensure that the manual closed system process is meeting the goals of the REMS.

A formal request for data correspondence was issued to the Department of Defense (DoD) on 27 May 2016.

Investigation

In the request for data in May 2015, the DoD Representative had proposed that the TIRF REMS Access program provide REMS authorization data from the TIRF REMS Access program so that they could match it to their pharmacy data. Therefore, on 04 August 2016, the TIRF REMS Access program provided data for all sites (accounting for 100% of the enrolled population for the DoD) to the DoD for reconciliation. A response with the data was requested by 16 September 2016.

The requested data were received from DoD on 02 September 2016 and reconciled with authorization data from the TIRF REMS Access program. The dispensing records contained data from 01 May 2015 through 30 April 2016 and included 99 instances where a TIRF product had been dispensed during the monitoring period.

Findings

The closed system pharmacy dispensing data showed that 11 locations had 59 instances of dispensing TIRF medications without authorization. Of the 11 locations, 3 locations were not enrolled in the TIRF REMS Access program.

Outcome

The TIRF REMS Access program conducted research to determine whether the 3 non-enrolled sites were the same non-enrolled sites found to be non-compliant during the 48-month assessment period. On 03 October 2016 it was confirmed that 1 of the non-enrolled sites found during this reporting period was also a non-enrolled site identified in the 48-month assessment period. The AR was notified and confirmed that the three non-enrolled sites had been re-educated and would not be dispensing TIRF medicines in the future.

A third formal Notice for Non-Compliance for was issued on 06 October 2016 requiring a CAP by 12 October 2016. A CAP was received on 18 October 2016 stating the three non-compliant pharmacy locations were not aware of the prescription authorization requirement. All three locations were educated on the REMS requirements and were marked as deactivated locations that will no longer order or dispense TIRF products. Future plans have been made to conduct ongoing quarterly educational sessions to inform the military treatment facility on the REMS requirements until understanding, awareness, and compliance is stable. The NCRT approved the CAP on 17 November 2016.

6.3.1.1 Closed System Pharmacy Audit Acknowledgement Letter Items

In the 48-Month FDA Assessment Report Acknowledgement Letter, FDA requested that both CSP entities that were found to be non-compliant in the 48-month assessment reporting period be included in the 60-month CSP audits. All CSPs were included in the audit process, which included both CSPs that were found to be non-compliant in the 48-Month FDA REMS Assessment Report.

Additionally, the FDA requested that the TRIG should propose an outreach to CSPs to improve compliance if the TRIG does not favor a novel authorization process for all of the CSPs solely due to the poor performance of the governmental entities. Further, the FDA requested that the TRIG add the assessment of prescription processing times for prescriptions that do not experience any REMS-related rejections.

As described in Section 5.1.5.4 in response to FDA's request of consider a novel approach for prescription authorization at CSP locations, the TRIG does not favor the addition of a web-based process. As discussed in many of the CSP audit CAPs, one challenge related to updating the REMS authorization process at CSPs to be web-based is the transient nature of pharmacy staff at these locations. Regardless of adding a modality to the authorization process, there is still turnover at the pharmacy level that leads to education gaps. A novel authorization process would provide another modality to minimize the risk to bypass REMS edits but still would require education on the process. Additionally, through anecdotal information, the TRIG is aware that some CSP locations are unable to access outside websites and may not be able to utilize a novel authorization process. The TRIG will continue to monitor and assess the need for an alternate solution as appropriate. One potential process the TRIG is evaluating is quarterly review of CSP data rather than an annual review in the current audit process. In addition to this potential process change, the TRIG is discussing incorporating an assessment of prescription processing times for prescriptions that do not experience any REMS-related rejections.

6.3.2 Inpatient Hospital Pharmacy Audits [Metric 21]

The inpatient hospital pharmacy audit process is conducted through an audit questionnaire invitation that is faxed to authorized inpatient pharmacists of pharmacies enrolled in the TIRF REMS Access program requesting their participation. Once the authorized inpatient pharmacist agreed to participate, they received the audit questionnaire to complete, which included 2 qualifying questions to determine eligibility to participate in the audit:

1. Is your pharmacy a Hospital Pharmacy? Yes/No
2. In the previous 12 months, has your hospital pharmacy dispensed TIRF medicine? Yes/No

If the answer was no to either of the qualifying questions, the pharmacy did not qualify for the audit. If they answered yes to both qualifying questions, they were asked to finalize the questionnaire by completing the following 3 questions:

1. Provide the number of units dispensed within <insert date range>. (See NDC list for a current listing of TIRF NDCs)

   _____units of use of TIRFs dispensed to inpatients.
2. Did all pharmacists who dispensed TIRF medicines complete training on the TIRF REMS Access program prior to dispensing these products? Yes/No
3. Do you have procedures in place such as order sets/protocols to assure compliance with the TIRF REMS program requirements? Yes/No. If yes, are you willing to provide examples of an order set or protocol?

All completed questionnaires were to be returned to the TIRF REMS Access program via fax or phone by the date specified on the audit invitation.

A total of 12 enrolled inpatient locations were solicited for participation in the audit. Three of the 12 pharmacies did not respond to the audit invitation. The remaining 9 pharmacy locations agreed to participate and completed the qualifying questions associated with the audit questionnaire. Of the 9 pharmacies, 4 pharmacies answered no to at least one of the qualifying questions and were either not a hospital inpatient pharmacy facility or had not dispensed TIRFs in the previous 12 months. The remaining 5 qualified to participate in the audit, and proceeded with answering the 3 remaining audit questions.

Based on responses to the 3 audit questions, 4 of the 5 audited inpatient hospital pharmacies were found to be compliant with the TIRF REMS Access program requirements. One audited inpatient hospital pharmacy was found to be non-compliant with the REMS requirements and a non-compliance case was opened.

Inpatient Hospital Pharmacy Audit 6: ID#IA6 (Case #138176646)

Questionnaire Completion

On 12 May 2016, the Audit Invitation and Questionnaire were faxed to the inpatient pharmacy AR. Outreach was conducted on multiple occasions from 17 May 2016 to 31 May 2016 to confirm receipt and timeline for completion of the questionnaire. A completed questionnaire was received on 06 June 2016.

Findings

The inpatient pharmacy reported dispensing 7 units of TIRF medicines in the previous 12 months. The pharmacy indicated that all pharmacists who dispensed TIRF medicines did not complete training on the TIRF REMS Access program prior to dispensing these products.

Outcome

A Warning was issued to the pharmacy on 15 June 2016, requesting a CAP be submitted by 29 June 2016. A CAP was received on 29 June 2016 stating that the Medical Safety Pharmacist would be sending the link to the education to all pharmacists to ensure all pharmacists complete the training. Additionally, any new pharmacists will be required to complete the training. The Director of Pharmacy will enforce mandated training every 2 years (in alignment with the pharmacy enrollment renewal). The NCRT approved the CAP on 01 July 2016.

Based on the identification of non-compliance at this inpatient hospital pharmacy, the TRIG plans invite this same pharmacy for audit activities again in 2017.

7 SAFETY SURVEILLANCE

7.1 Adverse Event Reporting [Metric 29]

TIRF Sponsors process AE reports related to their specific products and report to the FDA according to current regulations outlined in 21 CFR 314.80 and the sponsor's respective SOPs.

7.2 TRIG Sponsor Adverse Event Data of Interest [Metric 30]

Based on the current Assessment Plan in the REMS Supporting Document, the TRIG has conducted an aggregate root cause analysis of all spontaneous AE reports of addiction, death, overdose, and pediatric exposure from the TIRF Sponsors. Based on this requirement the TRIG Sponsor companies used a third party, UBC, to conduct this analysis. The sponsors identified the appropriate Medical Dictionary for Drug Regulatory Activities (MedDRA) codes to provide data including narratives or MedWatch forms which UBC summarized based on the FDA's request (see Appendix 12.2). Reports were reviewed and duplicates consolidated, when possible. Originally case reports were selected based on the specified Preferred Terms (PTs); upon UBC's review of the narrative information, some case reports did not meet the specified criteria and were excluded from the analysis. Additionally, literature reports and reports from Poison Centers were excluded.

Metrics of interest included: the number of event reports in each event category of interest (addiction, death, overdose, pediatric exposures); counts of AEs related to inappropriate conversions between TIRF products; counts of AEs related to accidental and unintentional exposures; and counts of AEs that are associated with use of TIRF medicines in non-opioid tolerant patients.

In the 36-Month FDA Assessment Report Acknowledgement Letter, the FDA stated that none of the TRIG spontaneous AEs included a root cause analysis as specified in the Assessment Plan and requested that a root cause analysis of AEs be reported in subsequent assessment reports. The analysis has been added and data tables now report the potential causality for each case if sufficient information was available to make a determination. If there was insufficient

information available and the potential causality could not be determined, it was noted in the table.

The reporting period used for this analysis was 29 August 2015 to 28 August 2016.

There were 353 unique case reports that met the specified criteria. After a review of the 353 MedWatch Forms or narratives, no reports of inappropriate conversions between TIRF products were noted. None of the narratives indicated unintentional exposures, or non-opioid tolerance.

7.3 Number of Adverse Events of Special Interest

The total number of cases of interest reported during this reporting period is presented in Table 27 below. Of the 353 cases, 344 (97.5%) had an outcome of death, 6 (1.7%) were reports of addiction, 4 (1.1%) were reports of overdose, and 3 (0.8%) were pediatric exposures. There was an increase in deaths this reporting period versus the 48-Month FDA REMS Assessment Report (344 vs. 294). However, a decrease in deaths was observed from the 36-Month FDA REMS Assessment Report to the current reporting period. There was a noted decrease in addiction, overdose and pediatric exposure for this reporting period. From the 48-Month FDA REMS Assessment Report to the 60-Month FDA REMS Assessment Report, reports of addiction have decreased from 12 to 6 cases, overdose is down from 6 cases to 4 cases, and pediatric exposures are down from 4 cases to 3 cases.

Table 27 Number of Cases of Adverse Events of Special Interest

AEs of Interest	Current Reporting Period (29AUG2015-28AUG2016)Number of Reports[a] N (%)
Total Number of AEs of Interest	353
Addiction	6 (1.7)
Death	344 (97.5)
Overdose	4 (1.1)
Pediatric Exposure	3 (0.8)

[a] Cases may have more than one AE of interest.

Table 28 shows the current reporting period rates for each of the AEs of special interest per 100,000 prescriptions. During this reporting period, a TRIG sponsor noted cases that met the criteria for this analysis that had not been previously report. A total of 43 cases were identified including 41 death cases, 1 case of addiction (which resulted in death), and 2 cases of overdose. Identification of these cases impacted the rates previously reported. For this reason, the rates of the AEs of interest for the 36-month, 48-month, and 60-month reporting periods have been adjusted as presented in Table 28.

Table 28 Rate of Adverse Events by Total Prescriptions

			Data Reported in the 48-Month and 36-Month FDA REMS Assessment Reports				Updates to Data Reported in the 48-Month and 36-Month FDA REMS Assessment Reports			
	Current Reporting Period 29AUG2015-28AUG2016		Previous Reporting Period 29AUG2014-28AUG2015		Previous Reporting Period 29AUG2013-28AUG2014		Previous Reporting Period 29AUG2014-28AUG2015		Previous Reporting Period 29AUG2013-28AUG2014	
AEs of Interest	Number of AEs[a]	AE Rates per 100,000 Prescriptions (N=88,332)	Number of AEs[a]	AE Rates per 100,000 Prescriptions (N=112,522)	Number of AEs[a]	AE Rates per 100,000 Prescriptions (N=94,464)	Revised Number of AEs[a]	Revised AE Rates per 100,000 Prescriptions (N=112,522)	Revised Number of AEs[a]	Revised AE Rates per 100,000 Prescriptions (N=94,464)
Addiction	6	6.79	12	10.66	4	4.23	12	10.66	5	5.29
Death	344	389.44	291	258.62	362	383.21	294	261.28	400	423.44
Overdose	4	4.53	6	5.33	0	0.00	6	5.33	2	2.12
Pediatric Exposure	3	3.40	4	3.55	2	2.12	4	3.55	2	2.12

[a] Cases may have more than one AE of special interest.

Table 29 shows the current reporting period rates for each of the AEs of special interest per 100,000 population. The rates previously reported for AEs by total patients was also impacted by the additional 43 cases and revised rates have been calculated.

Table 29 Rate of Adverse Events by Total Patients

			Data Reported in the 48-Month and 36-Month FDA REMS Assessment Reports				Updates to Data Reported in the 48-Month and 36-Month FDA REMS Assessment Reports			
	Current Reporting Period 29AUG2015-28AUG2016		Previous Reporting Period 29AUG2014-28AUG2015		Previous Reporting Period 29AUG2013-28AUG2014		Previous Reporting Period 29AUG2014-28AUG2015		Previous Reporting Period 29AUG2013-28AUG2014	
AEs of Interest	Number of AEs[a]	AE Rates per 100,000 Patients (N=11,107)	Number of AEs[a]	AE Rates per 100,000 Patients (N=15,922)	Number of AEs[a]	AE Rates per 100,000 Patients (N=14,772)	Revised Number of AEs[a]	Revised AE Rates per 100,000 Patients (N=15,922)	Revised Number of AEs[a]	Revised AE Rates per 100,000 Patients (N=14,772)
Addiction	6	54.02	12	75.37	4	27.08	12	75.37	5	33.85
Death	344	3,097.15	291	1,827.66	362	2,450.58	294	1,846.50	400	2,707.83
Overdose	4	36.01	6	37.68	0	0.00	6	37.68	2	13.54
Pediatric Exposure	3	27.01	4	25.12	2	13.54	4	25.12	2	13.54

[a] Cases may have more than one AE of special interest.

Six cases were classified as cases of addiction. Of the 6 cases, 2 cases had an outcome of "not recovered/not resolved" at the time of the cut off (28 August 2016); and 3 cases had an outcome of "unknown; and 1 had an outcome of death. Table 30 provides details of these 6 cases and Table 31 presents the 1 new case of addiction received that falls in a previous reporting period.

Table 30 Cases of Addiction Received from TRIG Sponsors during the Reporting Period: 29 August 2015 - 28 August 2016

Patient			Date								
UBC ID	**Age**	**Gender**	**Event**	**Report**	**Preferred Term(s)**	**Indication(s)**	**TIRF Duration**	**Concomitant Medications**	**Co-Suspect Product(s)**	**Event Outcome**	**Potential Causality[a]**
1939	UNK	Unknown	Unknown	08OCT2015	Intentional product misuse, Product use issue	Lower back leg pain	Unknown	None reported	None reported	Unknown	Not Related
1988[b]	31	Male	10APR2014, 10APR2014, 10APR2014, 28DEC2011, 28DEC2011, 28DEC2011, 28DEC2011, 28DEC2011, 01JAN2011, 23JAN2008, 23JAN2008, 23JAN2008, 01JAN2008, 01JAN2008, 01JAN2008, 01JAN2008, 01JAN2008, 08AUG2007, 02JUN2007, 02JUN2007, 01JAN2007, 01JAN2007, 01JAN2006, Unknown, Unknown, Unknown	07DEC2015	Accidental overdose, Lethargy, Stupor, Anhedonia, Decreased appetite, Feeling abnormal, Insomnia, Suicidal ideation, Tooth abscess, Headache, Nausea, Vomiting, Anxiety, Depression, Neck pain, Skin abrasion, Stress, Migraine, Tooth impacted, Toothache, Fall, Ligament sprain, Drug dependence, Major depression, Product use issue, Toxicity to various agents	Headaches	2 Years	Elavil, Clonidine, Benadryl, Naproxen, Prochlorpera-zine, Nexium, Prilosec, Klonopin, Pantoprazole	Percocet, Lorazepam, Oxycodone, Xanax, Endocet	Death	Possibly Related

Patient			Date								
UBC ID	**Age**	**Gender**	**Event**	**Report**	**Preferred Term(s)**	**Indication(s)**	**TIRF Duration**	**Concomitant Medications**	**Co-Suspect Product(s)**	**Event Outcome**	**Potential Causality[a]**
2048	45	Male	03FEB2016, 02FEB2016	04FEB2016	Coma, Inappropriate schedule of drug administration	Pain, pain	Unknown	Nabilone	Ativan, Cocaine	Unknown	Possibly Related
2111	55	Male	APR2016, 28MAR2016, MAR2016, JAN2016, Unknown	28MAR2016	Underdose, Device failure, Pain, Product use issue, Intentional product misuse	Back pain, neuralgia	2016-01 - UNK	Calcium, Glucosamine, Multivitamin /07504101/, Oxycodone, Oxycontin, Saw Palmetto /00833501/, Warfarin	None reported	Not Recovered/ Not Resolved	Possibly Related
2152	59	Male	04JUN2016, Unknown	18MAY2016	Drug withdrawal syndrome, Drug dependence	Breakthrough cancer pain	2015-05 - UNK	Oxycontin	None reported	Unknown	Possibly Related
2259	UNK	Male	Unknown	15AUG2016	Drug dependence, Drug withdrawal syndrome	Breakthrough cancer pain	2014-08-07 - UNK	Amlodipine, Hydrochlorothiazide	None reported	Not Recovered/ Not Resolved	Possibly Related

[a] Potential causality was reported if sufficient information was available to make a determination. If there was insufficient information available and the potential causality cannot be determined, this was noted in the table.
[b] Patient 1988 is also described in the table for overdose and death found in Appendix 12.3.
UNK = Unknown

Table 31 New Cases of Addiction Received from TRIG Sponsors in 2016 from a Previous Reporting Period

Patient			Date								
UBC ID	**Age**	**Gender**	**Event**	**Report**	**Preferred Term(s)**	**Indication(s)**	**TIRF Duration**	**Concomitant Medications**	**Co-Suspect Product(s)**	**Event Outcome**	**Potential Causality[a]**
1889[b]	UNK	Male	Unknown	28JUL2014[c]	Abnormal behaviour, Disorientation, Drug interaction, Hepatic failure, Inappropriate schedule of drug administration	Breakthrough cancer pain	2014-05-30 - 2014-06-03	None reported	Nexavar	Death	Possibly Related

[a] Potential causality was reported if sufficient information was available to make a determination. If there was insufficient information available and the potential causality cannot be determined, this was noted in the table.
[b] Patient 1889 is also described in the table for death found in Appendix 12.3.
[c] Case initiated in prior reporting period but was not included in previous reports.
UNK = unknown.

As a result of this review, 344 reports of death were noted. In more than 100 of these cases, the patients died in the hospice setting. Of the 344 reports of death, 142 of the deaths noted the indication for product use was related to breakthrough pain/breakthrough cancer pain and/or a cancer diagnosis.

Of the 344 reports of death, 218 cases did not include enough information to allow for an assessment of potential causality. A total of 121 death cases were determined to be not related to the TIRF medication. Of the total 344 reports of death, 4 deaths had a causality of possibly related to the TIRF product. There was one death report that was determined to be related to the TIRF medication in which the prescribing physician confirmed inappropriate use in the case narrative.

A full line listing of deaths (cases of death received from TRIG Sponsors during the current reporting period and new cases received from TRIG Sponsors in 2016 from previous reporting periods is presented in Appendix 12.3.

There were 4 overdose cases reported during this reporting period (Table 32). Three of the 4 cases had an outcome of death, 2 of those had a causality reported as possibly related and 1 death had insufficient information with no potential causality. These 3 cases also appear in the death listings (Appendix 12.3). The 1 remaining case had an unknown outcome and was determined to be possibly related.

Table 33 presents the 2 new cases of overdose that were not previously reported.

Table 32 Cases of Overdose Received from TRIG Sponsors during the Reporting Period: 29 August 2015 - 28 August 2016

Patient			Date								
UBC ID	Age	Gender	Event	Report	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1988[b]	31	Male	10APR2014, 10APR2014, 10APR2014, 28DEC2011, 28DEC2011, 28DEC2011, 28DEC2011, 28DEC2011, 01JAN2011, 23JAN2008, 23JAN2008, 23JAN2008, 01JAN2008, 01JAN2008, 01JAN2008, 01JAN2008, 01JAN2008, 08AUG2007, 02JUN2007, 02JUN2007, 01JAN2007, 01JAN2007, 01JAN2006, Unknown, Unknown, Unknown	07DEC2015	Accidental overdose, Lethargy, Stupor, Anhedonia, Decreased appetite, Feeling abnormal, Insomnia, Suicidal ideation, Tooth abscess, Headache, Nausea, Vomiting, Anxiety, Depression, Neck pain, Skin abrasion, Stress, Migraine, Tooth impacted, Toothache, Fall, Ligament sprain, Drug dependence, Major depression, Product use issue, Toxicity to various agents	Headaches	2 Years	Elavil, Clonidine, Benadryl, Naproxen, Prochlorperazine, Nexium, Prilosec, Klonopin, Pantoprazole	Percocet, Lorazepam, Oxycodone, Xanax, Endocet	Death	Possibly Related
2198[c]	UNK	Unknown	Unknown	05JUL2016	Overdose	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2204	46	Female	07JUL2016, Unknown	07JUL2016	Oral mucosal blistering, Overdose	Breakthrough cancer pain	2016-06-28 - UNK	None reported	None reported	Unknown	Possibly Related
2217[d]	32	Female	25MAR2016	19JUL2016	Overdose	Breakthrough cancer pain	2016-07-28 - UNK	None reported	None reported	Death	Possibly Related

[a] Potential causality was reported if sufficient information was available to make a determination. If there was insufficient information available and the potential causality cannot be determined, this was noted in the table.
[b] Patient 1988 is also described in the table for addiction and death found in Appendix 12.3.
c Patient 2198 is also described in the death table found in Appendix 12.3.
[d] Patient 2217 is also described in the death table found in Appendix 12.3.
UNK = unknown.

Table 33 New Cases of Overdose Received from TRIG Sponsors in 2016 from a Previous Reporting Period

Patient			Date								
UBC ID	Age	Gender	Event	Report	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1858	UNK	Male	Unknown	07JAN2014[b]	Hospitalisation, Overdose	Crohn's disease	2015-06-08 - UNK	None reported	None reported	Unknown	Insufficient Information
1884	50	Female	MAY2014, MAY2014, 2014, 17AUG2013, 2013, Unknown	20JUN2014[b]	Accidental overdose, Drug dependence, Blood pressure increased, Off label use, Drug withdrawal syndrome, Back pain, Confusional state, Constipation, Decreased appetite, Diplopia, Dizziness, Drug ineffective, Dysphagia, Dysuria, Fall, Fatigue, Hallucination, Increased upper airway secretion, Lethargy, Local swelling, Nausea, Parosmia, Pruritus, Skin lesion, Vertigo, Vision blurred, Visual impairment, Vomiting	Neck pain, back pain, pain in hip	2013-08-17 - UNK	Flexeril, Opana, Prevacid	Fetzima, Vistaril	Not Recovered/ Not Resolved	Possibly Related

[a] Potential causality was reported if sufficient information was available to make a determination. If there was insufficient information available and the potential causality cannot be determined, this was noted in the table.
[b] Case was initiated in prior reporting period but was not included in previous reports.
UNK = unknown.

There were 3 pediatric cases reported during this reporting period (Table 34). No case had an outcome of death. One report was not resolved and 2 cases had an outcome of unknown at the time of this report.

In all reports, the medication was intentionally prescribed to the pediatric patient. No further details were obtained despite extensive follow-up attempts.

Table 34 Cases of Pediatric Exposures Received from TRIG Sponsors during the Reporting Period: 29 August 2015 - 28 August 2016

Patient			Date								
UBC ID	**Age**	**Gender**	**Event**	**Report**	**Preferred Term(s)**	**Indication(s)**	**TIRF Duration**	**Concomitant Medications**	**Co-Suspect Product(s)**	**Event Outcome**	**Potential Causality[a]**
2119	9	Male	01JAN2010, Unknown, Unknown, Unknown, Unknown	04APR2016	Product use issue, Blood albumin decreased, Drug administered to patient of inappropriate age, Haemoglobin decreased, Malnutrition	Epidermolysis bullosa pain	Unknown	Methadone, Neurontin, Morphine	None reported	Not Recovered/ Not Resolved	Pediatric Exposure Resulting From Off-label Prescribing
2181	14	Male	Unknown	21JUN2016	Drug administered to patient of inappropriate age	Unknown	Unknown	None reported	None reported	Unknown	Pediatric Exposure Resulting From Off-label Prescribing
2197	14	Female	Unknown	01JUL2016	Drug administered to patient of inappropriate age, Hospitalisation	Unknown	Unknown	None reported	None reported	Unknown	Pediatric Exposure Resulting From Off-label Prescribing

[a] Potential causality was reported if sufficient information was available to make a determination. If there was insufficient information available and the potential causality cannot be determined, this was noted in the table.
UNK = unknown.

7.4 TIRF Product Surveillance Data [Metric 31]

7.4.1 Background

Surveillance data focusing on events of abuse, misuse, and death were evaluated using data from the RADARS System for the time period July 2010 to June 2016. Based on FDA request, the data included in this report compare event rates for a time period prior to full implementation of the TIRF REMS and a time period after REMS implementation. The 48-Month FDA Assessment Report Acknowledgement Letter requested that the CII immediate-release opioid category be expanded to include oxycodone/acetaminophen, oxycodone/aspirin, and oxycodone/ibuprofen. The TRIG confirms that the CII immediate-release opioid category currently includes these products in the analysis.

Data from 5 programs that gather data from unique populations along the spectrum of drug abuse were used to monitor for the non-medical use (abuse and misuse) of TIRF products. The data sources and the specific events evaluated in each are shown in Table 35 below.

Table 35 RADARS System: Data Sources and Specific Events

Data Source	Abuse	Intentional Misuse	Unintentional Therapeutic Errors	Unintended General Exposures	Emergency Department Visits & Hospitalizations	Deaths	Major Medical Outcomes and Deaths[e]
1. Poison Center Program	✔ [a]	✔	✔	✔	✔	✔	✔
Treatment Center Programs							
2. Opioid Treatment Programs	✔ [b]						
3. Key Informants Survey	✔ [b]						
4. College Survey	✔ [c]						
5. Impaired Health Care Workers Program	✔ [d]						

[a] Abuse defined as exposure resulting from intentional improper or incorrect use of a substance where the victim was likely attempting to gain a high euphoric effect or some other psychotropic effect

[b] Abuse defined as a respondent endorsing the use of a product to get high in the past 30 days

[c] Abuse defined as endorsement of a non-medical use of a drug in the past 90 days

[d] All reported cases are considered abuse; data may include a small fraction of drug diversion information.

[e] This column includes the events included in the column titled “deaths” as well as major medical outcomes that did not lead to death

Trends over time for the TIRF products were compared to 3 comparator groups that are not directly impacted by the TIRF REMS to determine how the trend in TIRF rates compares to the secular trend in other opioids. The comparators used in this report were:

- Schedule II IR opioids
- Schedule II opioids
- Schedule II opioids excluding methadone

On 06 October 2014, IR hydrocodone was changed from a Schedule III opioid to a Schedule II opioid. As IR hydrocodone was not included in the group of Schedule II opioids in previous reports and was not a Schedule II drug for the entire study period, data were analyzed 2 ways. The primary analyses were conducted without IR hydrocodone in the Schedule II IR opioid group. Sensitivity analyses were then conducted as if IR hydrocodone was a Schedule II IR opioid for all quarters.

Data from IMS Health are used to estimate total prescriptions dispensed and total dosing units dispensed at the 3-digit ZIP-code level for all TIRF REMS opioids and comparator groups. Totals of prescriptions and dosing units in the 3-digit zip codes covered by the RADARS System Programs were computed and used as the denominators when calculating product availability rates. IMS data does not capture methadone dispensed through opioid treatment programs (OTPs), thus the count of methadone prescriptions is an undercount. Prescription rates will be scaled per 10,000 prescriptions and dosing rates will be scaled per 100,000.

Rates of abuse, misuse, overdose, unintentional therapeutic errors, unintentional general exposures, emergency department visits/hospitalizations, deaths, and major medical outcomes were calculated using the 2010 US decennial census estimated from the 3-digit zip codes covered in the RADARS System Programs as the denominator. Population rates will be scaled per 100,000 population.

Additional details regarding the data sources and specific events can be found in the RADARS System Report Protocol (Appendix 12.4).

7.4.2 RADARS Results

This RADARS System Report summary presents the results of an analyses of the effectiveness of the TIRF REMS drawn from 5 data sources (i.e., Poison Center Program, Treatment Center Programs combined [includes OTP survey and Survey of Key Informants' Patients {SKIP}], College Survey, and Impaired Healthcare Workers Program). The full report from the RADARS System Program including limitations of the analyses is included as Appendix 12.5.

Poisson regression was used to compare changes in rates of abuse, misuse, and serious medical consequences, including deaths, emergency department visits, therapeutic errors and accidental unsupervised ingestions, over time for the TIRF products to changes over time in rates among 3 comparator groups: Schedule II IR opioids, Schedule II opioids and Schedule II opioids excluding methadone. Two different methods of analysis were applied: a comparison of means model and a comparison of trends model. In the first model, separate means were fit to the pre and post TIRF REMS periods. The pre to post changes in the mean outcome rates were then compared across drug groups. For the second model, separate trend lines were fit to the pre and

post TIRF REMS data. Comparison of the change in intercepts and slopes were made. Time was divided into 2 periods: pre (3Q2010 through 2Q2012) and post (3Q2012 to 2Q2016).

The comparison of means model provided a better fit to the data than the comparison of trends and thus is the focus of this summary. For the Poison Center Program outcomes of intentional abuse, intentional misuse, unintentional therapeutic error, unintentional general, emergency department visits or hospitalization and for all 3 rate types (population, prescription and dosing unit rates), no significant pre to post REMS mean changes were noted in conjunction with implementation of the TIRF REMS. Further, when comparing pre to post mean changes for the TIRF REMS opioids to means changes for Schedule II IR opioids, Schedule II opioids and Schedule II opioids excluding methadone, no significant differences were found. For the outcome of major medical outcome or death, significant increases were seen for the pre to post TIRF REMS periods per prescriptions dispensed and dosing units dispensed. These increases differed significantly from the change for Schedule II IR opioids, Schedule II opioids and Schedule II opioids excluding methadone.

As in previous reports, only 2 deaths were reported in the Poison Center Program. Due to the infrequency of the death data, the planned statistical models could not be fit (did not converge).

The Treatment Center Programs Combined comprises the OTP and the SKIP Program. For the Treatment Center Programs Combined, the mean abuse outcome decreased from the pre to post period for population rates. There were no significant changes in the prescription- or dosing unit-adjusted rates. When comparing these mean changes for the TIRF opioids to that observed for Schedule II IR opioids, population rates differed significantly. For prescription dispensed rates, mean pre to post treatment decreases for the TIRF opioid differed from the change for Schedule II opioids and Schedule II opioids excluding methadone.

For the College Survey Program, the mean abuse outcome for the TIRF opioids significantly increased from the pre to post period for all 3 rate types: population, prescriptions dispensed and dosing units dispensed. These increases were different than for IR Schedule II opioid, Schedule II opioids, or Schedule II opioid excluding methadone per prescriptions dispensed only. No significant changes were observed in the Impaired Health Care Worker Program.

Lastly, for pediatric exposures, there were 9 cases of children (0-5 years) exposed in the pre period compared with 15 cases in the post period (9, 0-5 years; 5, 13-19 years; 1, age missing [19 or younger]).

Table 36 summarizes the results from all RADARS System Programs by outcome of interest and denominator. The percentage change in the cumulative rate from the period before the TIRF REMS was implemented to the period after the TIRF REMS was implemented is displayed with 95% confidence intervals. The p-value displayed in the table measures whether the change observed in comparator opioids is different from the change in TIRF products for a given outcome and rate.

Descriptively, population rates for the TIRF products across all outcome variables were low compared to rates for the three Schedule II opioid comparator arms; while prescription adjusted rates for the TIRF products were higher than the rates for the three Schedule II opioid comparator arms. Findings were similar in the sensitivity analysis including hydrocodone in the Schedule II opioids group. In the Poison Center Program, there were only 5 intentional abuse

mentions to TIRF products in the pre period, leaving little room for a decrease in the post period, and making this comparison under powered. Pre to post decreases were seen for 7 of the 24 outcome-rate combinations examined for TIRF products, yet only 1 was statistically significant (population rates among individuals entering opioid treatment programs). Lack of significance for the mean decreases may be due to lack of power driven by small event counts.

Table 36 Summary of RADARS Findings by Program, Outcome, and Denominator

Program	Outcome	Denominator	Drug group	Percentage change (95% CI) (b) (4)	Interaction p-value
Poison Center Program	Intentional abuse exposure	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
	Intentional misuse exposure	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
	Unintentional therapeutic error	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		

Program	Outcome	Denominator	Drug group	Percentage change	Interaction
			Schedule II Opioids Excluding Methadone	(b) (4)	
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
	Unintentional general exposure	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
	Emergency department visits/hospitalization exposure	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		

Program	Outcome	Denominator	Drug group	Percentage change (95% CI)	Interaction p-value
			Schedule II Opioids Excluding Methadone	(b) (4)	
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
	Major medical outcomes and death exposure	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
Treatment Center Programs Combined	Past month use to get high	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		

Program	Outcome	Denominator	Drug group	Percentage change (95% CI)	Interaction p-value
			Schedule II Opioids Excluding Methadone	(b) (4)	
College Survey Program	Past 3-month nonmedical use	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
Impaired Health Care Worker Program	Abuse	Population	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Prescriptions dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		
		Dosage units dispensed	TIRF Products		
			Schedule II IR Opioids		
			Schedule II Opioids		
			Schedule II Opioids Excluding Methadone		

8 PERIODIC SURVEYS OF STAKEHOLDERS

On 21 July 2016, FDA provided feedback on the patient, prescriber, and pharmacist surveys. After careful review of the requested changes, the TRIG notified FDA that in order to incorporate all changes, an extension for report submission would be required. As proposed by FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month KAB survey results will be submitted separately from the overall REMS assessment report on or before 17 February 2017.

In correspondence received from the FDA on 10 November 2016, the FDA acknowledged the agreement between the Agency and the TRIG that the survey results for the 60-Month FDA REMS Assessment Report will be submitted to the Agency on 17 February 2016.

9 FDA COMMUNICATIONS

REMS Modification 3 was approved by FDA on 24 December 2014. Since this last REMS modification, the TRIG has responded to FDA information requests and FDA feedback communications and has submitted Letters of Agreement as required for new sponsors to reference the Drug Master File (DMF).

Post-submission of the 48-Month FDA REMS Assessment Report and the Supplemental Report, the TRIG responded to information requests and FDA feedback communications. Per agreement with FDA a consolidated DMF submission will be made and will include all correspondence related to the 48-Month FDA REMS Assessment Report.

As proposed by FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month KAB survey results will be submitted separately from the overall REMS assessment report on or before 17 February 2017. Additional requests included in the 48-Month FDA Assessment Report Acknowledgement Letter will also be included in the 17 February 2017 submission as requested by FDA and detailed in Section 4.

10 POST-APPROVAL STUDIES AND CLINICAL TRIALS

FDA should refer to the most recent periodic safety report from each TIRF sponsor for updated information on post-approval studies and/or clinical trials.

11 DISCUSSION

The TIRF REMS Access program was approved on 28 December 2011 and successfully launched on 12 March 2012, approximately 11 weeks after approval. This 60-Month FDA REMS Assessment Report covers the timeframe between 29 October 2015 and 28 October 2016.

REMS enrollment continues to increase, with 1,446 new prescribers (Section 5.1.2), 1,537 new pharmacies (Section 5.1.3), and 1 new distributor (Section 5.1.4) enrolled in this reporting period. The number of prescribers and pharmacies enrolled as of the end of the reporting period has been relatively stable across the 48-month reporting period and the current reporting period. Conversely, newly enrolled patients have decreased by approximately 50% since the 48-Month

FDA REMS Assessment Report (from 8,740 newly enrolled patients in the 48-month reporting period to 4,255 during this current reporting period). This decrease may be attributed to the fact that the majority of patients with activity during the reporting period are continuing therapy and are not initiating therapy. Anecdotally, this decrease may be related to more prescribing restrictions in managed care setting as well as prescriber and patient awareness of the opioid epidemic making prescribers less likely to prescribe and patients less inclined to seek TIRF medicines.

During the reporting period, a total of 117,708 prescriptions were submitted for approval and 105,076 (89.3%) prescriptions encountered no REMS-related rejections prior to being authorized (Section 5.1.5). These data plus the ongoing stakeholder re-enrollment activity indicate that the program does not present a significant barrier to accessing these important medications while continuing to meet the safety goals of the REMS.

Prescription dispensing outside the established PPAF requirements was eliminated as a result of the corrective actions implemented during the previous reporting period to significantly reduce this occurrence (Section 5.1.6). In this 60-Month FDA REMS Assessment Report, there were no prescriptions for any patient dispensed beyond 10 days after patient enrollment compared with 1 prescription for 1 patient in the 48-Month FDA REMS Assessment Report, and 6 prescriptions for 1 patient in the 36-Month FDA REMS Assessment Report. The TIRF REMS Access program continues to monitor the electronic systems and stakeholder reports for issues and, where appropriate, corrective actions or system improvements are instituted.

During the current reporting period, 62 confirmed instances of stakeholder non-compliance with the TIRF REMS Access program were reviewed and investigated. This included 54 prescriber reports, 7 non-closed system pharmacy reports, and 1 wholesaler/distributer report (a total of 58 cases presented in Table 24 and 4 narratives included in Table 25). Of the cases presented by non-compliance scenario (Table 24), a decrease was seen in the number of confirmed instances of non-compliance between the 36-Month FDA REMS Assessment Report, the 48-Month FDA REMS Assessment Report, and this reporting period, respectively for inpatient pharmacy dispenses for outpatient use (1 vs. 0 vs. 0 reports), submission of a claim that did not go through REMS edits (14 vs. 12 vs. 7 reports), dispensing prescriptions outside of the closed system authorization process (7 vs. 0 vs. 0), and prescriber failure to have a complete PPAF on file in a timely manner (120 vs. 82 vs. 50 reports). There was one wholesaler/distributor report (filled an order for TIRF medicines for a non-enrolled stakeholder) and no closed system pharmacy reports during this reporting period (Section 6.2) compared with no reports for either during the last reporting period.

Audits of 6 closed system pharmacy entities were conducted during this reporting period. Four closed system entities were found to be non-compliant with the TIRF REMS Access program requirements. These pharmacies were re-educated, issued a notice through the NCRT and submitted a CAP which was approved by the NCRT. All cases have been closed (Section 6.3). The number of instances where a REMS authorization was not received prior to dispensing a TIRF product was static between the 48-Month FDA REMS Assessment Report and the current reporting period, and both showed a considerable decrease since the 36-Month FDA REMS Assessment Report (68 vs. 68 vs. 513 instances, respectively).

Audits of 5 inpatient pharmacies were conducted during this reporting period and 1 inpatient pharmacy was found to be noncompliant with a REMS requirement and a non-compliance case was opened.

Data collected through the RADARS System showed that population rates for the TIRF products across all outcome variables were low compared to rates for the 3 Schedule II opioid comparator arms; while prescription-adjusted rates for the TIRF products were higher than the rates for the 3 Schedule II opioid comparator arms. In the Poison Center Program, there were only 5 intentional abuse mentions to TIRF products in the pre period, leaving little room for a decrease in the post period, and making this comparison under powered. Pre to post decreases were seen for 7 of the 24 outcome-rate combinations examined, but only 1 reached statistical significance: population rates among individuals entering opioid treatment programs (Section 7.4).

The analysis of spontaneous reports of AEs of interest used aggregated data from the TRIG sponsors with currently marketed products. There were 353 unique case reports that met the specified criteria for addiction (n=6), overdose (n=4), death (n=344), and pediatric exposures (n=3). After a review of the associated MedWatch Forms or narratives for root cause analysis, no reports of inappropriate conversions between TIRF products were noted. There were 3 reports of pediatric exposure (Section 7.2). In all 3 reports, the medication was intentionally prescribed to the pediatric patient.

On 21 July 2016, FDA provided feedback on the patient, prescriber, and pharmacist surveys. After careful review of the requested changes, the TRIG notified FDA that in order to incorporate all changes, an extension for report submission would be required. As proposed by FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month KAB survey results will be submitted separately from the overall REMS assessment report on or before 17 February 2017. This submission will also include additional requests included in the 48-Month FDA Assessment Report Acknowledgement Letter.

CONCLUSION

Based on the data available in this TIRF REMS Access program assessment report (program and product utilization statistics, dispensing activity, program infrastructure and performance, non-compliance reporting, and safety surveillance data) the TRIG concludes that there is no indication that the REMS is not meeting its goals. However, the TRIG acknowledges that the data are limited and that FDA has requested further evaluation, as described in the 48-Month FDA Assessment Report Acknowledgement Letter, to determine whether the REMS is meeting its goals. The TRIG looks forward to discussing with FDA additional data to be used to evaluate and improve upon the REMS.

12 APPENDICES

12.1 Non-Compliance Protocol

TIRF REMS ACCESS PROGRAM NON-COMPLIANCE PROTOCOL

Version 7.0

October 26, 2015

Revision History

Version #	Date	Author	Description of Changes
1.0	February, 2012	Meagan Sampogna	Initial Release

2.0	October 10, 2012	Laura Baloun	• Added Revision History
			• Removed 'Draft-Review Required' Watermark
			• Added Sub-Sections to Section 5 (previously a separate document)
			  o Added 5.1 – Index of Scenarios
			  o Added 5.2 – Severity Reference
			  o Added 5.3 – Corrective Action Reference
			  o Added 5.4 – Monitoring Frequency Reference
			• Updated Scenario Numbering in Section 5.1
			• Revised Notices Measurement to clarify 2 Notices in 60 days = 1 Warning

3.0	November 2, 2012	Laura Baloun	• Revised Section 5.3, Reference – Corrective Actions to include review of multiple non-compliance events for a stakeholder to see if moving to the next level is warranted • Correct title of Section 5.4, Reference – Monitoring Frequency Guidelines

3.1	March 15, 2013	Laura Baloun	• Corrected misspellings throughout document
			• Revised Section 2 – Removed reference that process flow will be revised upon agreement of Protocol
			• Revised Section 2 - Non-Compliance Process Flow
			• Removed reference that Non-Compliance letters need to be developed from Section 4
			• Revised Section 5.1 – Non-Compliance Scenarios
			  o Revised the monitoring tool in Pharmacy Scenario 2 and Wholesaler/Distributor Scenario 1
			  o Revised Pharmacy Scenario 3

Version #	Date	Author	Description of Changes
			to be specific to suspended and deactivated stakeholders o Revised language in Pharmacy Scenarios 4, 5 & 6 for clarify o Added a new Pharmacy Scenario for altered claims o Revised Wholesaler/Distributor Scenario 1 to be specific to suspended and deactivated stakeholders o Revised language in Wholesaler/Distributor Scenario 2 for clarity o Revised Prescriber Scenario 1 to be specific to suspended and deactivated stakeholders o Revised language in Prescriber Scenario 2 for clarity o Re-defined 'timely manner' in Prescriber Scenario 2 o Revised language in Closed System Pharmacy Scenario 1for clarify o Added a Patient non-compliant scenario o Added an enrollment monitoring scenario for all stakeholders • Revised Section 5.4 – Reference – Monitoring Frequency Guidelines o Clarified new report requests will be handled via the Change Management Process o Changed 'Sponsor Data' to 'Sponsor Reporting' o Changed frequency of Sponsor Reporting from quarterly to every Non-Compliance Review Team Meeting and as needed o Changed frequency of Escalation Log from daily to every Quality Management Workstream meeting and as needed

Version #	Date	Author	Description of Changes
3.2	5/21/13	Laura Baloun	• Revised Section 5.1 – Non-Compliance Scenarios o Removed Pharmacy Scenario 4
4.0	5/24/13	Laura Baloun	Accepted all changes from versions 3.1 and 3.2
4.1	8/7/13	Laura Baloun	Added Section 6 – Non-Compliance Assessment Reporting
5.0	8/8/13	Laura Baloun	• Accepted all changes from version 4.1 • Corrected page numbers
5.0	8/15/13	Laura Baloun	• Approved by TRIG via vote during the 8/15/13 Program Status Call Meeting
5.1	12/17/13	Laura Baloun	• Revised Section 5.1 – Non-Compliance Scenarios o Revised Prescriber Scenario 2 definition for 'complete PPAF on file in a timely manner' • Revised Section 5.3 – Reference – Corrective Action o Change 'annually' to 'within 12 months'
6.0	12/19/13	Laura Baloun	• Accepted all changes from version 5.1
6.0	12/23/13	Laura Baloun	• Approved via TRIG e-mail vote
6.1	12/5/13	Amanda Bulkley	• Revised Section 5.1 – Non-Compliance Scenarios o Added Pharmacy Scenario 4: Pharmacy no longer has a valid DEA. o Added Prescriber Scenario 3: Prescriber no longer has a valid, schedule II DEA. o Added Prescriber Scenario 4: Prescribed TIRF medicines to an opioid non-tolerant individual. o Added Prescriber Scenario 5: Inappropriate conversions between TIRF products • Revised Section 5.2 – Severity Inclusion of language for repeat offenders when determined amount of time is reached without any suspected non-compliance

Version #	Date	Author	Description of Changes
			activity • Revised Section 5.3 – Corrective Action o Inclusion of language for repeat offenders when determined amount of time is reached without any suspected non-compliance activity o Grammatical corrections
7.0	10/26/15	Amanda Bulkley	• Accepted all changes from version 6.1

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1. Background

Opioids remain the mainstay of treatment of moderate to severe pain, especially for opioid-tolerant patients experiencing cancer breakthrough pain (BTP). Transmucosal immediate release fentanyl (TIRF) medicines are short-acting opioid products that have a rapid onset and relatively short duration of action and are designed for the treatment of episodes of BTP in opioid-tolerant patients with chronic cancer pain .

On December 28, 2011, the Food and Drug Administration (FDA) approved a single, shared Risk Evaluation and Mitigation Strategy (REMS) for TIRF products. The shared system strategy, called the TIRF REMS Access program, will be used by all sponsors of TIRF products and is designed to ensure access to important medications for appropriate patients.

The TIRF REMS Access program is in place to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

a. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

b. Preventing inappropriate conversion between fentanyl products.

c. Preventing accidental exposure to children and others for whom it was not prescribed.

d. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

Compliance with the TIRF REMS Access program ("program") is necessary in accordance with the appropriate use of TIRF products and proper patient selection. The TIRF REMS Access program includes a continuous evaluation process of compliance to the program. Any deviation from program procedures is evidence of non-compliance and may result in corrective measures, such as a notice, warning, suspension or program deactivation.

2. Goals and Objectives

The goal of the non-compliance protocol is to ensure that a system is in place to identify and investigate stakeholder non-compliance with the TIRF REMS Access program by monitoring possible program deviations detected through program reporting and spontaneous events identified by the program.

Suspected non-compliance is defined as an instance when it is believed that a stakeholder is not following a program requirement. Suspected non-compliance scenarios may be detected through standard program reports, spontaneous reports identified via the program's call center or vendor/sponsor reported events. A suspected non-compliant event is deemed compliant in the event the information presented on a stakeholder scenario does not clearly identify or support that a program deviation has occurred and/or no evidence of the program goals not being met are present.

A confirmed non-compliant event is when the information present clearly indicates that a program deviation has occurred and/or evidence of the program goals not being met through stakeholder actions is identified. Confirmation of a non-compliant stakeholder act will typically occur after further investigation has been completed and supportive data has been reviewed and presented to the TIRF REMS Access Non-Compliance Review Team.

The objectives of this non-compliance protocol are to:

- Describe the purpose and activities of the non-compliance Review Team
- Describe the purpose and activities of the non-compliance Working Group
- Describe the process to identify program non-compliance
- Outline an index of possible scenarios of non-compliance
- Identify data sources to review for suspected non-compliant events
- Describe suggested actions taken once non-compliance is confirmed
- Describe the process to monitor program deviations and occurrences of non-compliance

3. Non-Compliance Review Teams and Responsibility

A TIRF REMS Access Non-Compliance Review Team ("Review Team") will be created composed of membership from the TRIG Sponsors. The Review Team will be responsible for review, escalation, and decision-making of all non-compliance cases, and corrective measures are applied when necessary.

The responsibilities of the Review Team may not be delegated or transferred to other parties without prior consent of the TRIG sponsors. If the need arises, the Review Team shall have the authority to consult external advisors, experts, or consultants, in order to effectively assess and process cases of program non-compliance. If it is determined that a program modification may be warranted due to cases of non-compliance, the Review Team may need to consult with the

FDA for their review and approval of any changes impacting the REMS submission. Any proposed program modifications must be approved by the TRIG prior to implementation. The Review Team will meet regularly to discuss all issues of non-compliance and/or program modifications, at a frequency interval defined by the TRIG sponsors. The Review Team will consist of members with expertise from various specialties, which may include:

1. Regulatory Affairs
2. REMS specialist
3. Project Management
4. Legal
5. Quality Assurance
6. Commercial
7. Drug Safety and IT

Working practices will be developed to describe when the TRIG sponsors would participate in Review Team discussion in connection with potential or actual major deviations from the REMs program.

A Non-Compliance Working Group ("Working Group") will be created from program staff and will be responsible for collecting data and preparing reports for the Review Team, in compliance with Privacy Health Information (PHI) regulations. The Working Group will consist of program agents who have been working with and/or trained on the TRIG non-compliance protocol, as well as have background necessary to evaluate data and make objective decisions on instances of non-compliance, based on the data available.

The functions of the Working Group will be to:

1. Review reports, call center logs or audit report data to identify potential incidences of non-compliance
2. Conduct further investigation as needed to clarify the potential incident and identify root cause of deviation
3. Evaluate compliance with the TIRF REMS program stakeholder business rules
4. Respond to identified events of non-compliance in accordance with the established business rules. Propose solutions and actions for confirmed non-compliance events that are not addresses by such business rules.
5. Prepare reports for review and approval by the Review Team

Detailed business rules will outline the process, timeline and corrective action plan for each instance of suspected or confirmed program non-compliance identified by the Working Group.

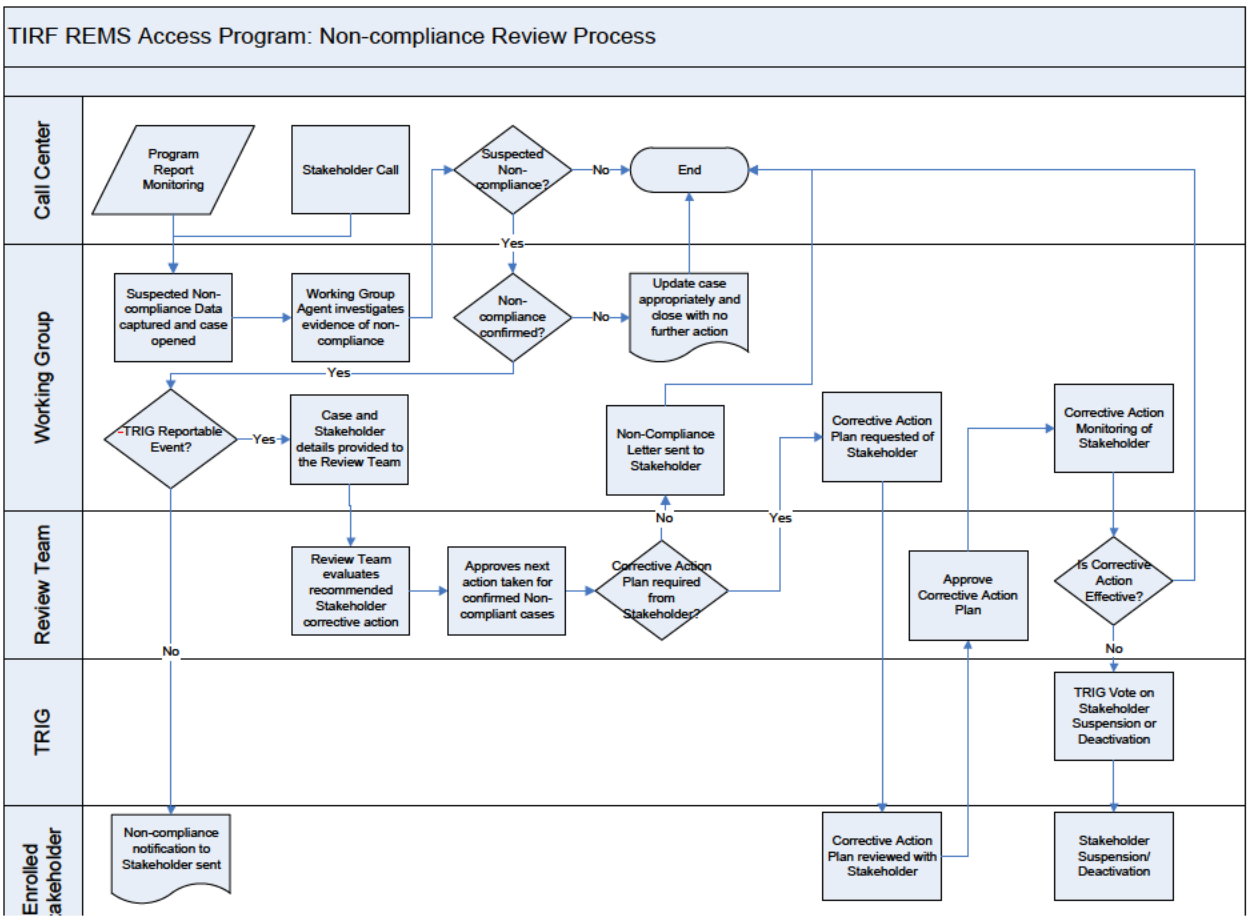
Stakeholders identified as having suspected or confirmed non-compliant events may be contacted by the Working Group via letters, phone calls or fax to resolve issues related to the identified program deviation all in accordance with such business rules.

The Working Group will provide the Review Team with reports in advance of their regularly scheduled meetings and will be available to address any questions or clarifications on the content of the report. The Working Group will provide a summary of the suspected or confirmed non-compliant events that they identified during the review period.

Once the Review Team receives the report, their responsibility will be to:

- Attend all regularly scheduled Review Team meetings to review, assess and make decisions on any non-compliance issues needing attention including any issue that the Working Group could not handle because it was beyond the scope of the business rules used by the Working Group.
- Identify if an audit of a stakeholder is required
- Determine if any report or communication should be made to the FDA outside of regular TIRF REMS assessment reports.
- Determine if changes to the business rules and/or this protocol need to be made, and make such changes.

The following process flow outlines the suggested interactions between the Working Group, the Review Team and the program stakeholders as necessary monitor, review and act upon suggested corrective actions for non-compliant scenarios identified.



Identification and Investigation Process of Non-Compliant Events

Identification Process

Call center staff in the TIRF REMS Program or TRIG sponsor companies will refer cases of potential non-compliance to the Working Group.

Investigation Process

If an instance of potential non-compliance is identified, further investigation will be conducted. This may include:

- Review case details to determine if evidence of non-compliance exists
- Make attempt(s) to contact relevant stakeholder to validate data/information and solicit further information
- Conduct further investigation of TIRF REMS Program databases

For instances of potential non-compliance that are not described in Section 5, a suggested course of action will be presented to the Review Team. The Working Group will consult with the Review Team if proprietary or commercially sensitive information arises that would not ordinarily be shared among TRIG representatives.

4. Corrective Actions for Instances of Non-Compliance

Corrective actions resulting from non-compliance will be determined according to the severity of the action. The stakeholders in this non-compliance protocol include prescribers, patients, distributors, and pharmacies. The primary elements for corrective action include; notices, warnings, suspension, and deactivation based on the requirements of the TIRF REMS Access program. If a prescriber, pharmacy or distributor is suspended or deactivated, information will be made available through the program to assist unaffected stakeholders in finding alternative access to product.

Each non-compliant event will be categorized based on the level of severity of the event. The event classifications are as follows:

Minor

An unintended (e.g., first-time) event. The corrective action will typically result in a written notice being sent to the stakeholder and re-education of the program requirements to prevent any re-occurrences of the event.

Moderate

A repeated event or a series of different [or distinct], unintended events. An investigation will be conducted by program staff to identify the root cause of the event. Program staff will also work with the stakeholder to create and implement a corrective plan of action. Once implemented, the stakeholder will be monitored for compliance with the plan of action, and provided with a written warning for their files.

Serious

An event that results in serious or significant injury or potential risk to a patient irrespective of the number of previous non-compliance occurrences, or continued non-compliant events after retraining has occurred. This level of offense will result in a suspension from the program and possible deactivation. Deactivated prescribers will not be able to participate in the TIRF REMS Access program for any existing or future patients, effectively barring their ability to provide TIRF medicines as a therapy for their patients. A deactivated stakeholder may request reinstatement in the TIRF REMS Access program.

Requests for reinstatement must be in writing and contain sufficient details of corrective actions taken to prevent any future incidents of non-compliance with elements of the program. Requests for reinstatement will be evaluated by the Review Team and the team will make the final determination on reinstatement.

Detailed business rules will outline the process, timeline and corrective action plan for each level of program non-compliance.

The Review Groups will determine whether a suspended pharmacy or distributor will be permitted to keep an inventory of TIRF medicines already acquired prior to suspension. Pharmacies may not dispense TIRF medicines from such existing inventory during the suspension and distributors may not sell and/or distribute TIRF medicines. If a suspended outpatient pharmacy or distributor is part of a larger entity, the parent entity will be notified of the noncompliant activity and resultant suspension.

Deactivated pharmacies and distributors will be required to return all existing TIRF medicine inventory. Patient notices that result from violations of program elements will be sent to a patient's prescriber.

5. Evaluation Process

5.1. Index of Non-Compliance Scenarios

Stakeholder	Scenario		Monitoring
	#	Non-Compliance Activity	Tool
Pharmacy	1	Submission of a claim that did not go through the REMS edits. A TIRF medicine was dispensed without verifying through the TIRF pharmacy management system that the prescriber is enrolled and active, and that the patient is enrolled or has not been inactivated in the program.	Audit or Spontaneous event reported
	2	Dispensing activity for enrolled outpatient pharmacies during reporting period not matching distributor shipment data for that pharmacy.	Audit or Sponsor reported
	3	Pharmacy is dispensing TIRF medicine while suspended or deactivated from the TIRF REMS Access program.	Audit or Spontaneous event reported
	4	Pharmacy no longer has a valid DEA	Audit or Spontaneous event reported
	5	Authorized Inpatient Pharmacy does not comply with the requirements of the TIRF REMS Access program.	Audit or Spontaneous event reported
	6	Inpatient Pharmacy dispenses for outpatient use	Audit or Spontaneous event reported
	7	Submission of inappropriately altered claim to meet TIRF REMS system requirements (e.g. changing prescriber)	Audit or Spontaneous event reported
Wholesaler/ Distributor	1	Wholesaler/Distributor is suspended or deactivated from the TIRF REMS Access program and is purchasing or distributing TIRF medicines.	Sponsor reported
	2	Wholesaler/Distributor fills an order for TIRF medicines for a non enrolled stakeholder.	Audit or Spontaneous event reported
Prescriber	1	Prescriber is prescribing TIRF medicines while suspended or deactivated from the TIRF REMS Access program.	Audit or Spontaneous event reported
	2	Prescriber failure to have a complete PPAF on file in a timely manner (5 or more patients enrolled by the prescriber without a complete PPAF on file, with each patient having greater than 10 working days lapse from intial enrollment date).	Program Report
	3	Prescriber no longer has a valid, schedule II DEA.	Audit or Spontaneous event reported
	4	Prescribed TIRF medicines to an opioid non-tolerant individual.	Audit or Spontaneous event reported
	5	Inappropriate conversions between TIRF products.	Audit or Spontaneous event reported

Closed System Pharmacy	1	Dispensing prescriptions outside of the closed system authorization process.	Program Report
Patient	1	The Patient receives prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame that is suggestive of misuse, abuse, or addiction	Audit or Spontaneous event reported
All Stakeholders	1	ENROLLMENT MONITORING ONLY: Monitor stakeholders who are not enrolled in TIRF and are associated with non-compliance cases.	Program Reports

5.2. Reference – Severity

Severity Guideline	
Level of Severity	**Definition**
Minor	First identification of a non-compliant event or since 24 months from the closure of a previous case.
Moderate	>1 non-compliance issue, without a warning on file
Serious	>1 non-compliance issue with a warning on file or an event that results in serious or significant injury or potential risk to a patient irrespective of the number of previous non-compliance occurrences

5.3. Reference – Corrective Action

Corrective Action Guideline	
Action	**Measure**
Notices	Patient notices will be sent to a patient's prescriber
	Minor violations that demonstrate a misunderstanding of the program requirements
	Notices are intended to re-educate stakeholders
	2 Notices in 60 days = Review by Non-Compliance Review Team to determine if a Warning is warranted
Warnings	Previous case resulted in a notice due to unsuccessful outreach attempts and unable to successfully outreach for current case.
	2 Warnings in 60 days = Review by Non-Compliance Review Team to determine if a Suspension is warranted
	>1 Warning and/or suspension in >60 days = Case-by-Case review for Suspension
Suspension	Temporary deactivation from the program
	A suspended pharmacy or distributor may keep existing TIRF inventory but may not purchase or acquire additional TIRF medicines
	Pharmacies may not dispense TIRF medicines from existing inventory and distributors may not sell/distribute TIRF medicines during suspension
	If the pharmacy or distributor is part of a larger entity that entity will be notified of the suspension
	1 Warning or 2 Notices while Suspended = Review by Non-Compliance Review Team to determine if a Deactivation is warranted
	2 Suspensions within 12 months = Review by Non-Compliance Review Team to determine if a Deactivation is warranted
Deactivation	Deactivations may result in multiple failures to comply with the program elements and/or non-compliance where there is no feasible corrective action
	Bars stakeholder to provide TIRF medicines as a therapy for their patients
	Pharmacies and distributors must return all existing TIRF medicine
	Patient deactivation will be sent to a patient's prescriber. Patients may only be reinstated into the program by a request from their prescriber

5.4. Reference – Monitoring Frequency Guidelines

Monitoring Frequency Guideline	
Report Category	**Frequency**
Existing Reports	Bi-Monthly
Report Does Not Exist	Cost/Timeline TBD - Report request will be handled via the Change Management Process
Sponsor Reported	During every Non-Compliance Review Team Meeting and as needed
KAB Surveys	12 and 24 months from the date of the REMS approval and as needed thereafter
Escalation Log	During every Quality Management Workstream meeting and as needed

6. Non-Compliance Assessment Reporting

Confirmed non-compliance events will be provided to the Companies' 3rd party vendor for inclusion in FDA assessment reports.

12.2 Safety Surveillance Aggregate Line Listing Preferred Terms

I. Case Criteria:

- Only US cases
- No American Association of Poison Control Center (AAPCC) or literature search cases
- In addition to performing searches on the below preferred terms, sponsors will search for:
  - All cases with an outcome of death
  - Cases related to patients aged 0 through 18
- Cases to be included in the reporting period date range will be based on MedWatch Form field "Date Received by Manufacturer" (G4)
- The data cut-off for the safety surveillance aggregate line listing is 28AUG of each year. Therefore, the current reporting period for the 60-Month FDA Assessment Report is 29AUG2015 to 28AUG2016

II. Case Identification

a. Addiction Line Listing

Cases of addiction will be identified through the following Preferred Terms. Sponsors are responsible for reviewing all cases pulled by these Preferred Terms and determining whether each is deemed as a case of addiction by their company. Only cases identified by a Sponsor's company as cases of addiction should be provided to UBC.

Preferred Terms for FDA Requested Cases of Addiction				
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**	**Notes**
Misuse				
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Intentional drug misuse	*Selected because it falls under the substance-related disorders*
Abuse				
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug abuse	
Inappropriate				
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Drug administered at inappropriate site	

Preferred Terms for FDA Requested Cases of Addiction				
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**	**Notes**
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Inappropriate schedule of drug administration	
Medication Error				
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect dose administered	
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Incorrect dosage administered	
Injury, poisoning and procedural complications	Medication errors	Maladministrations	Inappropriate schedule of drug administration	
Accidental				
Injury, poisoning and procedural complications	Medication errors	Accidental exposures to product	Accidental exposure to product	
Dependence				
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Dependence	
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence	
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence, antepartum	
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Drug dependence, postpartum	
Psychiatric disorders	Psychiatric disorders NEC	Substance-related disorders	Polysubstance dependence	

b. Overdose Line Listing

Cases of overdose will be identified through the following Preferred Terms.

Preferred Terms for FDA Requested Cases of Overdose				
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**	**Notes**
Overdose				
Injury, poisoning and procedural complications	Medication errors	Overdoses	Accidental overdose	*Also in the Accidental Section*
Injury, poisoning and procedural complications	Medication errors	Overdoses	Intentional overdose	
Injury, poisoning and procedural complications	Medication errors	Overdoses	Overdose	
Injury, poisoning and procedural complications	Medication errors	Overdoses	Prescribed overdose	
Injury, poisoning and procedural complications	Chemical injury and poisoning	Poisoning and toxicity	Accidental poisoning	

c. Death Line Listing

Cases of death will be identified through the following Preferred Terms or a reported outcome of death.

Preferred Terms for FDA Requested Cases of Death				
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**	**Notes**
Death				
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Accidental death	
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Brain death	
General Disorders and administration site conditions	Fatal outcomes	Death and sudden death	Cardiac death	
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Death	
General disorders and administrations site conditions	Fatal outcomes	Death and sudden death	Death neonatal	
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Sudden cardiac death	
General Disorders and administration site conditions	Fatal outcomes	Death and sudden death	Sudden death	
General disorders and administration site conditions	Fatal outcomes	Death and sudden death	Agonal death struggle	
General disorders and administration site conditions	General system disorders NEC	General signs and symptoms NEC	Apparent death	
General disorders and administration site conditions	Therapeutic and nontherapeutic effects (excl toxicity)	Therapeutic and nontherapeutic responses	Drug ineffective/death	
Cardiac disorders	Cardiac arrhythmias	Ventricular arrhythmias and cardiac arrest	Cardio-respiratory arrest	

Preferred Terms for FDA Requested Cases of Death				
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**	**Notes**
Cardiac disorders	Cardiac arrhythmias	Ventricular arrhythmias and cardiac arrest	Cardiac arrest	
Respiratory, thoracic and mediastinal disorders	Respiratory disorders NEC	Breathing abnormalities	Respiratory arrest	
Pregnancy, puerperium and perinatal conditions	Abortions and stillbirth	Stillbirth and foetal death	Foetal death	

d. Pediatric Exposure Line Listing

Cases of pediatric exposure will be identified through the following Preferred Terms or any case involving patients 0-18 years of age.

Preferred Terms for FDA Requested Cases of Pediatric Exposure				
Primary SOC	**High Level Group**	**High Level Term**	**Preferred Term**	**Notes**
Accidental				
Injury, poisoning and procedural complications	Medication errors	Accidental exposures to product	Accidental exposure to product by child	
Injury, poisoning and procedural complications	Product use issues	Product use issues NEC	Drug administered to patient of inappropriate age	
General disorders and administration site conditions	Product quality issues	Product packaging issue	Failure of child resistant mechanism for pharmaceutical product	

e. Case Identification for Any Table Through Text-string Searches

In addition to the agreed upon Preferred Terms, Sponsors will also provide cases based on text-string searches using the below terms. Sponsors will inform UBC if cases are provided that are not aligned with the approved Preferred Terms, but were identified through a text-string search.

Text-string Search Terms for Narratives			
Addiction	Multiple drug overdose	Son	Nephew
Overdose	Expired	Daughter	Aunt
Drug dependence	Passed away	Grandmother	Uncle
Death	Infant	Grandfather	Mom
Pediatric exposure	Child	Sister	Pop
Died	Mother	Brother	Dad
Fatal	Father	Niece	Inappropriate Conversion
Inappropriate	Accidental	Intentional	Non-opioid Tolerant

12.3 Safety Surveillance Aggregate Line Listing of Deaths

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1911	53	Male	Unknown	31AUG2015	Death	Breakthrough cancer pain	Unknown	Oxycontin, Sulfamethoxazole, Oxycodone, Valaciclovir, Oxycontin	None reported	Death	Insufficient Information
1912	61	Female	30AUG2015	31AUG2015	Neoplasm progression	Breakthrough cancer pain	2015-08-29 - UNK	None reported	None reported	Death	Not Related
1913	UNK	Male	DEC2013	31AUG2015	Death	Unknown	2015-08-29 - UNK	None reported	None reported	Death	Insufficient Information
1914	UNK	Male	Unknown	31AUG2015	NEOPLASM MALIGNANT DEATH	Unknown	Unknown	None reported	None reported	Death	Not Related
1915	UNK	Male	Unknown	01SEP2015	Lung neoplasm malignant	Unknown	Unknown	None reported	None reported	Death	Not Related
1916	51	Female	Unknown	02SEP2015	Death	Breakthrough cancer pain	Unknown	Megace, Lovenox, Sudafed, Mucinex, Lidocaine Viscous, Ventolin Hfa, Robaxin, Protonix, Omeprazole, Metoclopramide, Promethazine, Percocet, Effexor, Nasonex, Duragesic, Vesicare, Gabapentin, Lidoderm, Soma, Clonazepam	None reported	Death	Not Related
1917	UNK	Female	Unknown	02SEP2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1918	76	Male	Unknown	11SEP2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1919	77	Male	JUL2015, 23AUG2015	11SEP2015	Drug effect decreased, Cardiac failure congestive	Breakthrough pain, radiation associated pain, cardiac failure congestive, atrial fibrillation, product used for unknown indication	Unknown	Lasix, Multaq, Nitro Paste	Fentanyl Transdermal System	Death	Not Related
1920	82	Unknown	Unknown	14SEP2015	Death	Breakthrough cancer pain	Unknown	Fentanyl Patch	None reported	Death	Not Related
1921	UNK	Female	Unknown	14SEP2015	Death, Hospitalisation	Breakthrough cancer pain	Unknown	Fentanyl	None reported	Death	Insufficient Information
1922	55	Unknown	Unknown	14SEP2015	Death	Breakthrough cancer pain	Unknown	MS Contin	None reported	Death	Insufficient Information
1923	35	Female	Unknown	14SEP2015	Death	Breakthrough cancer pain	Unknown	MS Contin	None reported	Death	Insufficient Information
1924	UNK	Female	Unknown	14SEP2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1925	62	Female	05DEC2013	15SEP2015	Neoplasm progression	Breakthrough cancer pain, abdominal pain	2016-02-03 - UNK	Aloxi, Ambien, Dilaudid, Fentanyl, Lasix, Megace, Ondansetron, Prevacid, Prochlorperazine	None reported	Death	Insufficient Information
1926	UNK	Female	Unknown	16SEP2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1927	UNK	Female	Unknown	17SEP2015	Neoplasm progression	Breakthrough cancer pain, pain	2015-09-11 - UNK	Dilaudid, Fentanyl Patch	None reported	Death	Not Related
1928	UNK	Female	Unknown	18SEP2015	Death	Unknown	2016-02-03 - UNK	None reported	None reported	Death	Insufficient Information
1929	UNK	Male	Unknown	18SEP2015	Death	Unknown	2016-02-03 - UNK	None reported	None reported	Death	Insufficient Information
1930	UNK	Male	Unknown	18SEP2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1931	UNK	Male	Unknown	21SEP2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1932	50	Male	26FEB2014, Unknown, Unknown	21SEP2015	Neoplasm progression, Gastrointestinal haemorrhage, Jaundice cholestatic	Breakthrough cancer pain	2016-02-03 - UNK	Ciprofloxacin, Dilaudid, Fentanyl Injection, Flagyl, Lasix, Propofol	None reported	Death	Not Related
1933	63	Male	26OCT2014	21SEP2015	Neoplasm progression	Breakthrough cancer pain	2016-06-28 - UNK	None reported	None reported	Death	Not Related
1935	64	Female	05DEC2013	25SEP2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1936	65	Male	20SEP2015	28SEP2015	Neoplasm progression	Breakthrough cancer pain	2016-06-28 - UNK	Oxycodone	None reported	Death	Not Related
1937	47	Female	24FEB2014	05OCT2015	Death	Unknown	2015-05 - UNK	None reported	None reported	Death	Insufficient Information
1938	UNK	Male	Unknown	07OCT2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1940	UNK	Female	2014	12OCT2015	Death	Unknown	2015-12-01 - UNK	None reported	None reported	Death	Insufficient Information
1941	UNK	Female	Unknown	16OCT2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1942	83	Female	06JUN2015, 2015	19OCT2015	Death, Off label use	Pain	2015 - UNK	Hydrocodone, Morphine, Oxycodone	None reported	Death	Insufficient Information
1943	UNK	Unknown	NOV2013, 24FEB2014, Unknown, Unknown, Unknown	22OCT2015	Feeling abnormal, Disease progression, Confusional state, Mass, Weight decreased	Breakthrough pain	Unknown	Dilaudid, Folic Acid, Calcium, Lyrica, Dulcolax, Lovenox, Phenergan, Refmal329, Zofran	None reported	Death	Not Related
1944	46	Male	29DEC2013	22OCT2015	Disease progression	Breakthrough pain	Unknown	Fentanyl, Oxycodone and Acetaminophen	None reported	Death	Not Related
1945	73	Female	03FEB2015, 02FEB2015, Unknown	23OCT2015	Death, Haemoptysis, Upper respiratory tract infection	Skin cancer, chronic pain	2013-10 - UNK	Klonopin, Oxycodone, Oxycontin, Prozac, Topamax	None reported	Death	Not Related
1946	UNK	Female	2012	27OCT2015	Death	Unknown	2013-10 - UNK	None reported	None reported	Death	Insufficient Information

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1947	UNK	Female	Unknown	27OCT2015	Death	Unknown	2013-10 - UNK	None reported	None reported	Death	Insufficient Information
1948	UNK	Female	Unknown	27OCT2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1949	UNK	Unknown	31MAR2014	27OCT2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1950	75	Male	19OCT2015, Unknown	28OCT2015	Fall, Neutropenia	Breakthrough pain, pain	11 days	Dilaudid, 5-Fluorouracil, Allegra, Cis-Platinum, Dexamethasone, Fentanyl, Taxotere	None reported	Death	Not Related
1951	UNK	Unknown	Unknown	02NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1952	50	Male	27SEP2015	04NOV2015	Neoplasm progression	Breakthrough cancer pain	2015-05-20 - 2015-09-27	None reported	None reported	Death	Not Related
1953	UNK	Female	Unknown	04NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1954	UNK	Unknown	Unknown	05NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1955	UNK	Female	Unknown	05NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1956	UNK	Male	Unknown	10NOV2015	Death	Unknown	2015-04-20 - UNK	None reported	None reported	Death	Insufficient Information
1957	72	Female	Unknown	10NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1958	UNK	Male	Unknown	11NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1959	UNK	Male	2015	11NOV2015	Neoplasm progression	Cancer pain	2015-07-13 - UNK	Methadone	None reported	Death	Not Related
1960	UNK	Male	Unknown	12NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1961	UNK	Female	Unknown	12NOV2015	DEATH	Unknown	Unknown	None reported	None reported	Death	Insufficient Information

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1962	UNK	Female	Unknown	16NOV2015	Neoplasm progression	Breakthrough cancer pain	2014-12-22 - UNK	None reported	None reported	Death	Not Related
1963	UNK	Female	Unknown	16NOV2015	Neoplasm progression	Breakthrough cancer pain	2014-12-09 - UNK	None reported	None reported	Death	Not Related
1964	UNK	Male	Unknown	16NOV2015	Neoplasm progression	Breakthrough cancer pain	2015-06-17 - UNK	None reported	None reported	Death	Not Related
1965	UNK	Male	Unknown	16NOV2015	Neoplasm progression	Breakthrough cancer pain	2014-12-10 - UNK	None reported	None reported	Death	Not Related
1966	UNK	Male	Unknown	16NOV2015	Neoplasm progression	Breakthrough cancer pain	2014-12-12 - UNK	None reported	None reported	Death	Not Related
1967	UNK	Male	Unknown	16NOV2015	Neoplasm progression	Breakthrough cancer pain	2014-12-09 - UNK	None reported	None reported	Death	Not Related
1968	UNK	Male	Unknown	16NOV2015	Neoplasm progression	Breakthrough cancer pain	2013-12 - UNK	Methadone	None reported	Death	Not Related
1969	UNK	Female	Unknown	16NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1970	65	Female	05JUN2014	16NOV2015	DEATH	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1971	UNK	Male	Unknown	17NOV2015	Metastases to lymph nodes, Neoplasm progression	Breakthrough pain	2015-05-05 - UNK	Albuterol Sulphate, Fenofibrate, Folic Acid, Gabapentin, Ibuprofen, Lofexidine, Ondansetron, Pantoprazole, Percocet, Temazepam, Tizanidine	None reported	Death	Insufficient Information
1972	UNK	Male	Unknown	17NOV2015	DEATH	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1973	UNK	Female	Unknown	17NOV2015	DEATH	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1974	UNK	Unknown	26JAN2015	17NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Not Related
1975	86	Male	Unknown	18NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information

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UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1976	68	Female	Unknown	18NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1977	UNK	Female	Unknown	19NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1978	UNK	Male	Unknown	19NOV2015	Death	Ureteral cancer, renal cancer	Unknown	None reported	None reported	Death	Not Related
1979	UNK	Unknown	Unknown	23NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1980	55	Male	23NOV2015, 15NOV2015	23NOV2015	Death, Hospitalisation	Breakthrough cancer pain	2015-10-30 - 2015-11-23	None reported	None reported	Death	Not Related
1981	UNK	Unknown	Unknown	23NOV2015	Death	Breakthrough cancer pain	2015-11-04 - UNK	None reported	None reported	Death	Not Related
1982	69	Female	Unknown	24NOV2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1983	UNK	Female	Unknown	24NOV2015	Death	Unknown	2015-04-21 - UNK	None reported	None reported	Death	Insufficient Information
1984	65	Male	17NOV2015	25NOV2015	Death	Breakthrough cancer pain	2015-11-05 - 2015-11-17	None reported	None reported	Death	Not Related
1985	UNK	Male	Unknown	03DEC2015	Neoplasm progression	Breakthrough cancer pain	2015-05-18 - UNK	None reported	None reported	Death	Not Related
1986	67	Male	26NOV2015	03DEC2015	Neoplasm progression	Breakthrough cancer pain	2015-03-18 - UNK	None reported	None reported	Death	Not Related
1987	UNK	Male	Unknown	03DEC2015	Death	Breakthrough cancer pain	2015-03-18 - UNK	Fentanyl Patch, Marinol, Methadone	None reported	Death	Insufficient Information

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UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1988[b]	31	Male	10APR2014, 10APR2014, 10APR2014, 28DEC2011, 28DEC2011, 28DEC2011, 28DEC2011, 28DEC2011, 01JAN2011, 23JAN2008, 23JAN2008, 23JAN2008, 01JAN2008, 01JAN2008, 01JAN2008, 01JAN2008, 01JAN2008, 08AUG2007, 02JUN2007, 02JUN2007, 01JAN2007, 01JAN2007, 01JAN2006, Unknown, Unknown, Unknown	07DEC2015	Accidental overdose, Lethargy, Stupor, Anhedonia, Decreased appetite, Feeling abnormal, Insomnia, Suicidal ideation, Tooth abscess, Headache, Nausea, Vomiting, Anxiety, Depression, Neck pain, Skin abrasion, Stress, Migraine, Tooth impacted, Toothache, Fall, Ligament sprain, Drug dependence, Major depression, Product use issue, Toxicity to various agents	Headaches	2 Years	Elavil, Clonidine, Benadryl, Naproxen, Prochlorperazine, Nexium, Prilosec, Klonopin, Pantoprazole	Percocet, Lorazepam, Oxycodone, Xanax, Endocet	Death	Possibly Related
1989	UNK	Male	Unknown	08DEC2015	Neoplasm progression	Breakthrough cancer pain	2015-03-18 - UNK	None reported	None reported	Death	Not Related
1990	57	Unknown	26JAN2014	08DEC2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1991	60	Female	30MAR2016, 05NOV2015, 05NOV2015	09DEC2015	Completed suicide, Fatigue, Somnolence	Breakthrough cancer pain, leukemia	2015-11-05 - UNK	Dilaudid, Geodon, Glivec, Hydromorphone	None reported	Death	Not Related
1992	UNK	Female	Unknown	09DEC2015	DEATH	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1993	46	Female	07AUG2014	10DEC2015	Death	Breakthrough cancer pain	2013-12-04 - UNK	None reported	None reported	Death	Insufficient Information

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UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1994	UNK	Male	Unknown	17DEC2015	Neoplasm progression	Breakthrough cancer pain	2015-06-18 - UNK	Oxycodone, Oxycontin, Xarelto	None reported	Death	Not Related
1995	62	Male	15DEC2015	17DEC2015	Neoplasm progression	Breakthrough cancer pain	2015-08-25 - 2015-12-15	None reported	None reported	Death	Not Related
1996	59	Male	Unknown	21DEC2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1997	UNK	Female	Unknown	21DEC2015	Death	Unknown	2015-06-18 - UNK	None reported	None reported	Death	Insufficient Information
1998	UNK	Female	Unknown	22DEC2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
1999	UNK	Female	Unknown	22DEC2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2000	UNK	Female	Unknown	22DEC2015	Death	Unknown	2015-06-18 - UNK	None reported	None reported	Death	Insufficient Information
2001	48	Female	26OCT2014	22DEC2015	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2002	58	Male	23DEC2014	23DEC2015	Death	Unknown	2015-06-18 - UNK	None reported	None reported	Death	Insufficient Information
2003	UNK	Female	Unknown	23DEC2015	Death	Unknown	2015-08-25 - UNK	None reported	None reported	Death	Insufficient Information
2004	UNK	Male	Unknown	28DEC2015	Death	Unknown	2015-08-25 - UNK	None reported	None reported	Death	Insufficient Information
2005	81	Female	Unknown	29DEC2015	Death, Product use issue	Used prior to dressing changes to aid in pain relief	Unknown	Morphine	None reported	Death	Insufficient Information
2006	UNK	Male	OCT2015	29DEC2015	Neoplasm progression	Breakthrough cancer pain	2015-05 - UNK	Metoprolol	None reported	Death	Not Related
2007	32	Female	23NOV2015, Unknown	31DEC2015	Death, Headache	Pain	2015-10-22 - UNK	Ativan, Decadron, Fentanyl Patch, Oxycodone, Prilosec	None reported	Death	Not Related
2008	UNK	Male	Unknown	04JAN2016	Death	Unknown	2015-10-22 - UNK	None reported	None reported	Death	Insufficient Information

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UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2009	UNK	Male	Unknown	04JAN2016	Death	Unknown	2015-10-22 - UNK	None reported	None reported	Death	Insufficient Information
2010	UNK	Female	Unknown	04JAN2016	Death	Unknown	2015-10-22 - UNK	None reported	None reported	Death	Insufficient Information
2011	UNK	Male	Unknown	05JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2012	53	Male	07MAR2014, 07MAR2014	06JAN2016	Disease progression, Metabolic acidosis	Breakthrough cancer pain	2014-01-12 - UNK	Ativan, Fentanyl, Marinol	None reported	Death	Not Related
2013	UNK	Male	Unknown	07JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2014	46	Female	07JAN2016	07JAN2016	Death	Urinary bladder carcinoma	2014-04-28 - UNK	Elavil, Keppra, Msir, Oxycontin, Wellbutrin, Clonazepam	None reported	Death	Not Related
2015	68	Male	09JAN2016	11JAN2016	Cardiac arrest	Breakthrough cancer pain	2015-12 - 2016-01-08	None reported	None reported	Death	Not Related
2016	62	Male	17DEC2015, 17DEC2015, 17DEC2015, Unknown, Unknown	11JAN2016	Drug ineffective, Dysstasia, Fall, Cerebrovascular accident, Tumour rupture	Breakthrough cancer pain	2013-12-04 - UNK	Cipro	None reported	Death	Possibly Related
2017	UNK	Unknown	23MAR2014	11JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Not Related
2018	UNK	Female	Unknown	12JAN2016	DIABETES MELLITUS SYSTEMIC LUPUS ERYTHEMATOSUS PAIN DEATH	Unknown	Unknown	None reported	None reported	Death	Not Related
2019	UNK	Male	Unknown	13JAN2016	Death	Breakthrough cancer pain	2015-09-22 - 2016-01-05	None reported	None reported	Death	Insufficient Information
2020	58	Male	12JAN2016	13JAN2016	Neoplasm progression	Breakthrough cancer pain, lung cancer, metastases to brain	2015-12-14 - UNK	None reported	None reported	Death	Not Related
2021	UNK	Unknown	Unknown	13JAN2016	Neoplasm progression	Breakthrough cancer pain	2015-11-30 - 2016-01-13	None reported	None reported	Death	Not Related

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UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2022	68	Female	04JUN2015, Unknown	14JAN2016	Dizziness, Death	Unknown	Unknown	Ambien, Zanaflex, Valium, Morphine Pump	None reported	Death	Not Related
2023	61	Female	Unknown	14JAN2016	Death, Drug ineffective	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2024	76	Female	19FEB2013, 19FEB2013, 19FEB2013, Unknown	14JAN2016	Nervousness, Pruritus, Psychomotor hyperactivity, Death	Unknown	Unknown	Fentanyl, Effexor	None reported	Death	Insufficient Information
2025	UNK	Unknown	Unknown	15JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2026	74	Female	25AUG2014	15JAN2016	Death	Lung disease	2015-11-30 - UNK	Fentanyl	None reported	Death	Not Related
2027	UNK	Male	Unknown	15JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2028	UNK	Male	Unknown	18JAN2016	Death	Breakthrough cancer pain	2015-12-18 - UNK	None reported	None reported	Death	Insufficient Information
2029	UNK	Female	Unknown	19JAN2016	Death	Unknown	2015-12-03 - UNK	None reported	None reported	Death	Insufficient Information
2030	62	Female	09JUL2014	19JAN2016	Death	Breakthrough cancer pain	2014-06-10 - UNK	None reported	None reported	Death	Insufficient Information
2031	60	Female	22FEB2014	19JAN2016	Death	Breakthrough cancer pain	2014-01-15 - UNK	None reported	None reported	Death	Not Related
2032	61	Female	20OCT2015	21JAN2016	Neoplasm progression	Breakthrough pain	2015-09-08 - UNK	Fentanyl Patch	None reported	Death	Not Related
2033	71	Female	Unknown	22JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2034	58	Male	Unknown	25JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2035	49	Female	Unknown	25JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2036	27	Male	Unknown	25JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2037	52	Male	Unknown	25JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information

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UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2038	UNK	Male	Unknown	25JAN2016	Neoplasm malignant	Cancer pain	Unknown	None reported	None reported	Death	Not Related
2039	UNK	Male	Unknown	26JAN2016	Death, Off label use	Chronic pain	2015-12-01 - 2016-01-25	None reported	None reported	Death	Insufficient Information
2040	53	Female	Unknown	28JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2041	66	Female	30APR2014	28JAN2016	Neoplasm progression	Breakthrough cancer pain	2014-03-01 - UNK	Fentanyl Patch, Lovenox, Metformin, Naturethroid	None reported	Death	Not Related
2042	UNK	Female	Unknown	29JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2043	UNK	Male	Unknown	29JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2044	UNK	Male	Unknown	29JAN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2045	UNK	Male	Unknown	29JAN2016	Neoplasm progression	Bladder cancer	2014-07-30 - 2014-11-15	Oxycontin	None reported	Death	Not Related
2047	67	Male	DEC2014	03FEB2016	PULMONARY EMBOLISM CARDIAC DISORDER	Unknown	Unknown	None reported	None reported	Death	Not Related
2049	82	Male	15JAN2016, 10JAN2016	04FEB2016	Cardiac failure, Vomiting	Breakthrough cancer pain	2015-12 - UNK	None reported	None reported	Death	Possibly Related
2050	UNK	Male	Unknown	04FEB2016	Death	Unknown	2015-12 - UNK	None reported	None reported	Death	Insufficient Information
2051	UNK	Male	Unknown	04FEB2016	Death	Unknown	2015-12 - UNK	None reported	None reported	Death	Insufficient Information
2052	UNK	Male	Unknown	04FEB2016	Neoplasm progression	Cancer pain	2015-12-11 - 2016-01-27	None reported	None reported	Death	Not Related
2053	UNK	Female	NOV2014, Unknown	05FEB2016	Neoplasm progression, Thinking abnormal	Cancer	2015-12 - UNK	Dilaudid, Oxycodone	None reported	Death	Not Related
2054	68	Female	25JAN2016	05FEB2016	Pancreatic carcinoma	Breakthrough pain	Unknown	None reported	None reported	Death	Not Related
2055	46	Female	17JAN2016	08FEB2016	Neoplasm progression	Breakthrough cancer pain	2015-12 - UNK	None reported	None reported	Death	Not Related

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UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2056	UNK	Unknown	Unknown	08FEB2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2057	59	Male	24NOV2004	09FEB2016	DEATH OFF LABEL USE	Intervertebral disc degeneration	Unknown	None reported	None reported	Death	Not Related
2058	UNK	Unknown	08OCT2010	09FEB2016	SICKLE CELL ANAEMIA OFF LABEL USE	Sickle cell anaemia	Unknown	None reported	None reported	Death	Not Related
2059	54	Female	06DEC2014	10FEB2016	Death	Unknown	2014-05-28 - UNK	None reported	None reported	Death	Insufficient Information
2060	UNK	Female	Unknown	11FEB2016	Death	Cancer	2014-05-28 - UNK	None reported	None reported	Death	Insufficient Information
2061	49	Female	08FEB2016	12FEB2016	Death	Cancer pain	2015-10-23 - UNK	None reported	None reported	Death	Insufficient Information
2062	63	Female	10APR2015	15FEB2016	Cardiac arrest	Unknown	2014-02-12 - 2015-04-10	None reported	None reported	Death	Insufficient Information
2063	UNK	Female	Unknown	16FEB2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2064	UNK	Female	Unknown	16FEB2016	Death, Off label use	Pain	2016-02-05 - 2016-02-16	None reported	None reported	Death	Insufficient Information
2065	UNK	Male	Unknown	16FEB2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2066	56	Female	Unknown	17FEB2016	Death	Unknown	Unknown	Levaquin, Carboplatin, Paraplatin, Dexamethasone, Taxol, Zofran, Benadryl, Lyrica, Tramadol, Hydromorphone, Lorazepam, Ibuprofen, Oxycodone	None reported	Death	Insufficient Information
2067	57	Male	10FEB2016, Unknown	18FEB2016	Death, Off label use	Pain	2015-11-11 - 2016-02-10	None reported	None reported	Death	Not Related
2068	UNK	Unknown	11FEB2016	18FEB2016	Death	Unknown	2016-02-05 - UNK	None reported	None reported	Death	Insufficient Information

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UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2069	UNK	Male	Unknown	18FEB2016	Death	Unknown	2015-10-23 - UNK	None reported	None reported	Death	Insufficient Information
2070	UNK	Unknown	Unknown	18FEB2016	Death	Unknown	2015-10-23 - UNK	None reported	None reported	Death	Insufficient Information
2071	UNK	Unknown	Unknown	18FEB2016	Death	Unknown	2015-10-23 - UNK	None reported	None reported	Death	Insufficient Information
2072	UNK	Female	Unknown	19FEB2016	Death	Unknown	2015-10-23 - UNK	None reported	None reported	Death	Insufficient Information
2073	UNK	Male	Unknown	19FEB2016	Death	Cancer	2015-10-23 - UNK	None reported	None reported	Death	Not Related
2074	52	Female	Unknown	19FEB2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2076	UNK	Unknown	10SEP2015	22FEB2016	Death	Unknown	2016-02-01 - UNK	None reported	None reported	Death	Insufficient Information
2077	UNK	Male	Unknown	23FEB2016	Death	Unknown	2016-06-03 - UNK	None reported	None reported	Death	Insufficient Information
2078	UNK	Unknown	Unknown	24FEB2016	Death	Unknown	2016-02-01 - UNK	None reported	None reported	Death	Insufficient Information
2079	UNK	Male	Unknown	25FEB2016	Death	Unknown	2016-06-03 - UNK	None reported	None reported	Death	Insufficient Information
2080	75	Unknown	09FEB2016, Unknown	26FEB2016	Neoplasm progression, Hospitalisation	Unknown	2016-02-24 - UNK	None reported	None reported	Death	Not Related
2081	UNK	Female	Unknown	29FEB2016	Death	Unknown	2016-06-03 - UNK	None reported	None reported	Death	Insufficient Information
2082	UNK	Female	Unknown	01MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Not Related
2083	52	Female	Unknown, 26APR2015	01MAR2016	Arteriosclerosis, Myocardial infarction	Breakthrough pain, cardiomyopathy, bundle branch block left, pelvic pain, ischaemic heart disease prophylaxis, depression, anaemia, hypertension	3114 days	Coreg, Aspirin, Duragesic, Effexor, Ferrous Sulfate, Lisinopril	None reported	Death	Not Related
2084	UNK	Male	Unknown	02MAR2016	Death	Chronic pain	2016-02-01 - 2016-02-29	None reported	None reported	Death	Insufficient Information

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2085	UNK	Unknown	Unknown	02MAR2016	Death	Cancer pain	Unknown	None reported	None reported	Death	Insufficient Information
2086	UNK	Male	Unknown	03MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2087	UNK	Male	Unknown	07MAR2016	Asthenia, Diplegia, Neoplasm progression	Breakthrough cancer pain	2016-02-01 - UNK	Levaquin, Oxycodone, Suboxone	None reported	Death	Not Related
2089	42	Female	03MAR2016, Unknown	08MAR2016	Intracranial aneurysm, Off label use	Breakthrough pain	2016-02-01 - UNK	None reported	None reported	Death	Insufficient Information
2090	UNK	Male	Unknown	08MAR2016	Death	Unknown	2016-02-01 - UNK	None reported	None reported	Death	Insufficient Information
2091	64	Male	20JUL2015	10MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2092	51	Male	07MAR2016	11MAR2016	Hepatic failure	Breakthrough cancer pain, chronic pain	2014-12-09 - UNK	Fentanyl Patch	None reported	Death	Not Related
2093	UNK	Male	Unknown	11MAR2016	Death	Unknown	2014-12-09 - UNK	None reported	None reported	Death	Insufficient Information
2094	UNK	Female	2015	11MAR2016	DEATH	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2095	63	Female	Unknown	14MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2096	UNK	Female	Unknown	14MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2097	40	Female	01JAN2015	15MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2098	57	Male	04MAR2016	15MAR2016	Death	Breakthrough cancer pain, neoplasm bone	2016-02-24 - UNK	None reported	None reported	Death	Not Related
2099	32	Male	26FEB2016, Unknown, Unknown	16MAR2016	Toxicity to various agents, Incorrect route of drug administration, Off label use	Acute back pain, chronic back pain	2016-02-24 - UNK	Belsomra, Keflex, Lopressor, Vitamin D, Vitamin D3	Duragesic, Effexor, Klonopin, Marijuana, Morphine, Oxycontin, Xanax	Death	Related
2100	UNK	Male	Unknown	16MAR2016	Death	Cancer pain, cancer pain	2016-02-03 - UNK	Fentanyl Patch	None reported	Death	Not Related

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UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2101	UNK	Male	Unknown	17MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2102	UNK	Female	Unknown	18MAR2016	Death	Unknown	2015-05-18 - UNK	None reported	None reported	Death	Insufficient Information
2103	69	Male	19MAR2016	19MAR2016	Death	Breakthrough cancer pain	2016-02-23 - 2016-03-19	None reported	None reported	Death	Insufficient Information
2104	UNK	Female	Unknown	21MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2106	UNK	Female	Unknown	22MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2107	51	Male	27OCT2015	23MAR2016	Death	Unknown	2016-02-23 - UNK	None reported	None reported	Death	Insufficient Information
2108	UNK	Female	Unknown	23MAR2016	DEATH	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2109	UNK	Female	Unknown	24MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2110	UNK	Female	Unknown	24MAR2016	DEATH	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2112	60	Male	2010	28MAR2016	DEATH ACUTE KIDNEY INJURY SEPTIC SHOCK PNEUMONIA STAPHYLOCOCCAL CAPLAN'S SYNDROME OFF LABEL USE	Back pain	Unknown	Duragesic (Orphenadine Citrate, Paracetamol), Temazepam	None reported	Death	Not Related
2113	UNK	Male	Unknown	29MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2114	54	Female	29MAR2016	29MAR2016	Disease progression	Breakthrough cancer pain	2016-01-15 - 2016-03-29	None reported	None reported	Death	Not Related
2115	78	Male	29MAR2016, 24FEB2016	29MAR2016	Death, Off label use	Pain in hip	2016-02-24 - 2016-03-29	None reported	None reported	Death	Insufficient Information
2116	UNK	Female	Unknown	29MAR2016	Death	Breakthrough cancer pain	2016-02-05 - 2016-03-29	None reported	None reported	Death	Insufficient Information

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UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2117	46	Male	Unknown	31MAR2016	Death	Breatkthrough cancer pain	2 Years	Albuterol, Tessalon Perle, Ativan, Zofran, Adderall, Oxycontin, Phenergan	None reported	Death	Insufficient Information
2118	UNK	Male	Unknown	31MAR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2120	UNK	Female	Unknown	04APR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2121	UNK	Female	Unknown	04APR2016	Death	Unknown	2016-02-03 - UNK	None reported	None reported	Death	Insufficient Information
2122	UNK	Female	Unknown	06APR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2123	52	Male	07APR2016	09APR2016	Death	Breakthrough cancer pain	2015-08-21 - 2016-04-07	None reported	None reported	Death	Insufficient Information
2124	UNK	Female	Unknown	11APR2016	Death	Breakthrough cancer pain	2016-01-15 - 2016-04-06	None reported	None reported	Death	Insufficient Information
2125	UNK	Male	Unknown	11APR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2126	57	Female	Unknown	12APR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2127	UNK	Male	SEP2014	12APR2016	Death	Breakthrough cancer pain	2014-04-09 - UNK	None reported	None reported	Death	Insufficient Information
2128	UNK	Female	Unknown	13APR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2129	65	Female	07APR2016	14APR2016	Sepsis	Breakthrough cancer pain	2016-03-17 - UNK	Fentanyl, Humalog, Imodium, Lantus, Levothyroxine, Oxycodone, Vitamin B12, Vitamin D3	None reported	Death	Not Related
2130	46	Female	2014	19APR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2132	47	Male	20APR2016, Unknown	20APR2016	Death, Off label use	Pain	2015-12-30 - 2016-04-20	None reported	None reported	Death	Not Related
2133	70	Male	Unknown	25APR2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2134	UNK	Female	Unknown	26APR2016	Death	Unknown	2015-12-30 - UNK	None reported	None reported	Death	Insufficient Information
2135	UNK	Female	Unknown	27APR2016	HAEMATOLOGICAL MALIGNANCY	Cancer pain	Unknown	None reported	None reported	Death	Not Related
2136	73	Male	27APR2016	28APR2016	Neoplasm progression	Breakthrough cancer pain	2016-04-20 - UNK	Ambien, Amlodipine, Compazine, Duragesic, Fentanyl, Lisinopril, Nabuton, Oxycodone, Pravachol, Prednisone, Symbicort, Tramadol	None reported	Death	Not Related
2137	UNK	Female	Unknown	30APR2016	Neoplasm progression	Breakthrough cancer pain, cancer pain	2016-01-20 - UNK	Fentanyl Patch, Opana Er	None reported	Death	Not Related
2138	44	Female	Unknown	02MAY2016	Death, Product use issue	Pain	Unknown	Topamax, Dexamethasone, Opana, Tizanidine	None reported	Death	Insufficient Information
2139	UNK	Female	Unknown	02MAY2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2140	UNK	Male	Unknown	02MAY2016	Death, Neoplasm progression	Breakthrough cancer pain	2015-11-30 - UNK	None reported	None reported	Death	Not Related
2141	40	Female	Unknown	03MAY2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2142	32	Female	18SEP2015	03MAY2016	Death	Breakthrough cancer pain	2015-08 - UNK	None reported	None reported	Death	Not Related
2143	UNK	Male	Unknown	03MAY2016	DEATH	Unknown	Unknown	None reported	None reported	Death	Insufficient Information

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2145	UNK	Unknown	MAY2016	05MAY2016	Death	Cancer pain	2015-11-30 - UNK	None reported	None reported	Death	Insufficient Information
2146	UNK	Female	Unknown	06MAY2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2148	66	Male	22APR2016	06MAY2016	Neoplasm progression	Breakthrough cancer pain	2016-03-24 - 2016-04-22	Morphine, Oxycodone	None reported	Death	Not Related
2149	40	Female	31OCT2014	09MAY2016	DEATH	Unknown	Unknown	None reported	None reported	Death	Not Related
2150	UNK	Male	Unknown	10MAY2016	Neoplasm progression	Unknown	2016-03-24 - UNK	None reported	None reported	Death	Not Related
2151	UNK	Female	MAY2016	13MAY2016	Sarcoma	Breakthrough pain, cancer pain	2015-10-08 - UNK	Oxycodone, Oxycontin	None reported	Death	Insufficient Information
2153	UNK	Male	2015	18MAY2016	DEATH	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2154	UNK	Male	Unknown	20MAY2016	Death	Unknown	2015-05 - UNK	None reported	None reported	Death	Insufficient Information
2155	UNK	Female	Unknown	20MAY2016	Death	Unknown	2015-05 - UNK	None reported	None reported	Death	Insufficient Information
2156	62	Male	19JUN2014	23MAY2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2157	61	Male	10APR2016	26MAY2016	Death	Breakthrough cancer pain	2015-09-11 - UNK	None reported	None reported	Death	Insufficient Information
2158	UNK	Male	Unknown	31MAY2016	Neoplasm progression	Breakthrough cancer pain	2016-04-13 - 2016-05-30	None reported	None reported	Death	Not Related
2159	UNK	Male	Unknown	31MAY2016	Death	Unknown	2016-04-13 - UNK	None reported	None reported	Death	Insufficient Information
2160	UNK	Male	Unknown	31MAY2016	Neoplasm progression	Unknown	2014-05-28 - UNK	None reported	None reported	Death	Not Related
2162	51	Male	27MAY2016	03JUN2016	Completed suicide	Malignant neoplasm of bronchus and lung in situ	2015-11-03 - 2016-05-27	None reported	None reported	Death	Insufficient Information
2163	70	Female	02JUN2016	03JUN2016	Death	Low back pain, spondylitis, malignant neoplasm of pancreas	2016-05-11 - UNK	None reported	None reported	Death	Insufficient Information
2164	UNK	Female	Unknown	06JUN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2165	UNK	Female	Unknown	06JUN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2166	UNK	Unknown	MAY2016, Unknown	06JUN2016	Death, Off label use	Neoplasm malignant	Unknown	None reported	None reported	Death	Insufficient Information
2167	65	Female	19AUG2015	06JUN2016	Neoplasm progression	Breakthrough cancer pain	2015-06-17 - UNK	None reported	None reported	Death	Not Related
2168	62	Female	2016	09JUN2016	PNEUMONITIS	Cancer pain	Unknown	None reported	Chemotherapeutics (Unspecified)	Death	Not Related
2169	57	Male	30MAY2016	10JUN2016	Neoplasm progression	Breakthrough cancer pain	2015-06-17 - UNK	None reported	None reported	Death	Not Related
2171	57	Female	14MAY2016	13JUN2016	Death	Chronic pain, post laminectomy syndrome, lumbar radiculopathy, cervical radiculopathy	2013-08-07 - UNK	Dilaudid, Humira, Methadone	None reported	Death	Insufficient Information
2172	UNK	Male	Unknown	13JUN2016	Toxicity to various agents	Unknown	2015-11-30 - UNK	None reported	None reported	Death	Insufficient Information
2173	UNK	Male	Unknown	14JUN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2174	66	Male	18MAR2016	14JUN2016	Neoplasm progression	Breakthrough cancer pain	2015-11-30 - UNK	Coumadin, Marinol, Methadone, Morphine, Norco, Tramadol, Xeloda	None reported	Death	Not Related
2175	UNK	Male	Unknown	14JUN2016	Death	Bone cancer	Unknown	None reported	None reported	Death	Insufficient Information
2176	64	Male	30JUN2014	15JUN2016	Death	Unknown	2015-11-30 - UNK	None reported	None reported	Death	Insufficient Information
2177	UNK	Male	Unknown	16JUN2016	Death	Drug use for unapproved indication	Unknown	None reported	None reported	Death	Insufficient Information
2178	UNK	Female	Unknown	16JUN2016	Anal cancer metastatic	Unknown	Unknown	None reported	None reported	Death	Not Related
2179	UNK	Male	Unknown	16JUN2016	DEATH	Unknown	Unknown	None reported	None reported	Death	Not Related

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2180	64	Male	Unknown	21JUN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2182	UNK	Female	Unknown	21JUN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2183	51	Female	01JAN2008, Unknown	22JUN2016	Product use issue, Death	Interstitial cystitis	8 Years	Morphine	None reported	Death	Insufficient Information
2184	UNK	Male	Unknown	22JUN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2185	56	Male	04JUN2016	22JUN2016	Death	Malignant neoplasm of bronchus and lung in situ	2015-11-24 - UNK	None reported	None reported	Death	Insufficient Information
2186	91	Female	18JUN2016	24JUN2016	Death	Breakthrough cancer pain	2015-11-24 - UNK	None reported	None reported	Death	Insufficient Information
2188	43	Male	19JUN2016	24JUN2016	Neoplasm progression	Breakthrough cancer pain	2016-06-18 - UNK	None reported	None reported	Death	Not Related
2189	UNK	Male	Unknown	27JUN2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2190	89	Female	26JUN2016	27JUN2016	Death	Breakthrough cancer pain	2016-02-09 - 2016-06-26	None reported	None reported	Death	Insufficient Information
2191	80	Female	27JAN2016	27JUN2016	Death	Unknown	2016-06-03 - UNK	None reported	None reported	Death	Insufficient Information
2192	UNK	Female	Unknown	28JUN2016	Death	Unknown	2016-05-09 - 2016-06-28	None reported	None reported	Death	Insufficient Information
2193	51	Female	27JUN2016	28JUN2016	Neoplasm progression	Breakthrough cancer pain	2016-06-20 - UNK	Lorazepam	None reported	Death	Not Related
2194	68	Female	14JUN2016	28JUN2016	Neoplasm progression	Breakthrough cancer pain	2016-06-03 - UNK	Amlodipine, Doxycycline, Duragesic Patch, Gabapentin, Levothyroxin, Pantoprazole, Sertraline, Spiriva	None reported	Death	Not Related
2195	73	Female	29JUN2016	29JUN2016	Neoplasm progression	Breakthrough cancer pain	2016-04-01 - 2016-06-29	None reported	None reported	Death	Not Related

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2196	UNK	Female	Unknown	01JUL2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2198[c]	UNK	Unknown	Unknown	05JUL2016	Overdose	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2199	43	Female	01JUL2016	05JUL2016	Neoplasm progression	Breakthrough cancer pain, breakthrough cancer pain	2016-06-21 - UNK	Fentanyl Patch, Morphine, Oxycodone	None reported	Death	Not Related
2200	UNK	Female	Unknown	06JUL2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2201	59	Female	03JUL2016	06JUL2016	Neoplasm progression	Breakthrough cancer pain	2016-03-24 - UNK	Fentanyl	None reported	Death	Not Related
2202	UNK	Female	Unknown	06JUL2016	Death	Unknown	2016-03-24 - UNK	None reported	None reported	Death	Insufficient Information
2203	52	Female	25JAN2015	06JUL2016	Death	Unknown	2016-03-24 - UNK	None reported	None reported	Death	Insufficient Information
2205	57	Male	10JUL2016	11JUL2016	Neoplasm progression	Breakthrough cancer pain	2016-03-25 - 2016-07-10	None reported	None reported	Death	Not Related
2206	UNK	Female	01JUL2016	12JUL2016	Neoplasm progression	Unknown	2016-06-28 - 2016-07-01	None reported	None reported	Death	Not Related
2207	65	Female	10JUL2016	12JUL2016	Neoplasm progression	Breakthrough cancer pain	2016-03-25 - 2016-07-10	None reported	None reported	Death	Not Related
2208	68	Female	10JUN2016	12JUL2016	Death	Breakthrough cancer pain	2015-11-09 - UNK	Duragesic Patch	None reported	Death	Insufficient Information
2209	53	Male	13JUL2016	14JUL2016	Death	Breakthrough cancer pain	2016-05-23 - 2016-07-13	Oxycodone	None reported	Death	Not Related
2210	UNK	Female	Unknown	15JUL2016	Death	Unknown	2016-05-23 - UNK	None reported	None reported	Death	Insufficient Information
2211	UNK	Female	2015	15JUL2016	Death	Unknown	Unknown	None reported	None reported	Death	Not Related
2212	53	Male	Unknown	18JUL2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2213	48	Female	19JUN2016	18JUL2016	Death	Pain	2016-04-04 - 2016-06-19	None reported	None reported	Death	Not Related
2215	UNK	Female	Unknown	18JUL2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2216	55	Male	17JUL2016	19JUL2016	Neoplasm progression	Breakthrough pain	2016-07-28 - UNK	Oxycodone	None reported	Death	Insufficient Information
2217[d]	32	Female	25MAR2016	19JUL2016	Overdose	Breakthrough cancer pain	2016-07-28 - UNK	None reported	None reported	Death	Possibly Related
2218	62	Male	19JUL2016	19JUL2016	Neoplasm progression	Unknown	2016-04-11 - UNK	None reported	None reported	Death	Not Related
2219	49	Female	20JUL2016	20JUL2016	Death	Breakthrough cancer pain	2016-04-22 - 2016-07-20	None reported	None reported	Death	Insufficient Information
2220	58	Male	17OCT2014	20JUL2016	Neoplasm progression	Cancer pain	2014-08-19 - UNK	Fentanyl, Methadone, Oxycodone	None reported	Death	Not Related
2221	UNK	Male	Unknown	21JUL2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2222	UNK	Male	Unknown	21JUL2016	Neoplasm progression	Breakthrough cancer pain	2016-04-22 - UNK	None reported	None reported	Death	Not Related
2223	53	Male	21JUL2016	22JUL2016	Neoplasm progression	Breakthrough cancer pain	2016-04-11 - UNK	Fentanyl, Hydrocodone	None reported	Death	Not Related
2224	UNK	Male	19APR2016	22JUL2016	Death	Breakthrough cancer pain	2016-04-11 - UNK	Hydrocodone, Morphine	None reported	Death	Insufficient Information
2225	52	Female	01MAY2016	22JUL2016	Death	Breakthrough cancer pain	2016-04-11 - UNK	Oxycodone	None reported	Death	Insufficient Information
2226	UNK	Female	Unknown	23JUL2016	Chronic obstructive pulmonary disease	Sprain of septal cartilage of nose	2015-09-28 - 2016-07-23	None reported	None reported	Death	Not Related
2227	67	Female	12APR2015	25JUL2016	Death	Unknown	2016-04-11 - UNK	None reported	None reported	Death	Insufficient Information
2228	UNK	Female	Unknown	25JUL2016	Neoplasm progression	Breakthrough cancer pain	2016-04-22 - UNK	Fentanyl Patch, Hydrocodone, Morphine, Oxycodone	None reported	Death	Not Related
2229	52	Male	18FEB2015, 01AUG2014	28JUL2016	Death, Inappropriate schedule of drug administration	Cancer pain	6 Months	Fentanyl	None reported	Death	Insufficient Information

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2230	45	Female	08OCT2015	28JUL2016	Neoplasm progression	Complex regional pain syndrome, breakthrough cancer pain	2015-08-28 - UNK	Oxycodone	None reported	Death	Not Related
2231	73	Female	20JUN2016	28JUL2016	Death	Breakthrough cancer pain	2015-08-28 - UNK	None reported	None reported	Death	Not Related
2232	62	Male	18JUL2016	28JUL2016	Neoplasm progression	Breakthrough cancer pain	2015-08-28 - UNK	Fentanyl, Hydrocodone, Morphine	None reported	Death	Not Related
2233	UNK	Male	Unknown	28JUL2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2234	64	Male	20JUL2016	29JUL2016	Neoplasm progression	Malignant neoplasm of pancreas, part unspecified	2016-04-11 - 2016-07-20	None reported	None reported	Death	Not Related
2235	UNK	Male	Unknown	02AUG2016	Death	Breakthrough cancer pain	2016-04-11 - UNK	Hydromorphone	None reported	Death	Insufficient Information
2236	55	Female	Unknown	03AUG2016	Death	Unknown	Unknown	None reported	None reported	Death	Not Related
2237	UNK	Female	Unknown	03AUG2016	Cardiac arrest	Chronic pain	2012-12-28 - UNK	None reported	None reported	Death	Insufficient Information
2238	UNK	Male	Unknown	04AUG2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2239	UNK	Male	Unknown	04AUG2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2240	UNK	Female	Unknown	04AUG2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2241	90	Female	Unknown	04AUG2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2242	60	Male	20JUN2016	04AUG2016	Neoplasm progression	Breakthrough cancer pain	2016-04-12 - UNK	Enoxaparin, Fentanyl, Oxycodone	None reported	Death	Not Related
2243	UNK	Male	Unknown	05AUG2016	Death	Unknown	2016-04-12 - UNK	None reported	None reported	Death	Insufficient Information
2244	UNK	Male	Unknown	06AUG2016	Death	Breakthrough cancer pain	2016-04-12 - UNK	Fentanyl, Hydromorphone	None reported	Death	Insufficient Information

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2246	UNK	Female	Unknown	08AUG2016	Death	Neck pain	2016-04-12 - UNK	None reported	None reported	Death	Insufficient Information
2247	66	Male	Unknown	08AUG2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2248	78	Male	09AUG2016	09AUG2016	Death	Unknown	2016-04-12 - UNK	None reported	None reported	Death	Insufficient Information
2249	UNK	Female	Unknown	09AUG2016	Neoplasm progression	Breakthrough cancer pain	2016-04-12 - UNK	Fentanyl, Hydromorphone, Oxycodone	None reported	Death	Not Related
2250	UNK	Female	Unknown	10AUG2016	Neoplasm progression	Breakthrough cancer pain	2016-04-12 - UNK	Fentanyl Patch	None reported	Death	Not Related
2251	60	Female	08OCT2014	10AUG2016	Death	Breakthrough cancer pain	2014-08-07 - UNK	None reported	None reported	Death	Not Related
2252	37	Female	01JUL2016	11AUG2016	Neoplasm progression	Breakthrough cancer pain	2014-08-07 - UNK	Fentanyl	None reported	Death	Not Related
2253	UNK	Female	Unknown	11AUG2016	Death	Unknown	2014-08-07 - UNK	None reported	None reported	Death	Insufficient Information
2254	41	Female	02MAY2016	12AUG2016	Necrotising fasciitis	Breakthrough cancer pain	2014-08-07 - UNK	Morphine, Oxycodone	None reported	Death	Not Related
2255	63	Female	17MAY2016	12AUG2016	Neoplasm progression	Breakthrough cancer pain	2014-08-07 - UNK	Hydrocodone	None reported	Death	Not Related
2256	UNK	Female	Unknown	12AUG2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2257	UNK	Female	Unknown	15AUG2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2258	UNK	Male	Unknown	15AUG2016	Neoplasm progression	Breakthrough cancer pain	2014-08-07 - UNK	Fentanyl	None reported	Death	Not Related
2260	UNK	Male	Unknown	15AUG2016	DEATH	Unknown	Unknown	None reported	None reported	Death	Not Related
2262	67	Male	23JUN2016	16AUG2016	Death	Breakthrough cancer pain	2014-08-07 - UNK	Hydromorphone	None reported	Death	Insufficient Information
2263	UNK	Male	Unknown	17AUG2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information
2264	UNK	Male	Unknown	17AUG2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information

Cases of Death Received from TRIG Sponsors During the Reporting Period: 29AUG2015-28AUG2016

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
2265	UNK	Male	Unknown	17AUG2016	Death	Breakthrough cancer pain	2015-12 - UNK	Fentanyl	None reported	Death	Insufficient Information
2266	UNK	Male	Unknown	17AUG2016	Neoplasm progression	Breakthrough cancer pain	2015-12 - UNK	None reported	None reported	Death	Not Related
2267	UNK	Male	Unknown	19AUG2016	Neoplasm progression	Breakthrough cancer pain	2015-12 - UNK	Fentanyl	None reported	Death	Not Related
2268	62	Male	13AUG2016, 13AUG2016	20AUG2016	Hepatic failure, Neoplasm progression	Malignant neoplasm of head, face, and neck	2015-12-31 - 2016-08-13	None reported	None reported	Death	Insufficient Information
2269	76	Male	19AUG2016	20AUG2016	Neoplasm progression	Malignant neoplasm of head, face, and neck	2015-12-31 - UNK	None reported	None reported	Death	Not Related
2270	34	Male	20AUG2016	22AUG2016	Death	Crohn's disease	2015-12 - UNK	None reported	Ambien, Morphine, Oxycodone	Death	Insufficient Information
2271	68	Male	15AUG2016	23AUG2016	Death	Malignant neoplasm of spinal cord	2016-07-28 - 2016-08-15	None reported	None reported	Death	Insufficient Information
2272	UNK	Male	APR2016	24AUG2016	Death	Breakthrough cancer pain	2016-07-28 - UNK	Hydrocodone, Oxycodone	None reported	Death	Insufficient Information
2273	56	Male	25APR2016	24AUG2016	Death	Breakthrough cancer pain	2013-12-04 - UNK	Oxycodone	None reported	Death	Insufficient Information
2274	UNK	Male	Unknown	24AUG2016	Death	Unknown	2013-12-04 - UNK	None reported	None reported	Death	Insufficient Information
2275	83	Female	10AUG2016	25AUG2016	Death	Breakthrough cancer pain	2013-12-04 - UNK	Fentanyl	None reported	Death	Insufficient Information
2276	UNK	Female	Unknown	25AUG2016	Death	Unknown	2013-12-04 - UNK	None reported	None reported	Death	Insufficient Information
2277	31	Male	Unknown	26AUG2016	Death	Unknown	Unknown	None reported	None reported	Death	Insufficient Information

[a] Potential causality is reported if sufficient information is available to make a determination. If there is insufficient information available and the potential causality cannot be determined, this is noted in the table.
[b] Patient 1988 is also described in the table for addiction and overdose.
[c] Patient 2198 is also described in the table for overdose.
[d] Patient 2217 is also described in the table for overdose.
UNK = Unknown

New Cases of Death Received from TRIG Sponsors in 2016 from a Previous Reporting Periods

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1856	UNK	Female	Unknown	04DEC2013[b]	Neoplasm progression	Breakthrough cancer pain	2013-02-19 - UNK	None reported	None reported	Death	Not Related
1857	33	Female	12DEC2013	19DEC2013[b]	Death	Breakthrough pain	2015-06-08 - UNK	None reported	None reported	Death	Insufficient Information
1859	UNK	Female	Unknown	08JAN2014[b]	Death	Breakthrough cancer pain	2013-06-27 - UNK	None reported	None reported	Death	Not Related
1860	UNK	Male	Unknown	14JAN2014[b]	Death	Unknown	2013-05-14 - UNK	None reported	None reported	Death	Not Related
1861	UNK	Male	Unknown	16JAN2014[b]	Death	Unknown	2013-10-17 - UNK	None reported	None reported	Death	Not Related
1862	UNK	Female	JAN2014	12FEB2014[b]	Neoplasm progression	Breakthrough cancer pain	2013-10-07 - UNK	Fentanyl, Methadone	None reported	Death	Not Related
1863	UNK	Male	Unknown	12FEB2014[b]	Death	Breakthrough pain	2013-02-14 - UNK	None reported	None reported	Death	Insufficient Information
1864	UNK	Female	Unknown	19FEB2014[b]	Death	Breakthrough pain	2014-01-28 - UNK	None reported	None reported	Death	Not Related
1865	UNK	Female	Unknown	19FEB2014[b]	Death	Breakthrough cancer pain	2014-01-07 - UNK	None reported	None reported	Death	Not Related
1866	UNK	Male	Unknown	21FEB2014[b]	Death	Breakthrough cancer pain	2013-07-09 - UNK	None reported	None reported	Death	Not Related
1867	UNK	Female	Unknown	28FEB2014[b]	Death	Malignant neoplasm of bronchus and lung in situ, cancer pain	2015-07-02 - UNK	None reported	None reported	Death	Insufficient Information
1868	UNK	Female	Unknown	04MAR2014[b]	Death	Breakthrough cancer pain	2013-08-29 - UNK	None reported	None reported	Death	Not Related
1869	UNK	Female	Unknown	05MAR2014[b]	Death	Cancer pain	2013-03-13 - UNK	None reported	None reported	Death	Not Related
1870	UNK	Female	Unknown	05MAR2014[b]	Death	Breakthrough pain	2013-05 - 2014-01-04	None reported	None reported	Death	Not Related
1871	UNK	Unknown	Unknown	06MAR2014[b]	Death	Lung cancer, bone cancer, breakthrough cancer pain	2013-06-28 - UNK	None reported	None reported	Death	Not Related
1872	UNK	Male	Unknown	13MAR2014[b]	Death	Breakthrough cancer pain	2014-02-06 - UNK	None reported	None reported	Death	Not Related

New Cases of Death Received from TRIG Sponsors in 2016 from a Previous Reporting Periods

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1873	UNK	Unknown	Unknown	14MAR2014[b]	Death	Unknown	2013-03-13 - UNK	None reported	None reported	Death	Insufficient Information
1874	UNK	Female	Unknown	17MAR2014[b]	Death, Off label use	Lumbar disc degeneration	2013-06 - UNK	None reported	None reported	Death	Insufficient Information
1875	UNK	Male	Unknown	20MAR2014[b]	Death	Unknown	2013-06-28 - UNK	None reported	None reported	Death	Insufficient Information
1876	UNK	Male	Unknown	28MAR2014[b]	Neoplasm progression	Breakthrough cancer pain, metastatic carcinoma	2013-11-14 - UNK	Diazepam, Oxycontin, Prednisone, Synthroid, Vancomycin, Zofran	None reported	Death	Not Related
1877	UNK	Unknown	Unknown	02APR2014[b]	Death	Unknown	2013-08 - UNK	None reported	None reported	Death	Not Related
1878	UNK	Male	Unknown	14APR2014[b]	Neoplasm progression	Breakthrough cancer pain	2014-02-19 - UNK	None reported	None reported	Death	Not Related
1879	UNK	Male	Unknown	06MAY2014[b]	Death, Malaise	Unknown	2013-07 - UNK	None reported	None reported	Death	Insufficient Information
1880	UNK	Unknown	Unknown	08MAY2014[b]	Death	Unknown	2013-05-20 - UNK	None reported	None reported	Death	Insufficient Information
1881	UNK	Male	Unknown	13MAY2014[b]	Death	Unknown	2012-06-29 - UNK	None reported	None reported	Death	Insufficient Information
1882	UNK	Unknown	Unknown	14MAY2014[b]	Death	Breakthrough cancer pain	2013-05-15 - UNK	None reported	None reported	Death	Not Related
1883	UNK	Female	Unknown	17JUN2014[b]	Death, Migraine	Cancer pain	2014-10-13 - UNK	None reported	None reported	Death	Possibly Related
1885	UNK	Female	Unknown	23JUN2014[b]	Neoplasm progression	Cancer pain	2013-08-17 - UNK	None reported	None reported	Death	Not Related
1886	UNK	Female	Unknown	01JUL2014[b]	Neoplasm progression	Breakthrough cancer pain	2014-06-05 - UNK	Oxycodone	None reported	Death	Not Related
1887	UNK	Female	Unknown	08JUL2014[b]	Death	Breakthrough cancer pain	2014-06-11 - UNK	None reported	None reported	Death	Insufficient Information
1888	UNK	Male	Unknown	09JUL2014[b]	Respiratory distress	Breakthrough cancer pain, breakthrough cancer pain	2014-06-11 - UNK	Ativan, Fentanyl, Norco	None reported	Death	Possibly Related

New Cases of Death Received from TRIG Sponsors in 2016 from a Previous Reporting Periods

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]
1889[c]	UNK	Male	Unknown	28JUL2014[b]	Abnormal behaviour, Disorientation, Drug interaction, Hepatic failure, Inappropriate schedule of drug administration	Breakthrough cancer pain	2014-05-30 - 2014-06-03	None reported	Nexavar	Death	Possibly Related
1890	UNK	Female	Unknown	28JUL2014[b]	Death	Unknown	2014-05-30 - UNK	None reported	None reported	Death	Insufficient Information
1891	UNK	Unknown	Unknown	28JUL2014[b]	Death	Unknown	2014-05-30 - UNK	None reported	None reported	Death	Insufficient Information
1892	57	Unknown	10DEC2013	31JUL2014[b]	Death	Unknown	2014-05-30 - UNK	None reported	None reported	Death	Insufficient Information
1893	UNK	Male	Unknown	12AUG2014[b]	Neoplasm progression	Unknown	2014-02-11 - UNK	None reported	None reported	Death	Not Related
1894	UNK	Male	Unknown	12AUG2014[b]	Death	Breakthrough cancer pain	2014-06-19 - 2014-07-18	None reported	None reported	Death	Not Related
1895	UNK	Male	Unknown	25AUG2014[b]	Death	Unknown	2014-06-19 - UNK	None reported	None reported	Death	Insufficient Information
1907	58	Male	01JUN2015, Unknown	01JUN2015[b]	Drug ineffective, Death	Cancer pain, chronic pain	2014-10 - UNK	Atorvastatin Calcium, Baby Aspirin, Diazepam, Dronabinol, Fentanyl Patch, Nuvigil, Oxycodone	None reported	Death	Insufficient Information
1908	UNK	Unknown	Unknown	16JUN2015[b]	Death	Unknown	2014-06-19 - UNK	None reported	None reported	Death	Insufficient Information
1910	72	Male	14NOV2015, 14NOV2015	13AUG2015[b]	General physical health deterioration, Neoplasm progression	Breakthrough cancer pain, breakthrough cancer pain	2015-06-15 - UNK	Albuterol, Miralax, Mobic, Morphine, Phenergan, Ranitidine, Senna, Synthroid	Fentanyl Patches	Death	Not Related

New Cases of Death Received from TRIG Sponsors in 2016 from a Previous Reporting Periods

UBC ID	Patient Age	Patient Gender	Event Date	Report Date	Preferred Term(s)	Indication(s)	TIRF Duration	Concomitant Medications	Co-Suspect Product(s)	Event Outcome	Potential Causality[a]

[a] Potential causality is reported if sufficient information is available to make a determination. If there is insufficient information available and the potential causality cannot be determined, this is noted in the table.
[b] Case initiated in prior reporting period but was not included in previous reports.
[c] Patient 1889 is also described in the table for addiction.
UNK = Unknown

12.4 RADARS System Program Report Protocol

Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS): Surveillance Monitoring Protocol

For
The TIRF REMS Industy Group

Actavis Laboratories FL, Inc.

BioDelivery Sciences International, Inc. (BDSI)

Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)

Depomed, Inc.

Insys Therapeutics, Inc.

Mallinckrodt Pharmaceuticals

Mylan Inc.

Par Pharmaceutical, Inc.

Sentynl Therapeutics, Inc.

August 3, 2016

Confidential

7. Appendices

7.1 Shell Tables

Table <number>

The RADARS System <Program of interest>

<outcome of interest> per <scaled denominator (e.g. 100,000 population)>

Means Model

From July 2010 to June 2016

Drug group	Time period	Rate (95% CI)	Percentage change (95% CI)	p-value	p-value for interaction
TIRF Products	Pre TIRF REMS	x.xxxx (x.xxxx, x.xxxx)			
	Post TIRF REMS	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	
Schedule II IR Opioids	Pre TIRF REMS	x.xxxx (x.xxxx, x.xxxx)			
	Post TIRF REMS	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	0.xxx
Schedule II Opioids	Pre TIRF REMS	x.xxxx (x.xxxx, x.xxxx)			
	Post TIRF REMS	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	0.xxx
Schedule II Opioids Excluding Methadone	Pre TIRF REMS	x.xxxx (x.xxxx, x.xxxx)			
	Post TIRF REMS	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	0.xxx

Table <number>

The RADARS System <Program of interest>

<outcome of interest> per <scaled denominator (e.g. 100,000 population)>

Piecewise Linear Model

From July 2010 to June 2016

Drug group	Time period	Parameter	Estimate (95% CI)	Percentage change (95% CI)	p-value	p-value for interaction
TIRF Products	Pre TIRF REMS	Intercept	x.xxxx (x.xxxx, x.xxxx)			
		Slope	x.xxxx (x.xxxx, x.xxxx)			
	Post TIRF REMS	Intercept	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	
		Slope	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	
Schedule II IR Opioids	Pre TIRF REMS	Intercept	x.xxxx (x.xxxx, x.xxxx)			
		Slope	x.xxxx (x.xxxx, x.xxxx)			
	Post TIRF REMS	Intercept	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	0.xxx
		Slope	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	0.xxx
Schedule II Opioids	Pre TIRF REMS	Intercept	x.xxxx (x.xxxx, x.xxxx)			
		Slope	x.xxxx (x.xxxx, x.xxxx)			
	Post TIRF REMS	Intercept	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	0.xxx
		Slope	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	0.xxx
Schedule II Opioids Excluding Methadone	Pre TIRF REMS	Intercept	x.xxxx (x.xxxx, x.xxxx)			
		Slope	x.xxxx (x.xxxx, x.xxxx)			
	Post TIRF REMS	Intercept	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	0.xxx
		Slope	x.xxxx (x.xxxx, x.xxxx)	xx.xx% (-xx.xx %, xx.xx %)	0.xxx	0.xxx

Table <number>

The RADARS System
Cumulative Mention Rates of <Drug group of interest>
per 100,000 Population, 10,000 Prescriptions and 100,000 Dose Units
From July 2010 to June 2016

	Total	
Cumulative Rates	**Pre TIRF REMS July 2010-June 2012**	**Post TIRF REMS July 2012-June 2016**
Poison Center Program Abuse Cases/Mentions	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxx	x.xxx
Treatment Center Programs Combined Cases/ Endorsements	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxx	x.xxx
Opioid Treatment Program Cases/ Endorsements	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxx	x.xxx
Survey of Key Informants' Patients Program Cases/ Endorsements	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxxx	x.xxxx
College Survey Program Cases/ Endorsements	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxxx	x.xxxx
Impaired Health Care Worker Program Mentions	x/x	x/x
Population Rate per 100,000	x.xxxx	x.xxxx
Prescription Rate per 10,000	x.xxxx	x.xxxx
Dose Unit Rate per 100,000	x.xxxx	x.xxxx

Table <number>

The RADARS System Poison Center Program
Reported Deaths by Age, Medical Outcome and Period
From July 2010 to June 2016

Time Period	Case Number	Year Quarter	Age Group	Exposure Reason	Medical Outcome
xxxxx	xxxx	xxxxQx	xx-xx	xxxx	Death
	xxxx	xxxxQx	xx-xx	xxxx	Death

Table <number>

The RADARS System Poison Center Program

Reported Pediatric Exposures Listing

From July 2010 to June 2016

Time Period	Case Number	Year Quarter	Age Group	Exposure Reason	Medical Outcome

12.5 RADARS System Program Report

RADARS® SYSTEM REPORT

Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS): Surveillance Monitoring

December 13, 2016

FOLLOWING THIS PAGE, FDA_4212 TO FDA_4682 WITHHELD IN FULL AS B(4)/CCI

Accenture LLP
1160 West Swedesford Road
Berwyn, PA 19312
www.accenture.com

February 17, 2017

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
Drug Master File Staff
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: DMF #: 027320
Holder: McKesson Specialty Health (McKesson)
DMF Subject: Transmucosal Immediate Release Fentanyl (TIRF) Access Program
Re: REMS Shared Program
DMF Type: V
DMF Submission Information: Clinical/Clinical Information
REMS Submission Identifier: Not Applicable
eCTD Sequence Number: 0028

Dear Drug Master File Staff:

This Type V DMF contains the Risk Evaluation and Mitigation Strategy (REMS) for Transmucosal Immediate Release Fentanyl for the Shared System REMS program.

Please find the "60-Month FDA REMS Supplemental Assessment Report (10 February 2017)" that completes the 60-Month FDA REMS Assessment Report submission and addresses some of the FDA requested items included in the 48-Month FDA Assessment Report Acknowledgement Letter. This supplemental assessment report is located in Module 1.16 of this submission.

McKesson states that information provided in this Master File is current and assures that the material furnished will meet the specifications described herein. McKesson also confirms that the Holder obligations are observed.

We request that all information in this file be treated as confidential commercial information to the Food and Drug Administration pursuant to 21 C.F.R. §20.61, and that no information from this file be provided to any unauthorized persons without written consent.

If you have any questions or concerns regarding this submission, please do not hesitate to contact Debra Hackett, U.S. Agent for McKesson, at 610-407-1729 or alternatively via email at debra.hackett@accenture.com.

Sincerely,

Debra Hackett, U.S. Agent
Accenture, LLP

Attachments: Table of Contents for the submission
Electronic Submission Specifications

REMS CORRESPONDENCE

Module Section	Description
1.2 Cover Letter	Cover Letter w/ Attachments
1.16 – Risk Management Plans	REMS History TIRF REMS Access Program 60-Month FDA REMS Supplemental Assessment Report

Electronic Submission Specifications

This submission is compliant with FDA's Guidelines for Industry and current eCTD specifications.

All files were checked and verified to be free of viruses prior to transmission through the electronic submission gateway.

Anti-Virus Program	Symantec Endpoint Protection Edition
Program Version	12.1.5337.5000
Virus Definition Date	02/15/2017 rev. 18
Submission Size	Approx. 4.3 MB

The IT point of contact for this submission is:

Name	Matt Francis
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ADMINISTRATIVE INFORMATION

Holder's Name: McKesson Specialty Health (McKesson)

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Contact's Address: 4343 N. Scottsdale Road
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Scottsdale, AZ 85251

Contact's Phone: 480-663-4009

Contact's Fax: 480-663-4973

Contact's Email address: laura.baloun@mckesson.com

Statement of Commitment: Attached, please find a signed statement of commitment. The statement certifies that the DMF 027320 is current and that McKesson will comply with the statements made in it.

Agent's Name: Accenture, LLP

Agent's Address: 1160 West Swedesford Road, Building One
Berwyn, PA 19312

Agent's Contact Person: Debra Hackett, Senior Regulatory Project Manager, Regulatory Affairs

Contact's Address 1160 West Swedesford Road, Building One
Berwyn, PA 19312

Contact's Phone: 610-407-1729

Contact's Fax: 610-407-8433

Contact's E-mail address: debra.hackett@accenture.com

Modification No.	Date Approved	Documents Affected	Overview of Modification
1	June 5, 2012	• REMS • Prescriber Program Overview • Education Program • Prescriber Enrollment Form • Patient Provider Agreement Form • Patient and Caregiver Overview • Dear Healthcare Provider Letter • Outpatient Pharmacy Overview • Chain Pharmacy Overview • Inpatient Pharmacy Overview • Outpatient Pharmacy Enrollment Form • Chain Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Outpatient Pharmacy Letter • Inpatient Pharmacy Letter • Dear Distributor Letter • Distributor Enrollment Form • Supporting Document	**Sequence 0002**: Edits to Patient-Prescriber Agreement Form, the addition of the Closed System Pharmacy Enrollment Form*, the addition of the newly approved TIRF product, Subsys (fentanyl sublingual spray) and minor editorial changes. *The Closed System Pharmacy Enrollment Form was not formally submitted through the Gateway but was submitted via email on May 18, 2012 and included in the June 5, 2012 FDA approval letter.

Modification No.	Date Approved	Documents Affected	Overview of Modification
N/A	N/A	Assessment Report 1 at 6 months – due 06/28/2012	**Sequence 0003**: Assessment report covering 12/28/2011 to 04/27/2012
2	November 7, 2013	Draft Documents submitted on or before 09/28/2012 • Chain Pharmacy Enrollment Form • Outpatient Pharmacy Enrollment Form • Closed System Pharmacy Overview • Education Program • Frequently Asked Questions (FAQ) • Outpatient Pharmacy Letter • REMS • Supporting Document	**Sequence 0004**: Modification proposed to: • Incorporate closed system pharmacies into the TIRF REMS Access Program • Correct minor inconsistencies between the FDA provided versions and the current PDF versions of REMS materials
N/A	N/A	Assessment Report 2 at 1 year – due 12/28/2012	**Sequence 0005**: Assessment Report covering 04/28/2012 to 10/28/2012
2	November 7, 2013	Amendment to 09/28/2012 supplement: • Chain Outpatient Pharmacy Enrollment Form • Independent Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient	**Sequence 0006**: Modification proposed to: • Revised terminology, processes, and definitions for outpatient pharmacies • Revised attestations for physicians and patients to address concerns regarding patient access • Revised Program Overview and Frequently Asked Questions to improve clarity and content

Modification No.	Date Approved	Documents Affected	Overview of Modification
		Pharmacy Enrollment Form • Distributor Enrollment Form • Prescriber Enrollment Form	• Updated REMS materials to reflect the completion of the transition phase for the
		• Patient Provider Agreement Form • Chain Outpatient Pharmacy Overview • Independent Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Patient and Caregiver Overview • Prescriber Overview • Education Program • Knowledge Assessment • Frequently Asked Questions (FAQ) • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Healthcare Provide Letter • Dear Distributor Letter • REMS	TIRF REMS Access Program

Modification No.	Date Approved	Documents Affected	Overview of Modification
		• Supporting Document • Website Landing Page	
N/A	N/A	Assessment Report 3 at 2 years – due 12/28/2013	**Sequence 0007: Assessment Report covering 10/29/2012 to 10/28/2013**
N/A	N/A	Safety Surveillance Report #1 – due 03/31/2014	**Sequence 0008: Safety surveillance data covering Q4 2012 to Q3 2013**
3	December 24, 2014	• REMS • Prescriber Program Overview • Education Program • Prescriber Enrollment Form • Patient and Caregiver Overview • Independent Outpatient Pharmacy Overview • Chain Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Independent Outpatient Pharmacy Enrollment Form • Chain Outpatient	**Sequence 0009**: Modification proposed to: • Updated REMS materials to eliminate product specific information which does not impact the safe use of TIRF products • Updated REMS materials to reference the currently approved TIRF products list on the FDA Approved REMS website • Updated REMS materials to remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe • Incorporated revised assessment metrics into the Supporting Document • Revised Education Program to emphasize and strengthen appropriate conversion

Modification No.	Date Approved	Documents Affected	Overview of Modification
		Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Distributor Enrollment Form • FAQ	and patient counseling information • Updated REMS and Supporting Document to clarify deactivation of a patient PPAF as opposed to the patient record • Updated pharmacy overview documents and
		• Supporting Document • Website Prototype	• FAQ to call out cash claim requirement • Updated TIRF REMS Access website to incorporate items above and link respective Full Prescribing Information and Medication Guides to DailyMed
N/A	N/A	Cash Claim Information Request Response – due 05/30/2014	**Sequence 0010: Response to 5/16/2014 FDA Cash Claim Information Request**
N/A	N/A	DMF Annual Report – due 08/20/2014	**Sequence 0011: DMF Annual Report**
3	December 24, 2014	• REMS • Prescriber Program Overview • Education Program • Knowledge Assessment • Prescriber Enrollment Form • Patient and Caregiver Overview • Independent Outpatient	**Sequence 0012**: Modification proposed to: • Updated REMS materials to eliminate product specific information which does not impact the safe use of TIRF products • Updated REMS materials to reference the TIRF Products webpage on the TIRF REMS Access website • Updated REMS

Modification No.	Date Approved	Documents Affected	Overview of Modification
		Pharmacy Overview • Chain Outpatient Pharmacy Overview • Closed System Outpatient Pharmacy Overview • Inpatient Pharmacy Overview • Independent Outpatient Pharmacy Enrollment Form • Chain Outpatient Pharmacy Enrollment Form • Closed System Outpatient Pharmacy Enrollment Form • Inpatient Pharmacy Enrollment form • Distributor Enrollment Form • FAQ • Supporting Document • Website Prototype	materials to remove reference to deactivating patients shown to have multiple prescribers in an overlapping timeframe • Incorporated revised assessment metrics into the Supporting Document • Revised Education Program to emphasize and strengthen appropriate conversion and patient counseling information • Updated REMS and Supporting Document to clarify deactivation of a patient PPAF as opposed to the patient record • Updated pharmacy overview documents and FAQ to call out cash claim requirement • Updated TIRF REMS Access website to incorporate items above and link respective Full Prescribing Information and Medication Guides to DailyMed • Updated Education Program and Knowledge Assessment to incorporate approved labeling supplement

Modification No.	Date Approved	Documents Affected	Overview of Modification
3	December 24, 2014	Unchanged from Sequence 0012, plus: • Dear Healthcare Provider Letter • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Distributor Letter	**Sequence 0013**: Unchanged from Sequence 0012, plus: • Dear Healthcare Provider Letter • Dear Outpatient Pharmacy Letter • Dear Inpatient Pharmacy Letter • Dear Distributor Letter
N/A	N/A	Assessment Report 4 at 3 years – due 12/28/2014	**Sequence 00014: Assessment Report covering 10/29/2013 to 10/28/2014**
N/A	N/A	BioDelivery Sciences International – Letter of Authorization	**Sequence 0015: BioDelivery Sciences International – Letter of Authorization**
N/A	N/A	Actavis Laboratories Inc. – Letter of Authorization	**Sequence 0016: Actavis Laboratories Inc. – Letter of Authorization**
N/A	N/A	DMF Annual Report – due 08/20/2015	**Sequence 0017: DMF Annual Report**
N/A	N/A	36-Month Assessment – Consolidated Information Requests	**Sequence 0018: Response to FDA 36-Month Assessment Information Requests**
N/A	N/A	Assessment Report 5 at 4 years – due 12/28/2015	**Sequence 00019: Assessment Report covering 10/29/2014 to 10/28/2015**
N/A	N/A	Sentnyl Therapeutics, Inc. – Letter of Authorization	**Sequence 00020: Sentnyl Therapeutics, Inc. – Letter of Authorization**
N/A	N/A	Withdraw Authorization for Galena BioPharma, Inc.	**Sequence 00021: Letter of Authorization/Withdrawn Letter of Authorization**

Modification No.	Date Approved	Documents Affected	Overview of Modification
N/A	N/A	Administrative Change; Change in US Agent	**Sequence 00022: Administrative Change; Change in US Agent**
N/A	N/A	48-Month REMS Supplemental Assessment Report	**Sequence 00023: 48-Month REMS Supplemental Assessment Report**
N/A	N/A	DMF Annual Report – due 08/20/2016	**Sequence 0024: DMF Annual Report**
N/A	N/A	Administrative Change; Change in US Agent	**Sequence 00025: Administrative Change; Change in US Agent**
NA	N/A	Assessment Report 6 at 5 years (60-Month) – due 12/28/2016	**Sequence 0027: 60-Month Assessment Report covering 10/29/2015 to 10/28/2016**
N/A	N/A	48-Month FDA Assessment Report Consolidated Information Requests	**Sequence 0026: TIRG REMS Access Program 48-Month FDA Assessment Report Consolidated Responses to FDA Information Requests**
N/A	N/A	60-Month REMS Supplemental Assessment Report (10 February 2017)	**Sequence 00028: 60-Month REMS Supplemental Assessment Report**

Title:	Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program 60-Month Supplemental Assessment Report
Reporting Timeframe:	29 October 2015 to 28 October 2016
Document Number:	FINAL v 1.0
Product Name:	Transmucosal Immediate-Release Fentanyl
Sponsor:	TIRF REMS Industry Group (TRIG) of Companies: Actavis Laboratories FL, Inc. BioDelivery Sciences International, Inc. Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Insys Therapeutics, Inc. Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc. Sentynl Therapeutics, Inc.
Date	10 February 2017

Confidentiality Statement

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LIST OF ABBREVIATIONS

ANDA	Abbreviated New Drug Application
CI	Confidence Interval
FDA	Food and Drug Administration
HCP	Healthcare Provider
KAB	Knowledge, Attitude, and Behavior
NDA	New Drug Application
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
TIRF	Transmucosal Immediate-Release Fentanyl
TIRF Medicines	Transmucosal Immediate-Release Fentanyl products
TIRF REMS Access program	REMS program for TIRF medicines
TIRF Sponsors	The group of sponsors that are submitting this REMS
TRIG	TIRF REMS Industry Group

1 OVERVIEW

The Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of Transmucosal Immediate-Release Fentanyl (TIRF) medicines. The TIRF REMS Access program was approved by the FDA on 28 December 2011 for ABSTRAL®, ACTIQ®, FENTORA®, LAZANDA®, ONSOLIS®, SUBSYS® and their generic equivalents, if applicable. The TIRF REMS Access program was successfully launched on 12 March 2012, approximately 11 weeks after the REMS approval.

This report completes the 60-Month FDA REMS Assessment Report submission and addresses some of the FDA requested items included in the 48-Month FDA Assessment Report Acknowledgement Letter. The TIRF REMS Industry Group (TRIG) of sponsors who are submitting this 60-Month FDA REMS Supplemental Assessment Report (Actavis Laboratories FL, Inc., BioDelivery Sciences International, Inc., Cephalon, Inc. [a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.], Depomed, Inc., Insys Therapeutics Inc., Mallinckrodt Pharmaceuticals, Mylan, Inc., Par Pharmaceutical, Inc., and Sentynl Therapeutics, Inc.) are herein referred to as TIRF Sponsors. The TIRF REMS Access program is administered by McKesson Specialty Health and RelayHealth. This report has been prepared by United BioSource Corporation.

The TIRF medicines subject to the TIRF REMS are itemized in Table 1 below.

Table 1 TIRF Medicines

Product Name (active ingredient)/formulation
NDA 22510, ABSTRAL (fentanyl) sublingual tablets
NDA 20747, ACTIQ (fentanyl citrate) oral transmucosal lozenge and its authorized generic
NDA 21947, FENTORA (fentanyl buccal tablet)
NDA 22569, LAZANDA (fentanyl) nasal spray
NDA 22266, ONSOLIS (fentanyl) buccal soluble film
NDA 202788, SUBSYS (fentanyl) sublingual spray
ANDA 77312, fentanyl citrate oral transmucosal lozenge
ANDA 78907, fentanyl citrate oral transmucosal lozenge
ANDA 79075, fentanyl buccal tablet

Abbreviations: ANDA=Abbreviated New Drug Application; NDA=New Drug Application

On 21 July 2016, the FDA provided feedback on the patient/caregiver, prescriber, and pharmacist surveys. After careful review of the requested changes, the TRIG notified the FDA that in order to incorporate all changes, an extension for report submission would be required. As proposed by the FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month knowledge, attitude, and behavior (KAB) survey results will be submitted separately from the overall REMS assessment report on or before 17 February 2017. The KAB survey

results presented in this supplemental report cover the same time period as the 60-Month FDA REMS Assessment Report submitted in December 2016.

In addition to the KAB survey results, this supplemental report also addresses items included in the 48-Month FDA Assessment Report Acknowledgement Letter received in November 2016 per the FDA request. These additional requests are summarized in Table 2. Item #2a requested a timeline to further evaluate the findings of the IMS Health Study submitted in the 48-Month FDA Supplemental Assessment Report. However, to evaluate this request a separate letter from the FDA providing additional details of this evaluation is needed. As TRIG Sponsors started receiving this letter on 23 January 2017, this request is not included in this submission. The remaining items from the 48-Month FDA Assessment Report Acknowledgement Letter (#3d, #3e, and #3g) are currently being discussed by the TRIG and no additional response is available at this time.

Table 2 48-Month FDA REMS Assessment Report: the FDA Acknowledgement Letter Requests

Request Number*	FDA Request	Response Location
2a.	Regarding the assessment of opioid tolerance submitted in the 48-Month FDA REMS Assessment Report, approximately 42% of patients prescribed TIRF products were not opioid tolerant. The TRIG needs to further investigate this concerning finding. A timeline for a plan to further evaluate this finding should be submitted with the 17 February 2017, submission of the 60-month REMS assessment survey results. At a minimum, further evaluation of this finding will include product-specific assessments of opioid tolerance that each member sponsor will submit only to their NDA or ANDA. Additional details regarding this evaluation will be communicated in a separate letter.	The timeline for further evaluation of findings from the IMS Study submitted in the 48-Month FDA REMS Supplemental Assessment Report is not included in this submission, as TRIG sponsors just started receiving the second letter from the FDA on 23 January 2017. The evaluation requested by the FDA is currently in progress.
2b.	Regarding the persistency analysis submitted by the TRIG, these data indicate that the number of patients who may be exposed to "inappropriate conversion between TIRF medicines" is not insignificant. Thus these TIRF product switches need to be further assessed by the TRIG and a protocol developed to assess the starting doses of the TIRF products that existing TIRF patients switch to in order to ascertain what proportion of these switches are conducted as per products' labeling. In addition, if the data system used has outcome data, this would be informative as to whether or not any switch marked as "inappropriate" resulted in any adverse sequelae. Limitations of the databases and/or approaches used are to be included in the protocol. Please submit this protocol with the 17 February 2017, submission of the 60-month REMS assessment survey results; if additional time for protocol development is needed, please request an extension.	A protocol for phase II of the Persistency Analysis is included in this submission in Appendix 4.1.

Request Number*	FDA Request	Response Location
3a.	In the FDA's 36-Month FDA Assessment Report Acknowledgement Letter (date 03 August 2015), the TRIG was asked to "Conduct outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons and report the results in your next Assessment Report. We are concerned about potential patient access issues." In the 48-Month FDA REMS Assessment Report, the TRIG responded that: "Based on…analysis, there is no barrier to patient access and further outreach is unwarranted." The TRIG states that 516 prescribers (8.6%) chose to not re-enroll and that these prescribers had an average of no more than 4 prescriptions total over the course of the reporting period. However, the reasons why these prescribers withdrew from the program are unknown as are the reasons why 1,134 prescribers had their enrollment expire this reporting period and remain expired. Additionally, the reasons why 412 pharmacies chose not to re-enroll are not presented. It is therefore important that the TRIG proceed with conducting an "…outreach to a representative sample of those health professionals and pharmacies who did not re-enroll in the TIRF REMS Access Program so as to ascertain their reasons… we are concerned about potential patient access issues." Submit a timeline for the plan to conduct this outreach in the 17 February 2017, submission of the 60-month REMS assessment survey results.	A timeline for outreach to a representative sample of health professionals and pharmacies who did not re-enroll to ascertain their reasons for not re-enrolling is included in this submission (see Section 2.1).
3d.	Regarding the 3 instances where a non-closed system pharmacy dispensed a TIRF product after a TIRF REMS rejection, all 3 reports were brought to the attention of the TRIG only after the pharmacy contacted the REMS. The TRIG should develop a more active mechanism by which to identify and prevent such occurrences.	The TRIG is looking into a more active mechanism to identify and prevent instances where a non-closed system pharmacy dispenses a TIRF product after a TIRF REMS rejection is received.
3e.	Although results for both governmental (Veteran's Health Administration and Department of Defense) and closed-pharmacy systems appear to have improved from the 36-month audit, they continue to be unsatisfactory. The 36-Month FDA Assessment Report Acknowledgement Letter requested that the TRIG "Re-evaluate whether a novel authorization process is warranted or technically feasible at this time for the closed system pharmacies and report your conclusions with your next Assessment Report." The TRIG has issued the following response: "The TRIG has determined that the current prescription authorization volume for closed system pharmacies is less than 1% of all TIRF prescriptions and due to the absence of complaints with the current process, no changes are warranted at this time." An absence of complaints does not necessarily mean that a closed pharmacy system process is functioning optimally.	The TRIG is discussing incorporating an assessment of prescription processing times for prescriptions that do not experience any REMS-related rejections.

Request Number*	FDA Request	Response Location
	These audits are likely one of the best sources of information regarding the performance of these closed-system pharmacies in meeting the REMS requirements. If the TRIG does not favor a novel authorization process for all of the closed-system pharmacies solely due to the poor performance of the governmental entities, the TRIG should propose an outreach to these programs to improve compliance. In addition, the TRIG should be sure to include both governmental entities in the 60-month audit so that their performance in the REMS can continue to be monitored. Lastly, the TRIG presents the process times for prescriptions that have experienced at least one REMS-related rejection. However, data on the overall processing time of a prescription that does not meet with any rejections is unclear. Given that one of the pieces of information solicited during the closed-system audits is "Date and time of each prescription transaction," this is an excellent opportunity for the TRIG to assess prescription processing times for prescriptions that do not experience any REMS-related rejections. The TRIG should add this component to their closed-system audits	
3g.	The TRIG reports a number of instances where prescribers were either unaware of requirements to submit a PPAF or chose not to do so. It is important that the TRIG investigate mechanisms to reinforce to prescribers the necessity of timely completion of PPAFs.	The TRIG will further query non-compliant prescribers to determine more specific reasons of why they were not compliant with the REMS requirements. The TRIG will assess these responses to determine appropriate actions.

Abbreviations: ANDA=Abbreviated New Drug Application; FDA=Food and Drug Administration; PPAF=Patient-Prescriber Agreement From; REMS=Risk Evaluation and Mitigation Strategy; TIRF=Transmucosal Immediate Release Fentanyl; TRIG=TIRF REMS Industry Group

*Numbering is aligned with the numbering of the FDA requests communicated in the 48-Month FDA's Assessment Report Acknowledgement Letter.

2 RESULTS

2.1 Timeline for Outreach to Sample of Health Professionals and Pharmacies to Ascertain Reasons for Not Re-enrolling

In response to the request from the FDA, a timeline has been developed to perform outreach to a representative sample of those health professional and pharmacies that did not re-enroll in the TIRF REMS Access program to ascertain their reasons for not re-enrolling. The TRIG has initiated activities to collect these data and results will be included in the 72-Month FDA REMS Assessment Report.

2.2 Knowledge, Attitude, and Behavior Surveys

Surveys were conducted to assess patients'/caregivers', pharmacists', and prescribers' KAB regarding the safe use of TIRF medicines as described in the educational materials for all stakeholders including the enrollment form (pharmacists and prescribers only), Full Prescribing Information (pharmacists and prescribers only), medication guides (prescribers and patients) for each product, and the Patient-Prescriber Agreement Form (PPAF; prescribers and patients only). The survey protocols describe the administration of the individual surveys that were conducted among patients who are treated with TIRF medicines or their caregivers, prescribers, and pharmacists. The KAB survey reports include summarization of all data collected during the survey (see Appendix 4.2, Appendix 4.3, and Appendix 4.4, respectively, for the patient, pharmacist, and prescriber KAB reports which include the protocol and survey). Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

The questions and statements within the KAB surveys for patients/caregivers, pharmacists, and prescribers were constructed to test the stakeholders' understanding of the key risk messages of the REMS. The TRIG established a desired threshold of 65%. A correct response rate of 65% or greater was considered to represent adequate understanding of each concept or key risk message. The purpose of this threshold was to assist TRIG in tracking and monitoring the data for each key risk message across each wave ultimately providing direction in determining which area(s) would require improvement to ensure the patient/caregiver, pharmacist, and prescriber KAB surveys were meeting the goals of the REMS.

A summary of the patient/caregiver, pharmacy, and prescriber survey data are discussed in Sections 2.2.1, 2.2.2, and, 2.2.3 respectively.

2.2.1 Patient Report

The specific goals of the TIRF medicines patient/caregiver KAB survey were to evaluate the level of knowledge and assess the attitudes and behavior of patients/caregivers regarding TIRF medicines. The focus of the survey included the following: 1) TIRF medicines can cause life-threatening breathing problems that can lead to death, patients should take TIRF medicines only if they are opioid-tolerant, and patients should strictly follow the directions of the healthcare provider (HCP), 2) patients should not switch from a TIRF medicine to another medicine that contains fentanyl without talking to a HCP, 3) patients should not give TIRF medicines to anyone else even if they have the same symptoms, and 4) TIRF medicines should be stored in a

safe place away from children and properly disposed. The survey also included questions about whether patients received, read, and understood the product-specific Medication Guide and the PPAF.

The patient survey launched on 26 September 2016 and closed on 21 November 2016. Patients who were passively enrolled in the TIRF REMS Access program and had received a TIRF medicine in the previous 4 months (120 days) were invited to participate. From the total of 394 patients/caregivers who accessed the survey, 321 (81.5%) respondents met eligibility criteria, and of those who met eligibility criteria, 310 (96.6%) completed the survey, exceeding the target of 300 completed surveys.

Changes to the 60-month KAB survey for patients/caregivers based on the FDA feedback included the addition of 6 survey questions and the revision of 4 survey questions. The change to Question 11 (*TIRF medicines should only be taken by patients who are opioid tolerant*), and the addition of Question 18 Items 18a through 18c (*Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you*) are discussed with the key risk message results below. For questions not included as part of key risk messages, new Questions 37 through 41 showed most respondents indicated someone in the doctor's office told them not to share the TIRF medicines with anyone else, counseled them that accidental exposure to TIRF medicines by a child may be fatal, told them to keep TIRF medicines out of reach of children to prevent accidental exposure, and told them about proper disposal of any unused or partially used TIRF medicines; and over half indicated someone in the doctor's office asked them about the presence of children in their home. In addition, Questions 9, 15, and 16 that ask patients about prescriber activities and were revised to allow pharmacists as a potential source of information, showed most respondents indicated someone in the doctor's office discussed the risks and possible side effects of the prescribed TIRF medicine, that someone in the doctor's office explained how to use the prescribed TIRF medicines, and someone in the doctor's office advised them on the proper storage of the prescribed TIRF medicines.

The overall knowledge score of 84.8 (95% confidence interval [CI]: 83.5 86.0) for the survey indicates most respondents demonstrated understanding of the key risk messages. The average knowledge score for each of the key risk messages was greater than 88 for 5 of the 6 key risk messages and was 70.3 for Key Risk Message 3 (TIRF medicines should be taken exactly as prescribed by the healthcare provider). The lower average knowledge score for Key Risk Message 3 reflected the 3 items (described below) with correct response rates <65%.

Of the 22 questions/items included as part of key risk messages, 16 items had a correct response rate >80%, and 3 items had a correct response rate between 65% and 80%. The remaining 3 items within Key Risk Message 3 had a correct response rate that fell below the desired level of understanding of 65%. These 3 items included 2 items from Question 10: *For which of the following conditions should you use a TIRF medicine?* Correct response rate for Item 10d (*Pain after surgery [*correct response: No]) was 64.2%, and correct response rate for Item 10e (*Long-lasting pain not from cancer, like arthritis joint pain [*correct response: No]) was 39.0%. In addition, the correct response rate for Item 12b (*a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine*) was 39.7%. These items also had a low correct response rate across all patient/caregiver KAB surveys conducted (annual waves from the 12-month through the 60-month survey).

When comparing correct response rates from the 12-month KAB survey through the 60-month KAB survey, knowledge and understanding of the key risk messages has generally remained stable over time, including the items mentioned above that fell below the desired level of understanding of 65% for this wave and have had lower correct response rates for all survey waves. Question 11 had a notably improved correct response rate (nearly 90%) once the question was revised back to the original 36-month survey question for this survey. In addition, over 92% of respondents correctly responded that a side effect of TIRF medicines is the chance of abuse or addiction, that TIRF medicines can be misused by people who abuse medicines or street drugs, and TIRF medicines should be kept in a safe place (new Question 18).

For complete data and results, see Appendix 4.2.

In general, knowledge and understanding of the key risk messages has remained stable over time (Appendix 4.2, Table 21). Patients scored consistently low on 3 of 22 items: that TIRF medicines should not be taken for pain after surgery; that TIRF medicines should not be taken for long-lasting pain not from cancer, like arthritis joint pain; and that a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.

Overall, this 60-month survey shows a high level (greater than or equal to 65% for all but 3 items) of patient understanding of key risk messages based on the REMS goals. The TRIG acknowledges that there is room for improvement around patient knowledge related to conditions for use of a TIRF medicine and stopping a TIRF medicine when stopping their around-the-clock opioid pain medicine.

2.2.2 Pharmacy Report

The specific goals of the TIRF medicines pharmacist KAB survey were to assess pharmacist understanding of the risks associated with TIRF medicine use, the specific indications for treatment with TIRF medicines, and that TIRF medicines are contraindicated in opioid non-tolerant patients. The survey also included questions about whether pharmacists received, read, understood, and used the product-specific educational materials, and included questions about compliance with the REMS requirements.

The pharmacy survey launched on 26 September 2016 and closed on 13 December 2016. Subjects to complete the pharmacist survey were recruited from pharmacies enrolled in the TIRF REMS Access program as of 02 September 2016 who had dispensed a TIRF medicine in the last 6 months. Out of the total of 561 pharmacists who accessed the survey, 333 (59.4%) pharmacists met eligibility criteria, and of those who met eligibility criteria, 318 (95.5%) completed the survey, exceeding the target of 300 completed surveys.

Changes to the 60-month KAB survey for pharmacists based on the FDA feedback included the addition of 3 survey questions and a change to the recruitment strategy to limit the survey to pharmacists who had dispensed TIRF medicines in the past 6 months and attempt to recruit more closed system pharmacists and non-supervisory pharmacists. The addition of Question 12 (*TIRF medicines should only be taken by patients who are opioid tolerant [True/False]*) and Question 13 (*Which of the following risks are associated with the use of TIRF medicines?[True/False for each of the following: misuse, abuse, addiction, overdose, hypothyroidism, and infection]*) is discussed below with the key risk message results. Question 15 (*How frequently do you perform the following activities when dispensing TIRF*

medicines?) included 3 response items about pharmacist-reported activity. For each item, most respondents selected *Always* or *Only with the first prescription*; and few respondents selected *Sometimes*, *Never*, or *I don't know*. Changes to recruitment efforts included a revised invitation letter addressed to the "pharmacist-in-charge" including 3 letters with unique codes; the pharmacist-in-charge was asked to distribute these letters to non-supervisory staff involved in the dispensing of TIRF medicines. This strategy was successful, with 74.8% of respondents indicating they were not the pharmacist-in-charge.

The overall knowledge score of 85.7 (95% CI: 84.4 87.0) for the survey indicates most respondents demonstrated understanding of the key risk messages. The average knowledge score was ≥83.8 for 3 of the 4 key risk messages and was 75.4 for Key Risk Message 2 (TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older [16 years of age and older for Actiq® brand and generic equivalents] who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain); the lower average knowledge score for Key Risk Message 2 reflected 3 linked questions/items (described below) with correct response rates <65%. Of the 36 questions/items included as part of key risk messages, 27 items of the key risk messages had a correct response rate >80%, and 6 items had correct response rates from 65.1% to 79.6%. Three questions/items of Key Risk Message 2 had a correct response rate below the desired threshold of 65% (Items 6a, 6c, and 9e). The correct response rate for Item 6a (*According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time*) was 61.9%. The correct response rate for Item 6c (*A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine*) was 41.2%. This item was added to the 48-month survey based on feedback provided by the FDA in the 24-month and the 36-Month FDA Assessment Report Acknowledgement Letters. The correct response rate for Item 9e (*Chronic non-cancer pain is not an indication for which TIRF medicines can be prescribed*) was 43.4% for this 60-month survey. Item 9e has also had a low correct response rate across all previous pharmacist KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys). The survey score for Item 9e may indicate that some respondents are dispensing TIRF medicines for non-cancer associated indications.

When comparing correct response rates from the 12-month KAB survey through the 60-month KAB survey, no trend was evident for this 60-month survey in knowledge and understanding of the key risk messages. As described above, 2 new survey questions (Question 12 and Question 13 [6 separate response items]) were added as part of key risk messages for the 60-month survey. Correct response rates for the new questions/items were ≥95.6% for Question 12 and 4 items of Question 13 and 84.0%-89.3% for the 2 false items of Question 13 (hypothyroidism and infection).

For complete data and results, see Appendix 4.3.

In general, there is an overall trend over time toward maintaining, or increasing, pharmacist knowledge and understanding of the key risk messages (Appendix 4.3, Table 24). Three exceptions where pharmacists scored low included understanding that a cancer patient may not start a TIRF medicine and an around-the-clock opioid at the same time, that a patient must stop

taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine, and that TIRF medicines are not indicated for chronic non-cancer pain, which may indicate that some respondents are dispensing TIRF medicines for non-cancer associated indications.

Overall, this 60-month survey shows a high level (≥65% for all but 3 items) of pharmacist understanding of key risk messages based on the REMS goals. TRIG acknowledges that there is room for improvement around pharmacist knowledge related to indications for TIRF medicines and safe use of TIRF medicines by patients also using around-the-clock opioid pain medicines.

2.2.3 Prescriber Report

The specific goals of the TIRF medicines prescriber KAB survey were to assess prescribers' understanding of the risks associated with TIRF medicine use, the selection of appropriate patients for treatment with TIRF medicines, preventing inappropriate conversion between TIRF medicines, and ensuring safe use of TIRF medicines while preventing exposure to children and others for whom TIRF medicines were not prescribed. The survey also included questions about whether prescribers received, read, understood, and used the product-specific educational materials, and included questions about compliance with the REMS requirements.

The prescriber survey launched on 26 September 2016 and closed on 20 December 2016. Subjects were recruited from a random sample of prescribers who were enrolled in the TIRF REMS Access program and who had prescribed a TIRF medicine in the last 6 months. From the total of 524 respondents who accessed the survey, 313 prescribers (59.7%) met eligibility criteria, and of those who met eligibility criteria, 294 (93.9%) completed the survey.

Changes to the 60-month KAB survey for prescribers based on the FDA feedback included the addition of 3 survey questions, the revision of 1 survey question, and a change to the recruitment strategy to limit the survey to prescribers who have prescribed TIRF medicines in the past 6 months. The change to Question 9 (*Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved*), and the addition of Question 21 (*TIRF medicines should only be taken by patients who are opioid tolerant*) and Question 22 (*Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements*) are discussed with the key risk message results below. Question 32 (*How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know)* included 3 response items about prescriber reported activity. For each item, most prescribers selected *Always* or *Only with the first prescription*; and few prescribers selected *Sometimes*, *Never*, or *I don't know*.

The overall knowledge score of 89.1 (95% CI: 88.0 90.2) for the survey indicates a high percentage of respondents demonstrated understanding of the key risk messages. The average knowledge score was greater than 86 for all 4 key risk messages. Of the 38 questions/items included as part of key risk messages, 28 questions/items had a correct response rate >80% and 10 questions/items had a correct response rate between 65% and 80%. None of the questions/items had a correct response rate that fell below the desired level of understanding of 65%.

When comparing correct response rates from the 12-month KAB survey through the 60-month KAB survey, knowledge and understanding of the key risk message questions has generally remained stable or improved over time. Correct response rates for 4 of the 5 items of the revised Question 9 were similar compared to the 48-month survey; however, the item pertaining to a response of 'chronic non-cancer pain' had a notably improved correct response rate. In addition, the 2 new survey questions (Question 21 and Question 22 [6 separate response items]) that were added as part of key risk messages for the 60-month survey based on the FDA feedback had a correct response rate of >96% for 5 questions/items and >78% for 2 items.

For complete data and results, see Appendix 4.4.

In general, there is an overall trend over time toward maintenance or improvement in prescriber knowledge and understanding of the key risk messages (Appendix 4.4, Table 26). The 60-month survey shows a high level (correct response rate greater than or equal to 65%) of prescriber understanding of key risk messages based on the REMS goals. However, TRIG acknowledges that there is room for improvement around prescriber knowledge related to conditions for use of a TIRF medicine, TIRF medicine use when stopping their around-the-clock opioid pain medicine, conversion of TIRF medicines, and definition of opioid tolerant.

3 DISCUSSION

As part of the evaluation of the TIRF REMS Access program, the FDA requested that a timeline be developed to perform outreach to health professionals and pharmacies to ascertain reasons for not re-enrolling in the program. The TRIG has initiated activities to collect these data and results will be provided in the 72-Month FDA REMS Assessment Report.

In addition, a protocol for phase II of the Persistency Analysis presented in the 48-Month FDA REMS Supplemental Assessment Report is included in Appendix 4.1.

The consistently high level of stakeholder understanding of key risk messages in the 60-month KAB surveys indicates that the goals of the TIRF REMS are being partially met with existing tools. The TRIG acknowledges that there are areas for improvement of prescriber, pharmacist, and patient knowledge and is in the process of evaluating changes to the existing REMS tools. Specific areas of improvement include conditions for use of a TIRF medicine, TIRF medicine use when stopping an around-the-clock opioid pain medicine, conversion between TIRF medicines, and the definition of opioid tolerant.

CONCLUSION

Based on the KAB survey data provided in this 60-Month FDA REMS Supplemental Assessment Report, the TRIG concludes that there is no indication that the REMS is not meeting its goals. However, the TRIG acknowledges that the data are limited and that the FDA has requested further evaluation, as described in the 48-Month FDA Assessment Report Acknowledgement Letter, to determine whether the REMS is meeting its goals. The TRIG looks forward to discussing with the FDA additional data to be used to evaluate and improve upon the REMS.

4 APPENDICES

4.1 Persistency Analysis Phase II Protocol

Title:	Conversion between Transmucosal Immediate-Release Fentanyl (TIRF) Medicines Analysis Protocol
Document Number:	Final 1.0
Product Name:	Transmucosal Immediate-Release Fentanyl
Sponsor:	TIRF REMS Industry Group (TRIG) of Companies: Actavis Laboratories FL, Inc. BioDelivery Sciences International, Inc. Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Insys Therapeutics Inc. Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc. Sentynl Therapeutics, Inc.

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1. GLOSSARY

Change Regimen	A change in regimen is defined as having a prescription filled for a TIRF medicine other than what composes the patient's current TIRF regimen (excluding generic equivalents). For example, if the index TIRF regimen consists of TIRF A and TIRF B and then TIRF C is later added, this new TIRF regimen consisting of three TIRF medicines is considered the "change regimen."
Concurrent Therapy	A patient can be prescribed more than one TIRF medicine. Concurrent therapy is defined as having a prescription filled for a TIRF medicine other than the index TIRF (excluding generic equivalents) prior to a gap occurring with the index TIRF, and a subsequent prescription for the index TIRF is filled to confirm its continued use. The same logic applies to concurrent therapy with a second regimen.
Gap in Therapy	A *permissible gap* in therapy is synonymous with a medicine's grace period, both meaning that the patient has a refill for the TIRF medicine or a fill for another TIRF medicine prior to the end of the initial TIRF medicine's grace period. There is no limit to the number of permissible gaps a patient can have during the study observation period. An *impermissible gap* in therapy is synonymous with a treatment discontinuation. If the patient later refills the same TIRF medicine after a treatment discontinuation, the TIRF medicine will be defined as having been re-initiated.
Grace Period	Based on results of the data exploration phase, the grace period for the persistency analysis is defined as 2.5 times the days' supply of medication dispensed.
Index TIRF Regimen	The first prescription filled for a TIRF medicine during the study observation period is the index TIRF medicine. The index TIRF regimen may consist of one or more individual TIRF medicines (see "Concurrent Therapy").
Patient Observation Period	The patient-level observation period for the persistency analysis extends from the date of the individual's index TIRF medicine fill until October 28, 2016, the pre-defined data cut-off date (see also "Study Observation Period").
Persistence	A patient is considered persistent with their TIRF regimen as long as the grace period for the regimen is not exceeded.
Study Observation Period	The study observation period for the persistency analysis is between March 12, 2012 and October 28, 2016.
Switch Regimen	A switch from a TIRF regimen is defined as having a prescription filled for a TIRF medicine other than the current TIRF regimen (excluding generic equivalents). A switch is only confirmed if the current TIRF regimen is not refilled. If the current TIRF regimen is refilled within its grace period, the patient is defined as having concurrent therapy, or if the grace period for the current TIRF has been exceeded, the regimen is considered discontinued and then re-initiated.
TIRF Regimen	TIRF regimens generally consist of only one TIRF medicine at a time. However, if "concurrent therapy" is observed, the TIRF regimen will include all individual TIRF medicines that make up the concurrent therapy regimen. The first TIRF regimen observed in the dataset is defined as the *index TIRF regimen*. Future TIRF regimens are described as second, third, fourth TIRF regimens, as appropriate.

Treatment Discontinuation	If the time between refills of a TIRF medicine exceeds the grace period, the TIRF medicine is considered discontinued.
Treatment Re-initiation	If a prescription is filled for a TIRF medicine that has previously been discontinued (see "Treatment Discontinuation"), the TIRF medicine is considered re-initiated.

2. BACKGROUND & OBJECTIVES

Following review of the 36-month Transmucosal Immediate-Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Assessment Report, the US Food and Drug Administration (FDA) requested that as one of the objectives of the REMS, a persistency analysis be conducted in order to document how many patients are potentially at risk for inappropriate conversion between TIRF medicines. In response to this request, a persistency analysis was designed and conducted, and the results were submitted to the FDA with the 48-month Assessment Report. Following review of the results of the persistency analysis,[1] the FDA indicated that,

> *"It is not possible to determine if the second objective (preventing inappropriate conversion between TIRF medicines) is being met. Though no instances of inappropriate conversions were submitted as a spontaneous report, the persistency analysis provided indicates that the number of patients who may be exposed to inappropriate conversion between TIRF medicines may be as high as 17.1-20.5% of patients receiving TIRF medicines. Further assessment of these findings is also warranted."*

The FDA further commented that,

> *"Regarding the persistency analysis submitted by the TRIG, these data indicate that the number of patients who may be exposed to 'inappropriate conversion between TIRF medicines' is not insignificant. Thus these TIRF product switches need to be further assessed by the TRIG and a protocol developed to assess the starting doses of the TIRF products that existing TIRF patients switch to in order to ascertain what proportion of these switches are conducted as per products' labeling. In addition, if the data system used has outcome data, this would be informative as to whether or not any switch marked as "inappropriate" resulted in any adverse sequelae. Limitations of the databases and/or approaches used are to be included in the protocol. Please submit this protocol with the February 17, 2017, submission of the 60 month REMS assessment survey results; if additional time for protocol development is needed, please request an extension."*

This protocol describes the proposed analysis approach to assess the occurrences of inappropriate conversion between TIRF medicines in patients who had a switch in their regimens.

3. DATA SOURCE

The analysis of appropriateness of conversion between TIRF medicines will use the TIRF REMS database (with one additional year of data) to maintain consistency with the above-referenced persistency analysis. The TIRF REMS database consists of complete outpatient TIRF prescription activity that has been processed through the 'switch,' including all outpatient

[1] Acknowledgement letter initially received November 10, 2016.

pharmacy types (independent and chain sub-stores), because all prescribers who prescribe and pharmacies that dispense TIRF medicines must enroll in the TIRF REMS Access program.

All prescription data collected within the TIRF REMS database from March 12, 2012 (launch of the REMS) until October 28, 2016[2] will be used in the analysis of appropriateness of conversion. McKesson/RelayHealth will deliver the dataset with anonymized data for all patients, excluding rejected transactions and reversed claims.

3.1. DATA VARIABLES

The following data elements are provided for each paid claim of TIRF medicine:

- Prescription number
- Unique patient ID
- Date of birth
- Prescription process date
- Product name (brand or generic, as dispensed)
- National drug code (NDC)
- Product strength
- Quantity dispensed
- Days' supply[3]

3.2. TIRF MEDICINES

TIRF medicines will be randomly assigned letter codes in presentations of data. The following TIRF medicines (and their generic equivalents) are included in the product conversion analysis:

- Abstral®
- Actiq® (fentanyl citrate lozenge)
- Fentora®
- Lazanda®
- Subsys®

4. ASSESSMENT OF CONVERSION

4.1. PATIENT ELIGIBILITY FOR INCLUSION

The study observation period, as defined by the data cutoff date for the 60-month REMS Assessment report, is between March 12, 2012, and October 28, 2016. Each patient's observation window within this period is determined by his/her first and last recorded prescription fill dates. Patients who fulfilled the inclusion and none of the exclusion criteria below will be included in the analysis set:

[2] October 28, 2016 was used as the cut-off date as this corresponds to the 60-month FDA Assessment Report.

[3] As recorded in the TIRF REMS database; may not equal actual days' supply since TIRF medicines are commonly used on an 'as needed' basis and pharmacists ascribe the days' supply amount at the time of medication fill.

Inclusion

- All patients who filled at least one TIRF medicine prescription during the study observation period

Exclusion

- Filled a one-time prescription
- Exposed to only one single TIRF medicine (including its generic equivalents)

4.2. STUDY DEFINITIONS & ANALYSIS ASSUMPTIONS

The analysis of the appropriateness of conversion is a continuation of the persistency analysis; therefore, it maintains the same parameter definitions (please refer to the glossary section). This section reviews some concepts from the persistency analysis that are relevant and describes new parameters that are specific to the present analysis.

The first TIRF medicine(s) filled by a patient during the observation period constitutes the ***index regimen*** for that patient. TIRF regimens generally consist of only one TIRF medicine at a time. However, if "concurrent therapy" is observed, the TIRF regimen will include all individual TIRF medicines that make up the concurrent therapy. Specifically, ***concurrent therapy*** occurs when a prescription is filled for a TIRF medicine that is not in the current regimen (excluding generic equivalents) while the current regimen is being filled continuously.

A ***gap in therapy*** occurs when a prescription is not filled before or on the day its days' supply expires plus a grace period[4] of 2.5 times of its days' supply. A ***switch in therapy*** occurs when the current regimen [or part of it] is discontinued and the patient fills a prescription for a different TIRF medicine(s). When a patient fills a prescription for a TIRF medicine that has previously been discontinued, the patients is ***re-initiating*** the medicine.

4.2.1. STARTING DOSE

For each patient in the REMS claims database, the first prescription of a TIRF medicine that appears in the prescription sequence is its first fill and therefore specifies the starting dose of that TIRF medicine.

4.2.2. CONVERSION

A ***conversion*** will be considered in either of the following scenarios of a switch in therapy:

Scenario 1: A monotherapy regimen was discontinued and then switched to another monotherapy regimen (excluding generic equivalents) (Figure 1).

Scenario 2: One or more TIRF medicines in a concurrent therapy regimen were discontinued, and one or more TIRF medicines were added to make up a new regimen (Figure 2).

[4] For the purpose of this persistency analysis, a grace period of 2.5 times of the days' supply of the filled regimen was derived based on the preliminary data exploration of the REMS claims data.

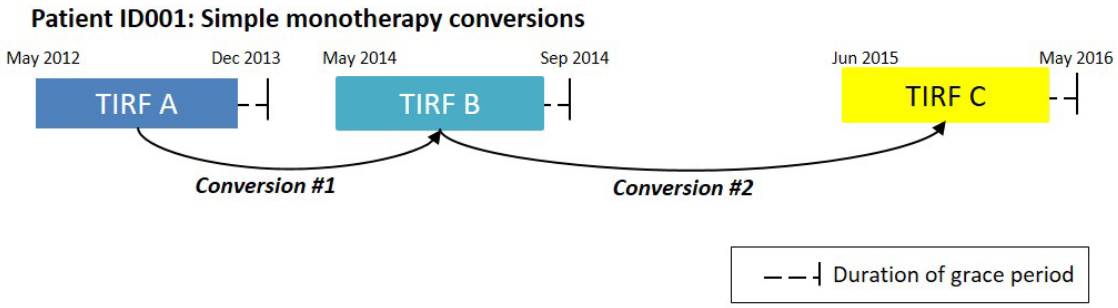


Figure 1. Case Demonstration of Scenario 1: Simple Conversions

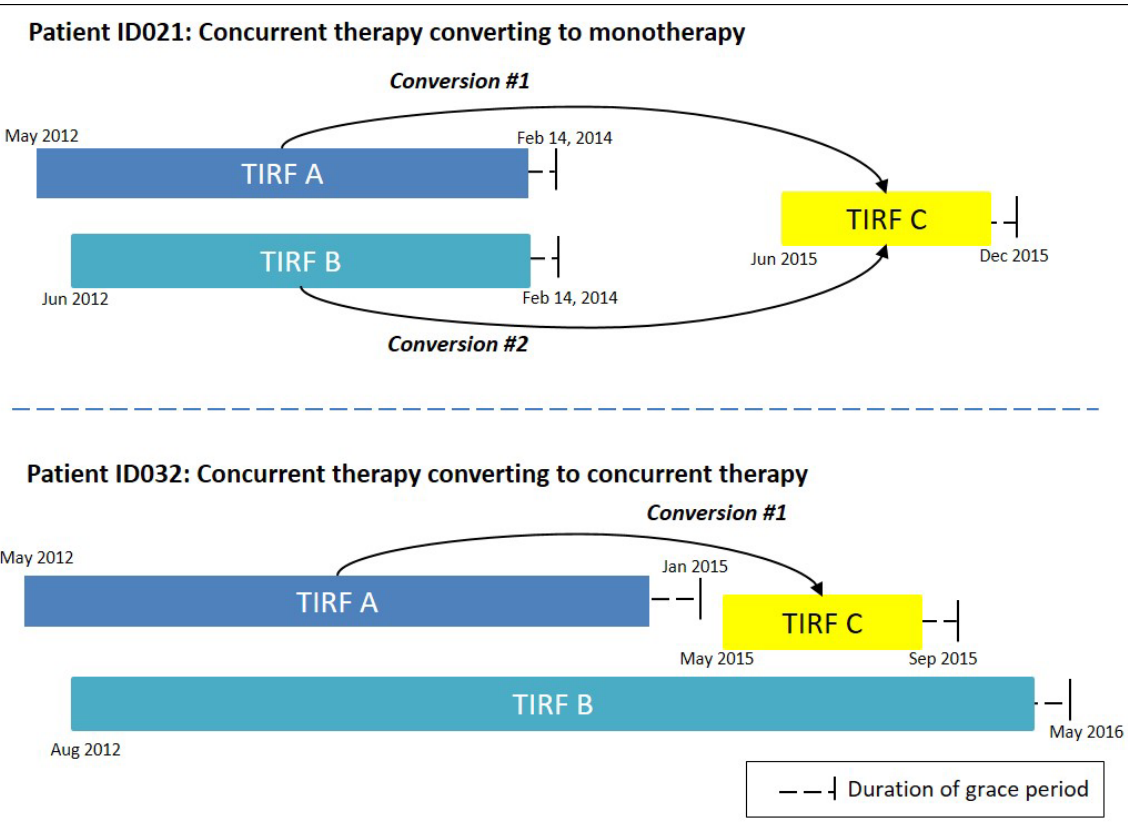


Figure 2. Case Demonstrations of Scenario 2: Concurrent Therapy Conversions

Figures 1 and 2 are simplified schematics where continuously filled prescriptions of TIRF medicines are represented by long solid color bars, which include grace periods between fills. The grace period of the most recent fill of a TIRF medicine is represented by a dashed horizontal line and a vertical line (i.e., vertical line denotes end date of grace period).

Figure 1 describes the simplest type of conversion, which is from one monotherapy to another, with no overlaps in the grace periods of the monotherapies. In the case of Patient ID001, she started with 'A', then converted to 'B' and then converted to 'C'.

The more complicated cases involving concurrent therapies are demonstrated in Figure 2. Patient ID021 converted from a concurrent therapy ('A+B') to a monotherapy ('C' only). However, since the grace periods of 'A' and 'B' ended on the same date, without prescribing instruction, the sequence of consumption of these medications cannot be determined, conversion to 'C' will be checked against both 'A' and 'B' (i.e., 'A to C' and 'B to C'). On the other hand, Patient ID0032 started with concurrent therapy ('A+B') and then switched to ('B+C'). In this case, only one conversion will be considered, which is 'A to C', because B continued to be filled.

Demonstrations in Figure 2 also showed that ***conversion*** will NOT be considered within a concurrent therapy (i.e., for both sample patients, 'A to B' is not considered a conversion, whether the two medicines were filled on the same day or in sequence, as long as their grace periods overlap and the definition of concurrent therapy is satisfied).

In addition, conversion will NOT be considered for re-initiations of TIRF monotherapy, as it is unknown if during gaps in therapy the patient had-received any TIRF medicine at an inpatient setting or if the patient had medication remaining from the first time period. However, the re-initiation of a TIRF medicine that was discontinued as part of a concurrent therapy will be considered for conversion on a regimen basis. Additional case examples illustrating more elaborated scenarios are provided in Appendix I.

4.2.3. APPROPRIATENESS OF CONVERSION

For each eligible conversion, the appropriateness of the [initiating] dose of the new TIRF medicine will be determined based on recommendations stated in the labels of the TIRF medicines (Appendix II). A dose conversion is deemed ***inappropriate*** when the starting dose of the newly initiated TIRF medicine was higher than recommended in its product label.

5. STATISTICAL ANALYSIS

5.1. ANALYSIS OUTCOMES

Characteristics of patients enrolled in the REMS during the study observation period will be summarized to describe the cohort. The primary outcomes of the analysis are the total number of inappropriate conversions that had occurred during the study observation period and the total number of patients who had at least one occurrence of inappropriate conversion. In addition, the average number of different TIRF products used per patient and total number of conversions assessed for the observation period will also be calculated. Moreover, the conversion dose of a TIRF medicine will be compared against its own starting dose where applicable. In instances where the conversion prescription [dose] is the initiating prescription [starting dose], then no comparison can be made. This occurrence will be reported as a percentage of all product conversions.

5.2. STATISTICAL METHODS

Unless otherwise stated in the statistical analysis plan (SAP), descriptive statistics will be presented and will include the mean, standard deviation, median, and minimum and maximum values for continuous variables, as well as counts and percentages for categorical variables. To take into account the differences of number of patients at risk of inappropriate conversion over

time, four mutually-exclusive patient cohorts will be created based on duration of follow-up from the time of initiating the index TIRF:

1) Up to 12 months of follow-up
2) Up to 24 months of follow-up
3) Up to 36 months of follow-up
4) Up to 48 months of follow-up

As in the persistency analysis, TIRF medicines will be randomly assigned letter codes in presentations of the assessment results for the appropriateness of conversion to avoid identification of individual products.

6. STUDY LIMITATIONS

The TIRF REMS database only contains prescription claims data; no prescribing or medical information is available to inform how the TIRF medicines were instructed to be taken (e.g., in terms of multiproduct prescriptions, it is not known whether the prescriber had instructed that the patient take the medicines in a certain sequence and at what frequency). This limitation leads to the assumption that TIRF medicines were taken in the sequence as they were filled.

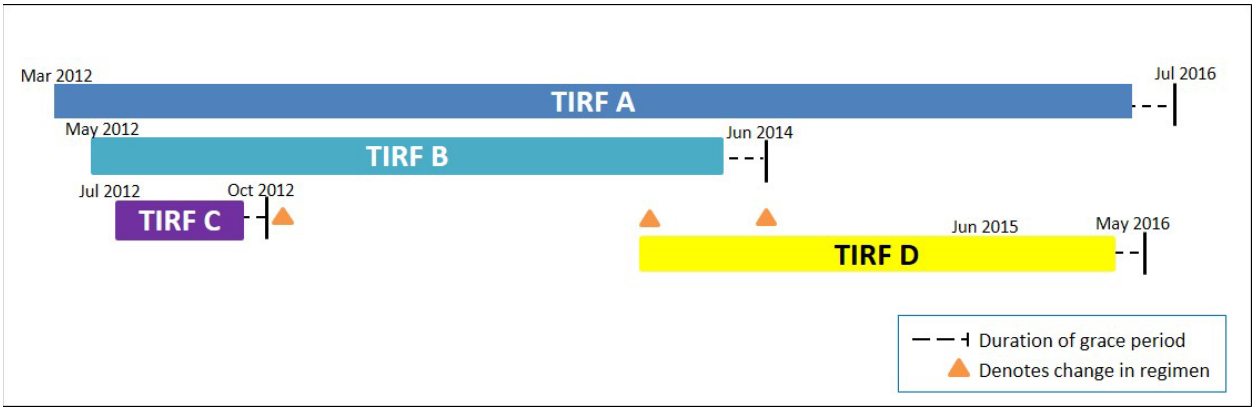
Also, the REMS database only contains outpatient pharmacy claims data, and only data from the beginning of REMS program is available for analysis. Although the first identified TIRF claim is defined as the index claim in our analysis, patients may have had prior TIRF prescriptions. Therefore, the appropriateness of the dose of the index TIRF regimen cannot be assessed, for it is unknown whether the patient was converting from another TIRF medicine. Moreover, a gap in therapy might be explained by a hospitalization, but the fact of hospitalization is unknown. A patient could have initiated the index TIRF regimen while in the hospital and was titrated up as an outpatient.

In addition, the FDA specifically requested this analysis, "*...assess the starting doses of the TIRF products that existing TIRF patients switch to in order to ascertain what proportion of these switches are conducted as per products' labeling."* Therefore, in this context, in concurrent therapies, the dose of newly initiated TIRF medicines will not be considered as a conversion, because the medicines in the current regimen were filled continuously, and there was no 'switch' in therapy. That is, a TIRF medicine was added and was not a switch.

As was in the previous persistency analysis, a regimen's grace period is calculated using the days' supply. While this information is provided by the pharmacist at the time of medication fill, and the quantity for this variable in the dataset corresponds to the adjudicated claim, it does not necessarily correspond to how many days the patient will or is expected to take the TIRF medicines. The TIRF medicines are to be taken on an 'as needed' basis.

APPENDIX I. CASE DEMONSTRATIONS

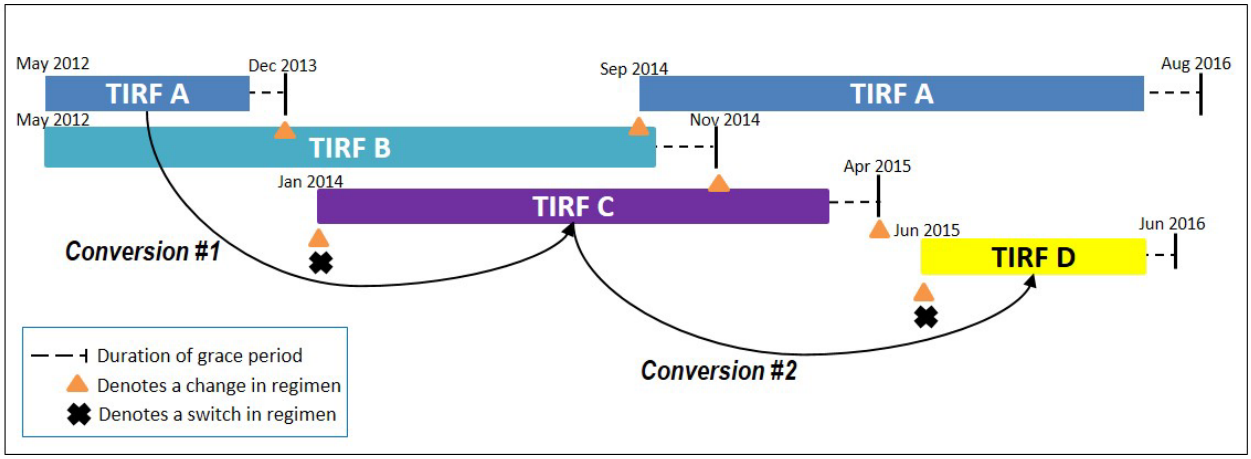
Case #1



Note: This is a simplified schematic where continuously filled prescriptions of TIRF medicines are represented by long solid color bars, which include grace periods between fills. The grace period of the most recent fill of a TIRF medicine is represented by a dashed horizontal line and a vertical line (i.e., vertical line denotes the end date of grace period).

- **Regimen sequence**
  - Index regimen A + B + C
  - Second regimen A + B
  - Third regimen A + B + D
  - Fourth regimen A + D
- **Number of conversion** 0
- **Notes**
  - There is no conversion in this patient's regimen sequence, because the patient initiated concurrent therapy as her index regimen, and 'D' was initiated as the last filled TIRF of concurrent therapy in the 3rd regimen with no TIRF medicine being discontinued from the 2nd regimen.
  - Finally, 'B' was dropped from the 3rd regimen; 'A' and 'D' remained as the 4th regimen with no new TIRF medicine added.

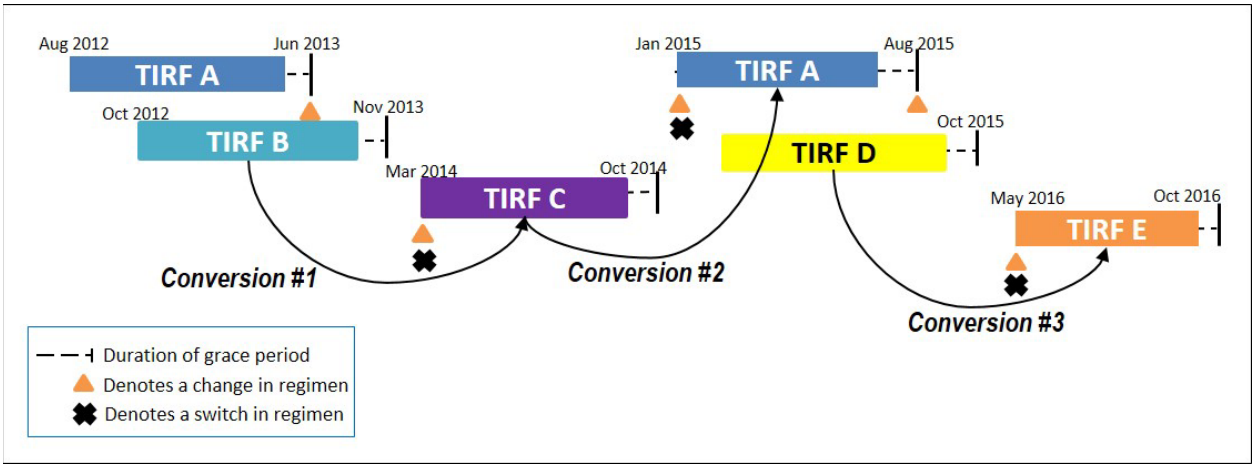
Case #2



Note: This is a simplified schematic where continuously filled prescriptions of TIRF medicines are represented by long solid color bars, which include grace periods between fills. The grace period of the most recent fill of a TIRF medicine is represented by a dashed horizontal line and a vertical line (i.e., vertical line denotes the end date of grace period).

- **Regimen sequence**
  - Index regimen A + B
  - Second regimen B + C
  - Third regimen B + C + A
  - Fourth regimen A + C
  - Fifth regimen A + D
- **Number of Conversion** 2
- **Conversion assessment**
  1. Conversion from 'A' (600 mcg) to 'C' (200 mcg) deemed appropriate, started 'C' at 200 mcg as recommended by label
  2. Conversion from 'C' (800 mcg) to 'D' (800 mcg) deemed inappropriate, started 'D' at 400 mcg instead of 100 mcg, inappropriate mcg per mcg basis conversion
  - 1 out of 2 conversions for this patient was deemed inappropriate
- **Notes**
  - 'C' in 2nd regimen was replacing 'A' in the index regimen; this was considered as a conversion.
  - 'A' was re-initiated as the last TIRF filled for the 3rd regimen as an add-on to the concurrent therapy in the 2nd regimen, thus not considered as a conversion, because no TIRF was discontinued from 2nd regimen.
  - 'B' was discontinued from the 3rd regimen, 'A' and 'C' remained in the 4th regimen.
  - In the 5th regimen, 'D' was added to 'A' to replace 'C'; conversion to 'D' was considered against 'C'.

Case #3



Note: This is a simplified schematic where continuously filled prescriptions of TIRF medicines are represented by long solid color bars, which include grace periods between fills. The grace period of the most recent fill of a TIRF medicine is represented by a dashed horizontal line and a vertical line (i.e., vertical line denotes the end date of grace period).

- **Regimen sequence**
  - Index regimen A + B
  - Second regimen B
  - Third regimen C
  - Fourth regimen A + D
  - Fifth regimen D
  - Sixth regimen E
- **Number of Conversion** 3
- **Conversion assessment**
  1. Conversion from 'B' (400 mcg) to 'C' (100 mcg) deemed appropriate, started 'C' at 100 mcg as recommended by label
  2. Conversion from 'C' (400 mcg) to 'A' (200 mcg) deemed appropriate, started 'A' at 200mcg as recommended by label
  3. Conversion from 'D' (400 mcg) to 'E' (400 mcg) deemed inappropriate, started 'E' at 400 mcg instead of 100 mcg as recommended by label; inappropriate mcg per mcg basis conversion
  - 1 out of 3 conversions for this patient was deemed inappropriate
- **Notes**
  - 'A' and 'B' were both discontinued from the index regimen and 'B' alone made up the 2nd regimen.
  - 'B' monotherapy was converted to 'C' monotherapy in the 3rd regimen.
  - 'A' was re-initiated as the first filled TIRF of the new switched 4th regimen; conversion was considered against 'C'.
  - 'A' was discontinued from the 4th regimen, and 'D' remained to be the 5th regimen.
  - 'D' monotherapy was converted to 'E' monotherapy in the 6th regimen.

APPENDIX II. TIRF PRODUCT LABELS

<table>
<tr><th colspan="2">LABEL CONVERSION INFORMATION</th></tr>
<tr><th>PRODUCT</th><th>CONVERSION SWITCHES BETWEEN TIRF PRODUCTS</th></tr>
<tr><td>ABSTRAL®</td><td>

Begin titration of all patients with an initial dose of Abstral of 100 mcg.
Due to differences in the pharmacokinetic properties and individual variability, even patients switching from other fentanyl containing products to ABSTRAL must start with the 100 mcg dose. However, for patients converting from Actiq, see Table 1: Initial Dosing Recommendations for Patients on ACTIQ.
Abstral is not equivalent on a mcg per mcg basis with all other fentanyl products, therefore, do not switch patients on a mcg per mcg basis from any other fentanyl product.

Conversion from Actiq
The initial dose of Abstral is always 100 mcg with the only exception being patients already using Actiq.
<ol type="a">
For patients being converted from Actiq, prescribers must use the Initial Dosing Recommendations for Patients on Actiq. See Table 1 for initial dosing recommendations. Patients must be instructed to stop the use of Actiq and dispose of any remaining units.
For patients converting from Actiq doses of 200 mcg and 400 mcg, initiate titration with 100 mcg and 200 mcg of Abstral, respectively and proceed using multiples of this strength.
For patients converting from Actiq doses of 600 and 800 mcg, initiate titration with 200 mcg and 200 mcg Abstral, respectively and proceed using multiples of this strength.
For patients converting from Actiq doses of 1200 and 1600 mcg, initiate titration with 200 mcg and 400 mcg Abstral, respectively and proceed using multiples of this strength.

Table 1: Initial Dosing Recommendations for Patients on Actiq
<table>
<tr><th>Current Actiq Dose (mcg)</th><th>Initial Abstral Dose (mcg)</th></tr>
<tr><td>200</td><td>100 mcg</td></tr>
<tr><td>400</td><td>200 mcg</td></tr>
<tr><td>600</td><td>200 mcg</td></tr>
<tr><td>800</td><td>200 mcg</td></tr>
<tr><td>1200</td><td>200 mcg</td></tr>
<tr><td>1600</td><td>400 mcg</td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th colspan="2">LABEL CONVERSION INFORMATION</th></tr>
<tr><th>PRODUCT</th><th>CONVERSION SWITCHES BETWEEN TIRF PRODUCTS</th></tr>
<tr><td>ACTIQ®</td><td>

When prescribing, DO NOT convert a patient to Actiq from any other fentanyl product on a mcg per mcg basis as Actiq and other fentanyl products are not equivalent on a mcg per mcg basis.
There are no safe conversion directions available for patients on any other fentanyl products. (This includes oral, transdermal, or parenteral formulations of fentanyl). Therefore, for opioid tolerant patients, the initial dose of Actiq should always be 200 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects.

</td></tr>
<tr><td>FENTORA®</td><td>

Fentora is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products.
There are no conversion directions available for patients on any other fentanyl products other than Actiq. (This includes oral, transdermal, or parenteral formulations of fentanyl).
All patients should be titrated from the 100 mcg dose.

Conversion from Actiq
The initial dose of Fentora is always 100 mcg with the only exception being patients already using Actiq.
a. For patients being converted from Actiq, prescribers must use the Initial Dosing Recommendations for Patient on Actiq table below (Table 1). The doses of Fentora in this table are starting doses and not intended to represent equianalgesic doses to Actiq. Patients must be instructed to stop the use of Actiq and dispose any remaining units.
Table 1: Initial Dosing Recommendations for Patients on Actiq
<table>
<tr><th>Current Actiq Dose (mcg)</th><th>Initial Fentora Dose (mcg)*</th></tr>
<tr><td>200</td><td>100 mcg tablet</td></tr>
<tr><td>400</td><td>100 mcg tablet</td></tr>
<tr><td>600</td><td>200 mcg tablet</td></tr>
<tr><td>800</td><td>200 mcg tablet</td></tr>
<tr><td>1200</td><td>2 x 200 mcg tablets</td></tr>
<tr><td>1600</td><td>2 x 200 mcg tablets</td></tr>
</table>
* From this initial dose, titrate patient to effective dose.
</td></tr>
</table>

LABEL CONVERSION INFORMATION	
PRODUCT	**CONVERSION SWITCHES BETWEEN TIRF PRODUCTS**
	b. For patients converting from Actiq doses equal to or greater than 600 mcg, titration should be initiated with the 200 mcg Fentora tablet and should proceed using multiples of this tablet strength. All Other Patients • The initial dose of Fentora is 100 mcg.
LAZANDA®	• Lazanda is NOT equivalent to other fentanyl products used to treat breakthrough pain on a mcg per mcg basis. • When prescribing Lazanda to a patient, DO NOT convert from other fentanyl products. • Directions for safely converting patients to Lazanda from other fentanyl products are not currently available. (This includes oral, transdermal, or parenteral formulations of fentanyl). Therefore, for opioid-tolerant patients starting treatment for breakthrough pain, the initial dose of Lazanda is 100 mcg. Individually titrate each patient's dose to provide adequate analgesia while minimizing side effects. • Begin treatment of **all** patients (including those switching from another fentanyl product) using ONE 100 mcg spray of Lazanda (1 spray in one nostril).
ORAL TRANSMUCOSAL FENTANYL CITRATE	• When prescribing, DO NOT convert a patient to oral transmucosal fentanyl citrate from any other fentanyl product on a mcg per mcg basis as oral transmucosal fentanyl citrate and other fentanyl products are not equivalent on a mcg per mcg basis. • There are no safe conversion directions available for patients on any other fentanyl products. (This includes oral, transdermal, or parenteral formulations of fentanyl). Therefore, for opioid tolerant patients, the initial dose of oral transmucosal fentanyl should **always** be 200 mcg. Each patient should be individually titrated to provide adequate analgesia while minimizing side effects.

LABEL CONVERSION INFORMATION	
PRODUCT	**CONVERSION SWITCHES BETWEEN TIRF PRODUCTS**
SUBSYS®	• SUBSYS is not bioequivalent with other fentanyl products. Do not convert patients on a mcg per mcg basis from other fentanyl products. • There are no conversion directions available for patients on any other fentanyl products other than Actiq. (This includes oral, transdermal, or parenteral formulations of fentanyl). **Conversion from Actiq** The initial dose of SUBSYS is always 100 mcg with the only exception being patients already using Actiq. a. For patients being converted from Actiq, prescribers must use the Initial Dosing Recommendations for Patient on Actiq table below (Table 1). Patients must be instructed to stop the use of Actiq and dispose any remaining units. **Table 1: Initial Dosing Recommendations for Patients on Actiq** Current Actiq Dose (mcg) / Initial SUBSYS Dose (mcg) 200 / 100 mcg spray 400 / 100 mcg spray 600 / 200 mcg spray 800 / 200 mcg spray 1200 / 400 mcg spray 1600 / 400 mcg spray b. For patients converting from **Actiq doses 400 mcg and below**, titration should be initiated with 100 mcg SUBSYS and should proceed using multiples of this strength. c. For patients converting from **Actiq doses of 600 mcg and 800 mcg**, titration should be initiated with 200 mcg SUBSYS and should proceed using multiples of this strength. d. For patients converting from **Actiq doses of 1200 mcg and 1600 mcg**, titration should be initiated with 400 mcg SUBSYS and should proceed using multiples of this strength.

LABEL CONVERSION INFORMATION	
PRODUCT	**CONVERSION SWITCHES BETWEEN TIRF PRODUCTS**
	All Other Patients • Individually titrate SUBSYS to a dose that provides adequate analgesia and minimizes adverse reactions. • Initiate treatment with SUBSYS for all patients (including those switching from another fentanyl product) using ONE 100 mcg spray sublingually. • When prescribing, DO NOT convert patients on a mcg per mcg basis from any other oral transmucosal fentanyl product to SUBSYS.

4.2 Patient KAB Report

Title:	**Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment** **Quantitative Testing of Patient/Caregiver Knowledge, Attitudes, and Behavior (KAB) about TIRF Products Safety and Use Information**
Document Number:	Wave 5, 60-Month FDA REMS Assessment Report Version 1.0
Survey Time Period:	26 September 2016 to 21 November 2016
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies:** Actavis Laboratories FL, Inc. BioDelivery Sciences International, Inc. (BDSI) Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Insys Therapeutics, Inc. Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc. Sentynl Therapeutics, Inc.
Date:	10 February 2017

Confidentiality Statement

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LIST OF ABBREVIATIONS

BDSI	BioDelivery Sciences International, Inc.
CI	Confidence Interval
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HCP	Healthcare Professional
KAB	Knowledge, Attitudes, and Behavior
KRM	Key Risk Message
N/A	Not Applicable or Not Available
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
SCC	Survey Coordinating Center
SD	Standard Deviation
TIRF	Transmucosal Immediate Release Fentanyl
TIRF medicines	Transmucosal Immediate Release Fentanyl products
TIRF REMS Access program	REMS program for TIRF medicines
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service

EXECUTIVE SUMMARY

The 60-month Knowledge, Attitudes, and Behavior (KAB) survey for patients receiving Transmucosal Immediate Release Fentanyl (TIRF) medicines or their caregivers was conducted as part of the 60-Month TIRF Risk Evaluation and Mitigation Strategy (REMS) Access program assessment. On 21 July 2016, the United States (US) Food and Drug Administration (FDA) provided feedback on the patient survey. After careful review of the requested changes, the TIRF REMS Industry Group (TRIG) notified FDA that in order to incorporate all changes, an extension for report submission would be required. As proposed by FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month KAB survey results were planned for a separate submission from the overall assessment report on or before 17 February 2017. The 60-month KAB survey for patients or their caregivers launched on 26 September 2016 and closed on 21 November 2016.

Patients who were passively enrolled in the TIRF REMS Access program and had received a TIRF medicine in the previous 4 months (120 days) were invited to participate. From the total of 394 patients/caregivers who accessed the survey, 321 (81.5%) respondents met eligibility criteria, and of those who met eligibility criteria, 310 (96.6%) completed the survey, exceeding the target of 300 completed surveys.

On 21 July 2016, FDA provided feedback on the KAB survey for patients/caregivers. Changes to the 60-month KAB Survey for Patients/Caregivers based on FDA feedback included the addition of 6 survey questions and the revision of 4 survey questions. The change to Question 11 (*TIRF medicines should only be taken by patients who are opioid tolerant*), and the addition of Question 18 Items 18a through 18c (*Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you*) are discussed with the key risk message results below. For questions not included as part of key risk messages, new Questions 37 through 41 showed most respondents indicated someone in the doctor's office told them not to share the TIRF medicines with anyone else, counseled them that accidental exposure to TIRF medicines by a child may be fatal, told them to keep TIRF medicines out of reach of children to prevent accidental exposure, and told them about proper disposal of any unused or partially used TIRF medicines; and over half indicated someone in the doctor's office asked them about the presence of children in their home. In addition, Questions 9, 15, and 16 that ask patients about prescriber activities and were revised to allow pharmacists as a potential source of information, showed most respondents indicated someone in the doctor's office discussed the risks and possible side effects of the prescribed TIRF medicine, that someone in the doctor's office explained how to use the prescribed TIRF medicines, and someone in the doctor's office advised them on the proper storage of the prescribed TIRF medicines.

The overall knowledge score of 84.8 (95% confidence interval [CI]: 83.5 86.0) for the survey indicates most respondents demonstrated understanding of the key risk messages. The average knowledge score for each of the key risk messages was greater than 88 for 5 of the 6 key risk messages and was 70.3 for Key Risk Message 3 (TIRF medicines should be taken exactly as prescribed by the healthcare provider). The lower average knowledge score for Key Risk Message 3 reflected the 3 items (described below) with correct response rates <65%.

Of the 22 questions/items included as part of key risk messages, 16 items had a correct response rate >80%, and 3 items had a correct response rate between 65% and 80%. The remaining 3 items within Key Risk Message 3 had a correct response rate that fell below the desired level of understanding of 65%. These 3 items included two items from Question 10: *For which of the following conditions should you use a TIRF medicine?* Correct response rate for Item 10d: *Pain after surgery.* (Correct Response: No) was 64.2%, and correct response rate for Item 10e: *Long-lasting pain not from cancer, like arthritis joint pain* (Correct Response: No); was 39.0%. In addition, correct response rate for Item 12b (*a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine*) was 39.7%. These items also had a low correct response rate across all patient/caregiver KAB surveys conducted (annual waves from the 12-month through the 60-month survey).

When comparing correct response rates from the 12-month KAB survey through the 60-month KAB survey, knowledge and understanding of the key risk messages has generally remained stable over time, including the items mentioned above that fell below the desired level of understanding of 65% for this wave and have had lower correct response rates for all survey waves. Question 11 had a notably improved correct response rate (nearly 90%) once the question was revised back to the original 36-month survey question for this survey. In addition, over 92% of respondents correctly responded that a side effect of TIRF medicines is the chance of abuse or addiction, that TIRF medicines can be misused by people who abuse medicines or street drugs, and TIRF medicines should be kept in a safe place (new Question 18).

1. PATIENT/CAREGIVER SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate release opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The FDA has determined that a shared system REMS is required to mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access program was approved by the FDA on 28 December 2011. This report describes the results from the patient/caregiver surveys conducted for the 60-month TIRF REMS Access program assessment, and reflects the REMS reporting period of 29 October 2015 to 28 October 2016. The 60-month KAB survey launched on 26 September 2016 and closed on 21 November2016.

The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and (where applicable) their respective generic equivalents. The TRIG includes Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; and Sentynl Therapeutics, Inc. One company joined the TRIG during the reporting period: Sentynl Therapeutics, Inc. replaced Galena Biopharma, Inc. on 09 January 2016.

The TIRF REMS Access program consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments. The goals of the TIRF REMS Access program are to mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2. Preventing inappropriate conversion between TIRF medicines.

3. Preventing accidental exposure to children and others for whom it was not prescribed.

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS Access program assessment is the conduct of quantitative evaluation surveys to assess patients'/caregivers' understanding and knowledge of the safe use of TIRF medicines as described in the TIRF REMS Access program educational materials. Administration of the surveys conducted among patients/caregivers enrolled in the TIRF REMS Access program is described in the protocol (See Appendix A). Note: Protocol and Survey question revisions from the 48-month assessment report are identified as tracked changes.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

1.1 Changes to the KAB Survey for Patients/Caregivers Based on FDA Feedback

On 21 July 2016, FDA provided feedback on the KAB survey for patients or their caregivers. After careful review of the requested changes, the TRIG notified FDA that in order to incorporate all changes, an extension for report submission would be required. As proposed by FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month KAB survey results were planned for a separate submission from the overall assessment report on or before 17 February 2017.

Specific updates made to the protocol and survey included:

- Addition of the following questions:
    - 18a (*A side effect of TIRF medicines is the chance of abuse or addiction.*)
    - 18b (*TIRF medicines can be misused by people who abuse prescription medicines or street drugs.*)
    - 18c (*TIRF medicines should be kept in a safe place to prevent it from being stolen.*)

- 37 ([PATIENT] *Did a doctor, nurse, or other healthcare professional in the doctor's office ever ask you about the presence of children in your home?*)
- 38 ([PATIENT] *Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you not to share the TIRF medicines with anyone else?*)
- 39 ([PATIENT] *Did a doctor, nurse, or other healthcare professional in the doctor's office ever counsel you that accidental exposure to TIRF medicines by a child may be fatal?*)
- 40 ([PATIENT] *Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you to keep TIRF medicines out of reach of children to prevent accidental exposure?*)
- 41 ([PATIENT] *Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you about proper disposal of any unused or partially used TIRF medicines?*)

- Revisions to Questions 9, 15, and 16 which ask patients about prescriber activities to allow pharmacists as a potential source of information. The 48-month survey questions that began with "*Did the doctor, nurse, or other healthcare professional in the doctor's office ever…*" were revised for the 60-month survey to "*Did a doctor, nurse, or other healthcare professional in the doctor's office ever…*".

- Update to Question 11 under Key Risk Message 2 to the original 36-month survey question "*TIRF medicines should only be taken by patients who are opioid tolerant"* instead of the revised 48-month survey question of "*TIRF medicines should only be taken by cancer patients who are opioid tolerant"*.

All of the above requested changes were incorporated prior to survey launch on 26 September 2016.

2. PATIENT/CAREGIVER SURVEY OBJECTIVES

The evaluation survey used a questionnaire to document the level of knowledge and assess the attitudes and behavior of patients and caregivers of patients regarding the following key information and risk messages communicated through the REMS:

1. TIRF medicines can cause life-threatening breathing problems that can lead to death.
2. Patients should not take TIRF medicines if they are not opioid tolerant.
3. TIRF medicines should be taken exactly as prescribed by the healthcare provider.
4. Patients should not switch from one TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.

5. Patients should not give TIRF medicines to anyone else even if they have the same symptoms.

6. TIRF medicines should be stored in a safe place away from children and properly disposed.

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions developed to test patient understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, provided in Appendix A.

3.1 Survey Sample

A sample of 300 patients or caregivers of patients who are being treated with a TIRF medicine is proposed for each survey wave. The survey sample size was determined based on both practical and statistical considerations. The survey was written to reflect wording for both methods of survey administration: Internet-based and telephone.

3.1.1 Eligibility

This survey was conducted on patients identified from the TIRF REMS Access program database. All patients 18 years or older who filled 1 or more prescriptions for at least 1 of the TIRF medicines during the 120 days prior to 26 September 2016 were eligible to participate; caregivers (age 18 years or older) of eligible patients who were unable to take the survey for themselves were eligible to participate. Respondents or respondents with immediate family members who had ever worked for any of the TRIG companies, RelayHealth, McKesson Specialty Care Solutions, United BioSource Corporation (UBC), or the FDA were not eligible to participate, nor were any respondents who participated in the previous waves of the survey (annual waves from the 12-month TIRF REMS Access program assessment through the 48-month TIRF REMS Access program assessment).

3.1.2 Recruitment

Patients who were passively enrolled in the TIRF REMS Access program as of 02 September 2016 and had received a TIRF medicine in the previous 4 months (120 days) were invited to participate via an invitation letter sent through the United States Postal Service (USPS) (see Section 5.1.1 for more details). Address verification was required on these data due to the limited data points collected on the Patient-Prescriber Agreement Form (PPAF). In order to obtain this additional information a public records database was used and those data combined with the TIRF REMS Access program data to distribute invitations to the patient population. Through use of these sources, a list of patients who had filled a prescription for a TIRF medicine within 4 months (120 days) prior to survey launch (first prescriptions and refills) was created. Full details are provided in the protocol (Appendix A).

If the required number of completed surveys was not achieved within a reasonable time frame, second and third mailings to non-respondents, as well as initial invitations to new samples of

patients , if the data were available, were sent as necessary based on the actual rate of survey accrual relative to the proximity of the target survey close date.

Each letter of invitation included a unique code needed to access the survey. The code was deactivated after the respondent had initiated the survey (whether or not the survey was completed). Respondents were given the option of taking the survey by telephone via the Survey Coordinating Center (SCC) or online via a secure website. The survey was estimated to take approximately 20 minutes to complete.

All respondents who completed the survey and provided their contact information were mailed a $50 gift card for participating. The mailing included a Thank You Letter, a copy of the product-specific Medication Guide, and a copy of the correct answers to the key risk message questions.

3.2 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the patients'/caregivers' understanding of the key risk messages of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that included statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I don't know" regarding statements about TIRF medicines.

For statements or questions that use "True" or "Yes" versus "False" or "No" response options, the desired response for key risk messages was generally "True" or "Yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions were formatted to have the respondent disagree with the statement as written by providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A). For better readability, only patient questions are presented in the key risk messages tables below. The same questions, with modified wording as appropriate for caregivers, are presented in the survey protocol (Appendix A).

3.2.1 Key Risk Message 1

Key Risk Message 1 refers to the patient's/caregiver's knowledge that TIRF medicines can cause life-threatening breathing problems.

Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
Question No.	**Question**	**Desired Response**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death.	***True***

3.2.2 Key Risk Message 2

Key Risk Message 2 refers to the patient's/caregiver's awareness that patients who are not opioid tolerant should not take TIRF medicines.

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.		
Question No.	**Question**	**Desired Response**
11	Please answer True, False, or I don't know for the following statement:	
	TIRF medicines should only be taken by patients who are opioid tolerant.	***True***
12	Please answer True, False, or I don't know for each of the following statements.	
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	***True***

3.2.3 Key Risk Message 3

Key Risk Message 3 refers to the patient's/caregiver's knowledge that TIRF medicines should be taken exactly as prescribed by the healthcare provider.

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.		
Question No.	**Question**	**Desired Response**
10	For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.	
10a	Headache or migraine pain	***No***
10b	Breakthrough pain from cancer	***Yes***
10c	Dental pain	***No***
10d	Pain after surgery	***No***
10e	Long-lasting pain not from cancer, like arthritis joint pain	***No***
12	Please answer True, False, or I don't know for each of the following statements.	
12b	A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	***True***
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13b	It is OK for patients to take TIRF medicines for headache pain.	***False***

13c	TIRF medicines should be taken exactly as prescribed by the doctor.	***True***
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	***False***

3.2.4 Key Risk Message 4

Key Risk Message 4 refers to the patient's/caregiver's knowledge of the interchangeability of TIRF medicines.

Key Risk Message 4: Patients should not switch from one TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.		
Question No.	**Question**	**Desired Response**
12	Please answer True, False, or I don't know for each of the following statements.	
12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	***False***

3.2.5 Key Risk Message 5

Key Risk Message 5 refers to the patient's/caregiver's awareness that TIRF medicines should not be given to anyone else even if they have the same symptoms.

Key Risk Message 5: Patients should never give TIRF medicines to anyone else even if they have the same symptoms.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each of the following statements.	
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	***False***
17/18	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a	Selling or giving away TIRF medicines is against the law.	***True***
18a	A side effect of TIRF medicines is the chance of abuse or addiction.	***True***
18b	TIRF medicines can be misused by people who abuse prescription medicines or street drugs.	***True***
18c	TIRF medicines should be kept in a safe place to prevent it from being stolen.	***True***

3.2.6 Key Risk Message 6

Key Risk Message 6 refers to the patient's/caregiver's knowledge that TIRF medicines should be stored in a safe place away from children and properly disposed.

Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.		
Question No.	**Question**	**Desired response**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a	TIRF medicines should be stored in a safe place out of the reach of children.	***True***
14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	***Get emergency help right away.***
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	***True***
17e	A TIRF medicine can cause an overdose and death in any child who takes it.	***True***

3.3 Additional Questions

Additional questions in the survey include inclusion/exclusion questions to confirm respondent eligibility; questions on knowledge of safe use of TIRF medicines; questions about receipt, reading and understanding the Medication Guide; questions about review and signing of the PPAF; and questions to collect demographic information.

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 All Respondents

The All Respondents population consisted of respondents that accessed the survey using a unique code. These respondents were used as the denominator for percentages in survey administration statistics unless otherwise specified.

4.1.2 Completed Surveys (Primary Population)

The primary population for analysis was all eligible respondents who completed the survey. Eligible respondents were defined as those respondents who answered Yes to Question 1 (agree to take part in survey), Yes to Question 2 (filled a prescription for a TIRF medicine in the last 4 months) or Yes to Question 3 (caregiver for someone who had filled a prescription for a TIRF medicine in the last 4 months), and No to Question 5 (participated in past survey), and No to Question 8 (worked for a TRIG company, McKesson Specialty Care Solutions, RelayHealth,

UBC, or FDA). Respondents also must have selected an age group ≥18 years of age for Question 6 (patient or caregiver). A survey was considered "completed" when an eligible patient/caregiver answered all relevant questions.

4.1.3 General Population

The general population consisted of all patients who received a prescription for a TIRF medicine as shown in IMS Health data (IMS data). This population was used to compare the population represented in the survey to the general population to determine whether those completing the survey were representative of the patient population. It was assumed that the IMS data covered the majority of patients receiving TIRF medicines in the outpatient setting. The analysis included calculation of p-values by a chi-square test.

4.2 Primary Analyses

Primary analyses were performed for all key risk messages. The primary analysis for a key risk message evaluated the number and percentage of correct responses for each individual question/item included in the key risk message. Confidence intervals (95% CI) were calculated using the exact binomial method around the percentage of correct responses.

Primary analyses were then stratified by questions/characteristics of interest:

1) Those who indicated they both received the Medication Guide and read most of it versus those who responded they did not receive, did not have access to, or did not read the Medication Guide (Questions 19, 24, and 25).
2) Those who indicated they understood all or most of the Medication Guide versus those who understood some of it versus those understood none or did not know if they understood versus those who did not know whether they received or read the Medication Guide (Question 26).
3) Whether the survey was completed via the Internet or telephone.
4) Highest level of education (Question 43).
5) Age group of respondent (Question 6).

Stratified analyses were conducted on all completed surveys.

4.3 Secondary Analyses

As an indicator of the overall level of comprehension of the entire key risk message, descriptive analyses of the number and percentage of responders who answered various proportions of the key risk message questions/items correctly are presented (i.e., the proportion who answered 1 question/item in the key risk message correctly, those who answered 2 questions/items correctly, those who answered 3 questions/items correctly, etc.).

A knowledge score was computed for each key risk message (KRM) and overall. The score was defined as the ratio of the number of correct responses to all KRM questions to the total number of possible correct responses to all KRM questions. The average knowledge score was calculated

as the mean of the score across all completed surveys; 95% CIs were calculated based on the normal distribution function.

4.4 Patient Report of a Potential Adverse Event, Product Complaint, or Medical Information Request during the Survey

A patient or caregiver may have reported a potential adverse event or other event experienced by a patient while taking a TIRF product either in free text fields while taking the online survey or while in conversation with the SCC Associate. If an event was mentioned to the SCC Associate, the Associate documented the event or complaint, the verbatim response, and the respondent's contact information, if provided. The respondent was also informed that a representative from the appropriate TIRF medicine sponsor might contact him/her to obtain additional information about the event. The Internet surveys were monitored for any comments recorded in the free text field. Information on all reports (Internet or telephone) that constituted an adverse event or other event was forwarded to the appropriate TIRF medicine sponsor for processing within 1 business day of awareness of the event as outlined in the Escalating Adverse Events, Product Complaints, and Medical Information Requests Identified During Execution of the Knowledge, Attitudes, and Behavior Survey Project Specific Procedure.

5. RESULTS

Unless otherwise indicated, data tables contain the question presented to the patients. Analyses were summarized by overall population, and not by type of respondent (patient vs. caregiver) since only 5 caregivers participated in the survey.

Results of the patient's/caregiver's responses to questions in the KAB survey are summarized in this section; the full set of summary tables and listings are provided in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

Survey recruitment was performed using the names obtained through the TIRF REMS Access program database (See Section 3.1 for survey methodology details). Based on the number of prescriptions filled or refilled during the 120 days prior to survey implementation (26 September 2016), the TIRF REMS Access program database identified 2945 potential participants. As shown in Table 1, all 2945 possible participants were sent a survey invitation letter. A total of 5397 reminder letters were sent to non-responders (some potential participants may have received more than 1 reminder letter). Successful survey recruitment through leveraging data collected by the TIRF REMS Access program (as described in Section 3.1), resulted in the patient/caregiver KAB survey closing early on 21 November 2016 once 310 surveys were collected.

From the total of 394 patients/caregivers who accessed the survey, 321 (81.5%) respondents met eligibility criteria, and of those who met eligibility criteria, 310 (96.6%) completed the survey. Of the 310 respondents who completed the survey, 207 (66.8%) completed the survey online, and 103 (33.2%) completed it by telephone (Table 3).

Table 1. Survey Administration Statistics

Parameter, n (%)	
Number of invitations distributed	2945
Number of invitations returned as undeliverable	399
Number of reminder letters distributed	5397
All Respondents[1]	394 (15.5)
Eligible Respondents[2]	321 (81.5)
Completed survey[3]	310 (96.6)
Did not complete the survey[3]	11 (3.4)
Respondents not eligible[2], [4]	73 (18.5)

Source: Appendix B: Survey Tables, Table 1.1
[1] Number of unique respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[2] Percentage is based on the number of all respondents.
[3] Percentage is based on the number of eligible respondents.
[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

As shown in Table 2, of the 394 respondents who accessed the survey, 378 patients/caregivers answered at least 1 survey question, and 16 respondents did not answer any of the survey questions (discontinued the survey before answering Question 1). During the screening process it was determined 54 of the 378 respondents who answered at least 1 survey question were not eligible to participate in the survey because they either did not agree to participate in the survey (2 respondents), indicated that they had filled a prescription for a TIRF medicine within the last 4 months either for themselves or as a the caregiver of a patient (13 respondents), that they had participated in or did not know whether they participated in a survey about TIRF medicines before (38 respondents), or that they or an immediate family member had worked for a TRIG company, the FDA, or UBC (1 respondent). In addition, 1 of the 378 respondents who answered at least 1 survey question discontinued the survey at Question 2, 1 respondent discontinued at Question 5, and 1 respondent discontinued at Question 8. Thus, there were 321 eligible participants (patients/caregivers) (Table 2).

For Question 4, respondents indicated prescriptions for Subsys® and Actiq® including generic versions were filled most frequently in the 4 months preceding the survey.

Table 2. Survey Participant Eligibility Results - All Respondents

Question	Patients/Caregivers (N=394) n (%)
Question 1: Do you agree to take part in this survey?	
Yes	376 (95.4)
No[1]	2 (0.5)
Discontinued	16 (4.1)
Question 2: Within the last 4 months (120 days), have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of any of these brands.	
Yes	357 (90.6)
No	15 (3.8)
I don't know	3 (0.8)
Question not asked [2]	2 (0.5)
Discontinued	17 (4.3)
Question 3: Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months (120 days)? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys® and the generic versions of any of these brands.	
Yes	5 (1.3)
No[1]	13 (3.3)
I don't know[1]	0
N/A *(Answered "Yes" to Question 2)*	357 (90.6)
Question not asked [2]	2 (0.5)
Discontinued	17 (4.3)
Question 4: For which TIRF medicines have you filled a prescription in the last 4 months (120 days)? Please select all that apply.[3], [5]	
Abstral	15 (3.8)
Actiq, including generic versions of Actiq	92 (23.4)
Fentora	69 (17.5)
Lazanda	17 (4.3)
Subsys	162 (41.1)
Other	23 (5.8)
I don't know	7 (1.8)
Question not asked [2]	15 (3.8)
Discontinued	17 (4.3)

Table 2. Survey Participant Eligibility Results - All Respondents

Question	Patients/Caregivers (N=394) n (%)
Question 5: Have you ever taken part in a survey about a TIRF medicine before?	
Yes[1]	26 (6.6)
No	323 (82.0)
I don't know[1]	12 (3.0)
Question not asked [2]	15 (3.8)
Discontinued	18 (4.6)
Question 6: Which of the following groups best describes your age?	
Under 18[1]	0
18 - 29	8 (2.0)
30 - 39	23 (5.8)
40 - 49	60 (15.2)
50 - 59	123 (31.2)
60 - 69	92 (23.4)
70 or older	17 (4.3)
Prefer not to answer[1]	0
Question not asked [2]	53 (13.5)
Discontinued	18 (4.6)
Question 7: Which of the following groups best describes the patient's age?[4]	
Under 16	0
16 - 29	0
30 - 39	0
40 - 49	1 (0.3)
50 - 59	1 (0.3)
60 - 69	3 (0.8)
70 or older	0
Prefer not to answer[1]	0
Question not asked [2]	372 (94.4)
Discontinued	17 (4.3)

Table 2. Survey Participant Eligibility Results - All Respondents

Question	Patients/Caregivers (N=394) n (%)
Question 8: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[5]	
Actavis Laboratories FL, Inc.[1]	0
Anesta LLC[1]	0
BioDelivery Services International (BDSI)[1]	0
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	0
Depomed, Inc.[1]	0
Galena Biopharma, Inc.[1]	0
Insys Therapeutics, Inc.[1]	0
Mallinckrodt Pharmaceuticals[1]	1 (0.3)
McKesson Specialty Care Solutions[1]	0
Mylan Inc.[1]	0
Par Pharmaceuticals, Inc.[1]	0
RelayHealth[1]	0
Sentynl Therapeutics. Inc.[1]	0
Teva Pharmaceuticals, Ltd.[1]	0
United BioSource Corporation[1]	0
FDA (Food and Drug Administration)[1]	0
No[6]	321 (81.5)
I don't know[1]	0
Question not asked[2]	53 (13.5)
Discontinued	19 (4.8)

Source: Appendix B: Survey Tables, Table 1.2
Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.
[1] Ineligible to participate in the survey.
[2] Question not asked due to termination response from a previous question or skip pattern.
[3] Question does not dictate eligibility for survey completion but is asked of all respondents who did not terminate prior to question presentation.
[4] Only caregivers are asked this question.
[5] More than one response can be selected, so percentages may not sum to 100%.
[6] Ineligible to participate in the survey if selected additionally to another response.

Those taking the survey online took a mean of 16.49 minutes to complete it, while those taking it by telephone took a mean of 22.44 minutes (Table 3).

Table 3. Time to Complete Survey - Completed Surveys

	Telephone	Internet	Total[1]
Summary Statistic (minutes)			
N	103	207	310
Mean (SD)	22.44 (6.012)	16.49 (7.987)	18.47 (7.895)
Minimum	15.7	6.1	6.1
Median	21.10	14.65	17.66
Maximum	46.3	49.2	49.2
Category, n			
0 to <5 Minutes	0	0	0
5 to <10 Minutes	0	39	39
10 to <15 Minutes	0	71	71
15 to <20 Minutes	39	47	86
20 to <25 Minutes	47	27	74
25 to <30 Minutes	10	8	18
30 Minutes or more	7	15	22

Source: Appendix B: Survey Tables, Table 1.3
[1] Total number of eligible respondents completing the survey.

5.1.2 Description of Eligible Patients/Caregivers who Completed the Survey

The demographic characteristics of respondents who completed the survey are shown in Table 4. The largest number of patients (116; 37.4%) were 50 to 59 years of age. More than half of the respondents (198; 63.9%) were females, and most respondents indicated their main language as English (305; 98.4%) and race as White (267; 86.1%). The majority of respondents (250; 80.6%) had at least some college education. Most participants (109; 35.2%) were from the South, followed by the West (95; 30.6%), Northeast (56; 18.1%), and Midwest (50; 16.1%) regions of the US.

Table 4. Description of Eligible Patients/Caregivers - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%)
Respondent's age based on Question 6: Which of the following groups best describes your age?	
18 - 29	8 (2.6)
30 - 39	21 (6.8)
40 - 49	59 (19.0)
50 - 59	118 (38.1)
60 - 69	88 (28.4)
70 or older	16 (5.2)
Patient's age based on Question 6/7: Which of the following groups best describes your age/the patient's age?	
Under 16	0
16 - 29	8 (2.6)
30 - 39	21 (6.8)
40 - 49	60 (19.4)
50 - 59	116 (37.4)
60 - 69	89 (28.7)
70 or older	16 (5.2)
Question 42: What is your gender?	
Male	110 (35.5)
Female	198 (63.9)
Prefer not to answer	2 (0.6)
Question 43: What is the highest level of education you have completed?	
Less than high school	1 (0.3)
Some high school	4 (1.3)
High school graduate/GED	52 (16.8)
Some college	97 (31.3)
Associate's degree	41 (13.2)
Bachelor's degree	72 (23.2)
Master's degree	25 (8.1)
Professional or Doctoral degree	15 (4.8)
Prefer not to answer	3 (1.0)

Table 4. Description of Eligible Patients/Caregivers - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%)
Question 44: What is the main language you speak at home?	
English	305 (98.4)
French	0
Spanish	2 (0.6)
Portuguese	0
Italian	0
German	0
Chinese	0
Japanese	0
Korean	0
Other	1 (0.3)
Prefer not to answer	2 (0.6)
Question 45: Are you Hispanic or Latino?	
Yes	16 (5.2)
No	289 (93.2)
Prefer not to answer	5 (1.6)
Question 46: For informational purposes only, which of the following U.S. census categories best describes your race?	
American Indian or Alaska Native	5 (1.6)
Asian (origins of Far East, Southeast Asia or the Indian subcontinent)	1 (0.3)
Black or African American	13 (4.2)
Native Hawaiian or Other Pacific Islander	1 (0.3)
White	267 (86.1)
Other	7 (2.3)
Prefer not to answer	9 (2.9)
Two or more races	7 (2.3)

Table 4. Description of Eligible Patients/Caregivers - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%)
Geographic Distribution (based on Question 47 - In which state do you live?)[2]	
Northeast	56 (18.1)
Midwest	50 (16.1)
South	109 (35.2)
West	95 (30.6)
Other	0
Prefer not to answer	0

Source: Appendix B: Survey Tables, Table 2
[1] Total number of eligible respondents completing the survey.
[2] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.

5.1.2.1 Comparison of Survey Respondents to the General Population of TIRF Users

A comparison of patients who completed the survey to the general population of patients based on IMS data is provided in (Table 5). There were statistically significant differences ($p<0.05$) observed in the demographics between the patients completing the survey compared with the general population of patients on the questions for highest level of education and race; all other characteristics between groups were similar. It is important to note the sample size of the general population of patients (N (b) (4) [or (b) (4) for race/ethnicity, language spoken in the home, and education level]) affects the power of the test, and therefore, may mean that even small differences between groups resulted in significant p-values. For the questions that showed statistically significant differences between the groups, it is important to review the proportional differences between the groups for each response within a question. For example, there were almost no differences between the patients completing the survey and the general population of patients for race where the response 'White' (86.1% vs. 89.3%) included the majority of responders in each group. The proportion of patients with completed college and graduate school were similar in the general population, but of those who participated in the survey, patients who completed 'some college' were overrepresented (44.4% versus 27.2% in the general population) and patients completed high school or less than high school were underrepresented (16.8 vs. 31.5% and 1.6 versus 5.6%), respectively. While the differences are statistically significant, these differences should not have an impact on the primary objectives of the survey since a relevant uniform impact of demographic characteristics on the knowledge of the key risk messages could not be detected.

Table 5. Comparison of Survey Respondents to General Population of TIRF Users

Question	Patients Completing Survey n (%)	Patients Who Have Received a TIRF Medicine Prescription in the Last 4 Months (120 days)[1] n (%)	p-value
	(N=310)	(N=(b) (4))	
TIRF Medicine Prescription(s) Filled in the last 4 Months (120 days)[2]			
Abstral	15 (4.8)	(b) (4)	
Actiq, including generic versions of Actiq	71 (22.9)		
Fentora	56 (18.1)		
Lazanda	16 (5.2)		
Subsys	146 (47.1)		
Other	20 (6.5)		
I don't know	5 (1.6)		
Age Group[3]			
Under 16	0	(b) (4)	0.3579
16 - 29	8 (2.6)		
30 - 39	21 (6.8)		
40 - 49	60 (19.4)		
50 - 59	116 (37.4)		
60 - 69	89 (28.7)		
70 or older	16 (5.2)		
Unknown	*N/A*		
Gender[4]			
Male	110 (35.5)	(b) (4)	0.2379
Female	198 (63.9)		
Prefer not to answer/Unknown	2 (0.6)		
Geographic Distribution[5]			
Northeast	56 (18.1)	(b) (4)	0.4656
Midwest	50 (16.1)		
South	109 (35.2)		
West	95 (30.6)		
Other[6]	0		
Prefer not to answer[6]	0		

Table 5. Comparison of Survey Respondents to General Population of TIRF Users

Question	Patients Completing Survey n (%)	Patients Who Have Received a TIRF Medicine Prescription in the Last 4 Months (120 days)[1] n (%)	p-value
	(N=310)	(N(b) (4))	
Highest Level of Education Completed[7]		(b) (4)	
Less than high school diploma	5 (1.6)		
High school	52 (16.8)		
Some college	138 (44.5)		<.0001
Completed college	72 (23.2)		
Graduate school	40 (12.9)		
Prefer not to answer	3 (1.0)		
Main Language Spoken at Home[8]		(b) (4)	
English	305 (98.4)		
French	0		
Spanish	2 (0.6)		
Portuguese	0		
Italian	0		0.0914
German	0		
Chinese	0		
Japanese	0		
Korean	0		
Other	1 (0.3)		
Prefer not to answer	2 (0.6)		
Hispanic or Latino[9]		(b) (4)	
Yes	16 (5.2)		0.3242
No	289 (93.2)		
Prefer not to answer	5 (1.6)		
Race According to US Census Categories[10]		(b) (4)	
American Indian or Alaska Native[6]	5 (1.6)		
Asian (origins of Far East, Southeast Asia or the Indian subcontinent)	1 (0.3)		<.0001
Black or African American	13 (4.2)		
Native Hawaiian or Other Pacific Islander[6]	1 (0.3)		

Table 5. Comparison of Survey Respondents to General Population of TIRF Users

Question	Patients Completing Survey n (%)	Patients Who Have Received a TIRF Medicine Prescription in the Last 4 Months (120 days)[1] n (%)	p-value
	(N=310)	(N=(b) (4))	
White	267 (86.1)	(b) (4)	
Two or more races[6]	7 (2.3)		
Other[6]	7 (2.3)		
Prefer not to answer/Unknown	9 (2.9)		

Source: Appendix B: Survey Tables, Table 2a
Note: Race/Ethnicity, language spoken in the home, and education level are only available for 1671 patients with a Consumer Profile. P-values are calculated by a chi-square test excluding prefer not to answer, other, and comparable categories.
N/A = Not available.
[1] Based on data from IMS provided on 01Dec2016. Data covered period of 05May2016 to 02Sep2016.
[2] Based on Question 4; More than one type of TIRF medicine could be selected.
[3] Based on Question 6/7; Percentages for the IMS data are calculated based on the sum of available counts, minus the count for "Unknown."
[4] Based on Question 42.
[5] Based on Question 47; U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.
[6] Level not provided and/or collected by the IMS data.
[7] Based on Question 43; Less than high school diploma includes "Less than high school" and "Some high school"; Some college includes "Some college" and "Associate's degree"; Completed college includes "Bachelor's degree"; Graduate school includes "Master's degree" and "Professional or Doctoral degree."
[8] Based on Question 44; "English" for the IMS data is calculated using the total of 1671 patients with a Consumer Profile, minus the sum of other available counts. In the IMS data, French, German, Italian, and Portuguese are reported as combined with a total of 10 patients, and individually as 5 patients for German, and 1-4 patients for French, Italian, and Portuguese. The count of 5 for German and the total of 5 for French, Italian, and Portuguese are used in the "English" calculation.
[9] Based on Question 45; "No" for the IMS data is calculated using the total of 1671 patients with a Consumer Profile, minus the count for "Yes."
[10] Based on Question 46; "White" for the IMS data is calculated by combining the individual categories of Caucasian (1379 patients) and Hispanic/Latino (113 patients) as reported in the IMS data.
* represents 1-4 patients.

5.1.3 TIRF Medicines Education Materials

Respondents were asked about their awareness of educational materials for TIRF medicines, specifically the Medication Guide (Table 6), and the PPAF (Table 7). Of the 310 respondents, 288 (92.9%) reported they had received the Medication Guide for the TIRF medicine prescribed for them. Of these 288 respondents, 164 respondents (56.9%) reported receiving the Medication

Guide from their doctor or doctor's office, with 134 of these respondents (81.7%) receiving it at the first appointment with the prescribing doctor. Of the 288 respondents who reported receiving the Medication Guide, most (265; 92.0%) reported receiving the Medication Guide from their pharmacy with 242 of these respondents (91.3%) stating they received the Medication Guide each time a prescription was filled.

Of the 288 respondents who received the Medication Guide, most (278; 96.5%) indicated they had read the Medication Guide; of these 278 respondents 258 respondents (92.8%) read all of it or most of it, and 253 respondents (91.0%) indicated understanding all of it or most it. Over half of the respondents who received the Medication Guide (194; 67.4%) indicated someone offered to explain the Medication Guide to them; of these, 131 respondents (67.5%) indicated the doctor or someone in the doctor's office offered to explain the Medication Guide and 161 respondents (83.0%) indicated their pharmacist offered to explain the Medication Guide. Of the 194 respondents who indicated someone offered to explain the Medication Guide, 125 (64.4%) indicated they accepted the offer to have the Medication Guide explained to them, and of those 125 respondents, 120 (96.0%) indicated they understood all or most of the explanation. A total of 10 (3.5%) respondents indicated they had questions about the information in the Medication Guide (See Appendix B, Listing 3).

Table 6. Responses to Questions about TIRF Educational Materials - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%)
Question 19: Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?	
Yes	288 (92.9)
No	5 (1.6)
I don't know	17 (5.5)
Question 20: Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?[2]	
Yes	164 (56.9)
No	104 (36.1)
I don't know	20 (6.9)
N/A (Answered "No" or "I don't know" to Question 19)	22
Question 21: When was the Medication Guide given to you? Please select all that apply.[2], [3]	
At the first appointment with the doctor who prescribed the TIRF medicine	134 (81.7)
At the last appointment with the doctor who prescribed the TIRF medicine	26 (15.9)
I don't remember	23 (14.0)
N/A (Answered "No" or "I don't know" to Question 19 or 20)	146

Table 6. Responses to Questions about TIRF Educational Materials - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%)
Question 22: Did you receive the Medication Guide for the TIRF medicine from the pharmacy?[2]	
Yes	265 (92.0)
No	16 (5.6)
I don't know	7 (2.4)
N/A (Answered "No" or "I don't know" to Question 19)	22
Question 23: How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?[2], [4]	
Only with the first filled prescription	10 (3.8)
Each time a prescription is filled	242 (91.3)
Other (please specify):	8 (3.0)
I don't know	5 (1.9)
N/A (Answered "No" or "I don't know" to Question 19 or 22)	45
Question 24: Did you read the Medication Guide?[2]	
Yes	278 (96.5)
No	7 (2.4)
I don't know	3 (1.0)
N/A (Answered "No" or "I don't know" to Question 19)	22
Question 25: How much did you read?[2]	
All of it	168 (60.4)
Most of it	90 (32.4)
Some of it	20 (7.2)
I don't know	0
N/A (Answered "No" or "I don't know" to Question 19 or 24)	32
Question 26: How much of the Medication Guide did you understand?[2]	
All of it	144 (51.8)
Most of it	109 (39.2)
Some of it	25 (9.0)
None of it	0
I don't know	0
N/A (Answered "No" or "I don't know" to Question 19 or 24)	32

Table 6. Responses to Questions about TIRF Educational Materials - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%)
Question 27: Did someone offer to explain the Medication Guide to you?[2]	
Yes	194 (67.4)
No	79 (27.4)
I don't know	15 (5.2)
N/A (Answered "No" or "I don't know" to Question 19)	22
Question 28: Who offered to explain the Medication Guide to you? Please select all that apply.[2], [3], [5]	
The doctor or another healthcare professional in the doctor's office	131 (67.5)
The pharmacist where the TIRF medicine prescription was filled	161 (83.0)
Someone else	16 (8.2)
N/A (Answered "No" or "I don't know" to Question 19 or 27)	116
Question 29: Did you accept the offer to have the Medication Guide explained to you?[2]	
Yes	125 (64.4)
No	66 (34.0)
I don't know	3 (1.5)
N/A (Answered "No" or "I don't know" to Question 19 or 27)	116
Question 30: How much of the explanation did you understand?[2]	
All of it	91 (72.8)
Most of it	29 (23.2)
Some of it	5 (4.0)
None of it	0
I don't know	0
N/A (Answered "No" or "I don't know" to Question 19, 27 or 29)	185

Table 6. Responses to Questions about TIRF Educational Materials - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%)
Question 31: Did you or do you have any questions about the information in the Medication Guide?[2], [6]	
Yes	10 (3.5)
No	275 (95.5)
I don't know	3 (1.0)
N/A (Answered "No" or "I don't know" to Question 19)	22

Source: Appendix B: Survey Tables, Table 4
[1] Total number of eligible respondents completing the survey.
[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[3] More than one response can be selected, so percentages may not sum to 100%.
[4] Verbatim text for Question 23 (Other frequency of receiving a Medication Guide in the pharmacy) is presented in Listing 1.
[5] Verbatim text for Question 28 (Other type of person explaining Medication Guide) is presented in Listing 2.
[6] Verbatim text for question about the Medication Guide (Question 32) is presented in Listing 3.

The responses to Questions 23, 28, and 31 are listed in Appendix B, Listing 1; Appendix B, Listing 2; and Appendix B, Listing 3 respectively.

5.1.4 Patient-Prescriber Agreement Form

After respondents were asked questions regarding the key risk messages, they were asked if they had received, read, and understood the PPAF. A total of 239 respondents (77.1%) indicated that someone at the doctor's office had explained the PPAF to them, and of the 239 respondents, 200 respondents (83.7%) understood all of it and 36 (15.1%) understood most of it. Of the 310 respondents, 237 (76.5%) reported signing a PPAF, and of these, 182 respondents (76.8%) reported receiving a copy (Table 7).

Table 7. Responses to Questions about the Patient-Prescriber Agreement Form - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%)
Question 33: Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?	
Yes	239 (77.1)
No	32 (10.3)
I don't know	39 (12.6)

Table 7. Responses to Questions about the Patient-Prescriber Agreement Form - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%)
Question 34: How much of the explanation did you understand?[2]	
All of it	200 (83.7)
Most of it	36 (15.1)
Some of it	3 (1.3)
None of it	0
I don't know	0
N/A (Answered "No" or "I don't know" to Question 33)	71
Question 35: Did you sign a Patient-Prescriber Agreement Form?	
Yes	237 (76.5)
No	15 (4.8)
I don't know	58 (18.7)
Question 36: Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?[2]	
Yes	182 (76.8)
No	16 (6.8)
I don't know	39 (16.5)
N/A (Answered "No" or "I don't know" to Question 35)	73

Source: Appendix B: Survey Tables, Table 5
[1] Total number of eligible respondents completing the survey.
[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

5.2 Key Risk Messages

5.2.1 Key Risk Message 1

Key Risk Message 1 states "TIRF medicines can cause life-threatening breathing problems that can lead to death." (Table 8).

Most patients/caregivers (91.6%, 95% CI: 88.0 94.4) were aware of the risk of life-threatening breathing problems with TIRF medicines.

Table 8. Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%) [95% CI][2]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.	
True[3]	284 (91.6) [88.0 - 94.4]
False	8 (2.6)
I don't know	18 (5.8)

Source: Appendix B: Survey Tables, Table 6.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

No trends were evident when the results for Key Risk Message 1 were stratified by whether the Medication Guide was received and read, if the Medication Guide was read and understood, modality for completing the survey (internet versus telephone), respondent highest level of education, or by the age group of the respondent (see Appendix B).

5.2.2 Key Risk Message 2

Key Risk Message 2 states "patients should not take TIRF medicines if they are not opioid tolerant." Two questions/items defined this key risk message (Table 9).

The majority of respondents (89.4%, 95% CI: 85.4 92.6) understood that TIRF medicines should only be taken by patients who are opioid tolerant.

Most respondents (88.1%, 95% CI: 83.9 91.5) also correctly indicated that opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.

Table 9. Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%) [95% CI][2]
Question 11: Please answer True, False, or I don't know for the following statement:	
TIRF medicines should only be taken by patients who are opioid tolerant.	
True[3]	277 (89.4) [85.4 - 92.6]
False	8 (2.6)
I don't know	25 (8.1)

Table 9. Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%) [95% CI][2]
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	
True[3]	273 (88.1) [83.9 - 91.5]
False	14 (4.5)
I don't know	23 (7.4)

Source: Appendix B: Survey Tables, Table 7.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

Overall, 82.9% of respondents provided correct responses for both questions/items of Key Risk Message 2 (Table 10).

Table 10. Secondary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Correct Responses	Patients/Caregivers (N=310)[1] n (%)
0 correct responses	17 (5.5)
1 correct response	36 (11.6)
2 correct responses	257 (82.9)

Source: Appendix B: Survey Tables, Table 7.2
[1] Total number of eligible respondents completing the survey.

No trends were evident when the results for Key Risk Message 2 were stratified by whether the Medication Guide was received and read, if the Medication Guide was read and understood, modality for completing the survey (internet versus telephone), respondent highest level of education, or by the age group of the respondent (see Appendix B).

5.2.3 Key Risk Message 3

Key Risk Message 3 states "TIRF medicines should be taken exactly as prescribed by the healthcare provider." Nine questions/items defined this key risk message (Table 11).

Almost all respondents (99.7%, 95% CI: 98.2 100.0) understood that TIRF medicines should be taken exactly as prescribed by the doctor.

Most respondents understood that TIRF medicines should not be used for dental pain (86.8%, 95% CI: 82.5 90.3) or headache or migraine pain (78.1%, 95% CI: 73.0 82.5), and should be used for breakthrough pain from cancer (72.6%, 95% CI: 67.3 77.5). Over half of the respondents understood the TIRF medicines should not be used for pain after surgery (64.2%, 95% CI: 58.6 69.5), that it is not okay for patients to take TIRF medicines for headache pain (67.4%, 95% CI: 61.9 72.6), and that is not okay to take TIRF medicines for short-term pain that will go away in a few days (85.2%, 95% CI: 80.7 88.9). Less than half of respondents (39.0%, 95% CI: 33.6 44.7) indicated they were aware that TIRF medicines are not indicated for long-lasting pain not caused by cancer. Similarly, less than half of respondents 39.7%, 95% CI:34.2 45.4) understood that if a patient stops taking around-the-clock opioid pain medicine, they must also stop taking the TIRF medicine.

Table 11. Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%) [95% CI][2]
Question 10: For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.	
10a: Headache or migraine pain	
Yes	34 (11.0)
No[3]	242 (78.1) [73.0 - 82.5]
I don't know	34 (11.0)
10b: Breakthrough pain from cancer	
Yes[3]	225 (72.6) [67.3 - 77.5]
No	81 (26.1)
I don't know	4 (1.3)
10c: Dental pain	
Yes	5 (1.6)
No[3]	269 (86.8) [82.5 - 90.3]
I don't know	36 (11.6)
10d: Pain after surgery	
Yes	69 (22.3)
No[3]	199 (64.2) [58.6 - 69.5]
I don't know	42 (13.5)

Table 11. Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%) [95% CI][2]
10e: Long-lasting pain not from cancer, like arthritis joint pain	
Yes	148 (47.7)
No[3]	121 (39.0) [33.6 - 44.7]
I don't know	41 (13.2)
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	
True[3]	123 (39.7) [34.2 - 45.4]
False	88 (28.4)
I don't know	99 (31.9)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13b: It is OK for patients to take TIRF medicines for headache pain.	
True	20 (6.5)
False[3]	209 (67.4) [61.9 - 72.6]
I don't know	81 (26.1)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.	
True[3]	309 (99.7) [98.2 - 100.0]
False	1 (0.3)
I don't know	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.	
True	9 (2.9)
False[3]	264 (85.2) [80.7 - 88.9]
I don't know	37 (11.9)

Source: Appendix B: Survey Tables, Table 8.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

Overall, 11.0% of respondents correctly answered all questions/items of Key Risk Message 3, 30.6% missed no more than 1 item, and 48.4% missed no more than 2 of the 9 items (Table 12).

Table 12. Secondary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Correct Responses	Patients/Caregivers (N=310)[1] n (%)
0 correct responses	0
1 correct response	0
2 correct responses	9 (2.9)
3 correct responses	13 (4.2)
4 correct responses	29 (9.4)
5 correct responses	45 (14.5)
6 correct responses	64 (20.6)
7 correct responses	55 (17.7)
8 correct responses	61 (19.7)
9 correct responses	34 (11.0)

Source: Appendix B: Survey Tables, Table 8.2
[1] Total number of eligible respondents completing the survey.

There was a significant difference in the correct response rate for Question 12b when stratified by modality for completing the survey (Table 13). No trends were evident when the results for Key Risk Message 3 were stratified by whether the Medication Guide was received and read, if the Medication Guide was read and understood, respondent highest level of education, or by the age group of the respondent (see Appendix B).

Table 13. Responses to Questions Linked to Key Risk Message #3 by Modality to Complete Survey - Completed Surveys (Questions/Items with Apparent Trends)

Question	Modality to Complete Survey	
	Internet (N=207) n (%) [95% CI][1]	Telephone (N=103) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.		
True[2]	94 (45.4) [38.5 - 52.5]	29 (28.2) [19.7 - 37.9]
False	55 (26.6)	33 (32.0)
I don't know	58 (28.0)	41 (39.8)

Source: Appendix B: Survey Tables, Table 8.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

5.2.4 Key Risk Message 4

Key Risk Message 4 states "patients should not switch from one TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider." (Table 14).

Of the 310 respondents, 95.8% (95% CI: 92.9 97.7) understood that it is not safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.

Table 14. Primary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%) [95% CI][2]
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	
True	6 (1.9)
False[3]	297 (95.8) [92.9 - 97.7]
I don't know	7 (2.3)

Source: Appendix B: Survey Tables, Table 9.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

No trends were evident when the results for Key Risk Message 4 were stratified by whether the Medication Guide was received and read, if the Medication Guide was read and understood, modality for completing the survey (internet versus telephone), respondent highest level of education, and by the age group of the respondent (see Appendix B).

5.2.5 Key Risk Message 5

Key Risk Message 5 states "patients should never give TIRF medicines to anyone else even if they have the same symptoms." Five questions/items defined this key risk message (Table 15).

Almost all respondents understood that a patient may not give TIRF medicines to another person if they have the same symptoms as the patient (97.7%, 95% CI: 95.4 99.1), and that selling or giving away TIRF medicines is against the law (99.4%, 95% CI: 97.7 99.9)). Similarly, most respondents correctly indicated that a side effect of TIRF medicines is the chance of abuse or addiction (92.6%, 95% CI: 89.1 95.2), that TIRF medicines can be misused by people who abuse prescription medicines or street drugs (97.4%, 95% CI: 95.0 98.9), and that TIRF medicines should be kept in a safe place to prevent it from being stolen (99.4%, 95% CI: 97.7 99.9).

Table 15. Primary Analysis of Responses to Questions Linked to Key Risk Message #5 - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%) [95% CI][2]
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	
True	6 (1.9)
False[3]	303 (97.7) [95.4 - 99.1]
I don't know	1 (0.3)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a: Selling or giving away TIRF medicines is against the law.	
True[3]	308 (99.4) [97.7 - 99.9]
False	1 (0.3)
I don't know	1 (0.3)
Question 18: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
18a: A side effect of TIRF medicines is the chance of abuse or addiction.	
True[3]	287 (92.6) [89.1 - 95.2]
False	5 (1.6)
I don't know	18 (5.8)

Table 15. Primary Analysis of Responses to Questions Linked to Key Risk Message #5 - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%) [95% CI][2]
18b: TIRF medicines can be misused by people who abuse prescription medicines or street drugs.	
True[3]	302 (97.4) [95.0 - 98.9]
False	0
I don't know	8 (2.6)
18c: TIRF medicines should be kept in a safe place to prevent it from being stolen.	
True[3]	308 (99.4) [97.7 - 99.9]
False	1 (0.3)
I don't know	1 (0.3)

Source: Appendix B: Survey Tables, Table 10.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

Overall, 87.7% of respondents correctly answered all questions/items of Key Risk Message 5 (Table 16).

Table 16. Secondary Analysis of Responses to Questions Linked to Key Risk Message #5 - Completed Surveys

Correct Responses	Patients/Caregivers (N=310)[1] n (%)
0 correct responses	0
1 correct response	0
2 correct responses	1 (0.3)
3 correct responses	2 (0.6)
4 correct responses	35 (11.3)
5 correct responses	272 (87.7)

Source: Appendix B: Survey Tables, Table 10.2
[1] Total number of eligible respondents completing the survey.

No trends were evident when the results for Key Risk Message 5 were stratified by whether the Medication Guide was received and read, if the Medication Guide was read and understood, modality for completing the survey (internet versus telephone), respondent highest level of education, and by the age group of the respondent (see Appendix B).

5.2.6 Key Risk Message 6

Key Risk Message 6 states "TIRF medicines should be stored in a safe place away from children and properly disposed." Four questions/items defined this key risk message (Table 17).

All respondents (100.0%, 95% CI:98.8 100.0) correctly responded that TIRF medicines should be stored in a safe place out of the reach of children. Most respondents (89.0%, 95% CI: 85.0 92.3) correctly indicated they should get emergency help right away if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine, that TIRF medicines must be disposed of as described in the specific product's Medication Guide (97.7%, 95% CI: 95.4 99.1), and that a TIRF medicine can cause an overdose and death in any child who takes it (94.2%, 95% CI: 91.0 96.5).

Table 17. Primary Analysis of Responses to Questions Linked to Key Risk Message #6 - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%) [95% CI][2]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a: TIRF medicines should be stored in a safe place out of the reach of children.	
True[3]	310 (100.0) [98.8 - 100.0]
False	0
I don't know	0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	
Wait an hour and see if the person is OK.	10 (3.2)
Get emergency help right away.[3]	276 (89.0) [85.0 - 92.3]
Do nothing.	0
I don't know.	24 (7.7)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.	
True[3]	303 (97.7) [95.4 - 99.1]
False	2 (0.6)
I don't know	5 (1.6)

Table 17. Primary Analysis of Responses to Questions Linked to Key Risk Message #6 - Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%) [95% CI][2]
17e: A TIRF medicine can cause an overdose and death in any child who takes it.	
True[3]	292 (94.2) [91.0 - 96.5]
False	5 (1.6)
I don't know	13 (4.2)

Source: Appendix B: Survey Tables, Table 11.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

Overall, 83.9% of respondents correctly answered all questions/items of Key Risk Message 6 (Table 18).

Table 18. Secondary Analysis of Responses to Questions Linked to Key Risk Message #6 - Completed Surveys

Correct Responses	Patients/Caregivers (N=310)[1] n (%)
0 correct responses	0
1 correct response	1 (0.3)
2 correct responses	7 (2.3)
3 correct responses	42 (13.5)
4 correct responses	260 (83.9)

Source: Appendix B: Survey Tables, Table 11.2
[1] Total number of eligible respondents completing the survey.

No trends were evident when the results for Key Risk Message 6 were stratified by whether the Medication Guide was received and read, if the Medication Guide was read and understood, modality for completing the survey (internet versus telephone), respondent highest level of education, and by the age group of the respondent (see Appendix B).

5.2.7 Key Risk Message Average Knowledge Scores

Table 19 presents the average knowledge score for each key risk message and an overall knowledge score for all key risk messages combined. The overall knowledge score of 84.8 (95% CI: 83.5 86.0) indicates most respondents demonstrated understanding of the key risk messages. The average knowledge score for each of the key risk messages was greater than 88 for 5 of the

6 key risk messages and was 70.3 for Key Risk Message 3 (TIRF medicines should be taken exactly as prescribed by the healthcare provider).

Table 19. Average Knowledge Scores - Completed Surveys

	Score [95% CI][1]
KRM #1	91.6 [88.5, 94.7]
KRM #2	88.7 [85.7, 91.7]
KRM #3	70.3 [68.1, 72.5]
KRM #4	95.8 [93.6, 98.1]
KRM #5	97.3 [96.4, 98.2]
KRM #6	95.2 [93.9, 96.6]
Overall Knowledge Score	84.8 [83.5, 86.0]

Source: Appendix B: Survey Tables, Table 12
[1] 95% CIs are constructed based on normal distribution function.

5.2.8 Other Survey Questions

5.2.8.1 Additional Questions about TIRF Medicines Safety

Table 20 summarizes the patients'/caregivers' responses to additional questions about the safe use of TIRF medicines beyond those associated with the key risk messages. The results generally indicate that respondents were educated by a healthcare professional (HCP) on the precautions to be taken to ensure safe use of TIRF medicines. See Section 5.2 for all key risk message question results.

The majority of respondents (265; 85.5%) indicated someone in the doctor's office discussed the risks and possible side effects of the prescribed TIRF medicine.

Most respondents (294, 94.8%) indicated that someone in the doctor's office explained how to use the prescribed TIRF medicines and 270 (87.1%) indicated someone in the doctor's office advised them on the proper storage of the prescribed TIRF medicines. The majority (238; 76.8%) were also aware that TIRF medicines are only available through the TIRF REMS Access program. Additionally, most respondents indicated someone in the doctor's office told them not to share the TIRF medicines with anyone else (268, 86.5%), counseled them that accidental exposure to TIRF medicines by a child may be fatal (237, 76.5%), told them to keep TIRF medicines out of reach of children to prevent accidental exposure (264, 85.2%), and told them about proper disposal of any unused or partially used TIRF medicines (237, 76.5%). Over half of respondents (191, 61.6%) indicated someone in the doctor's office asked them about the presence of children in their home.

Table 20. Responses to Additional Questions about the Safe Use of TIRF Medicines-Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%)
Question 9: Did a doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of these brands.	
Yes	265 (85.5)
No	37 (11.9)
I don't know	8 (2.6)
Question 15: Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for you?	
Yes	294 (94.8)
No	15 (4.8)
I don't know	1 (0.3)
Question 16: Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?	
Yes	270 (87.1)
No	35 (11.3)
I don't know	5 (1.6)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17d: TIRF medicines are only available to patients through a pharmacy enrolled in a special program (called the TIRF REMS Access program).	
True[2]	238 (76.8)
False	10 (3.2)
I don't know	62 (20.0)
Question 37: Did a doctor, nurse, or other healthcare professional in the doctor's office ever ask you about the presence of children in your home?	
Yes	191 (61.6)
No	89 (28.7)
I don't know	30 (9.7)
Question 38: Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you not to share the TIRF medicines with anyone else?	
Yes	268 (86.5)
No	34 (11.0)
I don't know	8 (2.6)

Table 20. Responses to Additional Questions about the Safe Use of TIRF Medicines-Completed Surveys

Question	Patients/Caregivers (N=310)[1] n (%)
Question 39: Did a doctor, nurse, or other healthcare professional in the doctor's office ever counsel you that accidental exposure to TIRF medicines by a child may be fatal?	
Yes	237 (76.5)
No	48 (15.5)
I don't know	25 (8.1)
Question 40: Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you to keep TIRF medicines out of reach of children to prevent accidental exposure?	
Yes	264 (85.2)
No	35 (11.3)
I don't know	11 (3.5)
Question 41: Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you about proper disposal of any unused or partially used TIRF medicines?	
Yes	237 (76.5)
No	48 (15.5)
I don't know	25 (8.1)

Source: Appendix B: Survey Tables, Table 3
[1] Total number of eligible respondents completing the survey.
[2] Correct response.

5.3 Spontaneous Reporting of Adverse Events, Product Complaints, or Medical Information Requests

Among all survey respondents (N 394; Table 1), there were 80 reports of a potential adverse event or product complaint associated with the use of TIRF medicines made during a telephone interview, while activating a gift card via telephone, or reporting a patient death via telephone (71 reports); within the survey free text field during the online survey (6 reports); or via US mail (3 reports of patient deaths). Verbatim statements are provided in Appendix B, Listing 4.

6. DISCUSSION AND CONCLUSIONS

Discussion

Survey invitations (and reminders) were sent to all known patients/caregivers who had filled a prescription within the 4 months prior to survey launch. From the total of 394 patients/caregivers

who accessed the survey, 321 respondents met eligibility criteria, and of those who met eligibility criteria, 310 (305 patients and 5 caregivers) completed the survey.

There were statistically significant differences observed in the demographics between the patients completing the survey compared with the general population of patients on the questions for highest level of education and race; for all other questions responses were similar (Table 5). It is important to note the sample size of the general population of patients (N 3134 [or 1671 for race/ethnicity, language spoken in the home, and education level]) affects the power of the test, and therefore, may mean that even small differences between groups resulted in significant p-values. There were almost no differences between the patients completing the survey and the general population of patients for race where the response 'White' (86.1% vs. 89.3%) included the majority of responders in each group. The proportion of patients with completed college and graduate school were similar in the general population, but of those who participated in the survey, patients who completed 'some college' were overrepresented (44.4% vs. 27.2% in the general population) and patients completed high school or less than high school were underrepresented (16.8 versus 31.5% and 1.6 versus 5.6%), respectively. While the differences are statistically significant, these differences should not have a big impact on the primary objectives of the survey since a relevant uniform correlation between demographic characteristics and the knowledge of the key risk messages could not be detected. Therefore, despite these differences, the TRIG concludes that the survey sample of 310 patients is a valid representation of the general population of TIRF patients.

The overall knowledge score of 84.8 (95% CI: 83.5 86.0) for the survey indicates most respondents demonstrated understanding of the key risk messages (Table 19). The average knowledge score for each of the key risk messages was greater than 88 for 5 of the 6 key risk messages and was 70.3 for Key Risk Message 3 (TIRF medicines should be taken exactly as prescribed by the healthcare provider).The lower average knowledge score for Key Risk Message 3 reflected the 3 items (described below) with correct response rates <65%. The title of Key Risk Message 3 may also be misleading. Two of the 3 low scoring items were related to the indication for use of a TIRF medicine, and this is not really captured by the key risk message title (TIRF medicines should be taken exactly as prescribed by the HCP). There is another item in this key risk message (TIRF medicines should be taken exactly as prescribed by the doctor) that was answered correctly by 99.7% of the respondents.

Of the 22 items included as part of key risk messages, 16 items had a correct response rate of greater than 80%, and 3 items had a correct response rate between 65% and 80%. The remaining 3 items within Key Risk Message 3 had a correct response rate which fell below the desired threshold of 65%.

Correct response rate for Question 10: *For which of the following conditions should you use a TIRF medicine?* Item 10d: *Pain after surgery.* (Correct Response: No) was 64.2%; and correct response rate for Item 10e: *Long-lasting pain not from cancer, like arthritis joint pain* (Correct Response: No); was 39.0% for this 60-month survey. However, for Items 10a through 10c, most respondents understood that TIRF medicines should not be used for headache or migraine pain (78.1%) and dental pain (86.8%); and should be used for breakthrough pain from cancer

(72.6%). In addition, the correct response rate for Item 12b (*a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine*) was 39.7% in this 60-month survey.

As previously discussed, the survey was updated prior to launch based on FDA feedback received on 21 July 2016. Over 92% of respondents correctly responded that a side effect of TIRF medicines is the chance of abuse or addiction, that TIRF medicines can be misused by people who abuse medicines or street drugs, and TIRF medicines should be kept in a safe place (added Question 18). Nearly 90% of respondents correctly indicated TIRF medicines should only be taken by patients who are opioid tolerant (revised Question 11). For questions not included as part of key risk messages, new Questions 37 through 41 showed most respondents indicated someone in the doctor's office told them not to share the TIRF medicines with anyone else, counseled them that accidental exposure to TIRF medicines by a child may be fatal, told them to keep TIRF medicines out of reach of children to prevent accidental exposure, and told them about proper disposal of any unused or partially used TIRF medicines; and over half indicated someone in the doctor's office asked them about the presence of children in their home. In addition, Questions 9, 15, and 16 that ask patients about prescriber activities and were revised to allow pharmacists as a potential source of information, showed most respondents indicated someone in the doctor's office discussed the risks and possible side effects of the prescribed TIRF medicine, that someone in the doctor's office explained how to use the prescribed TIRF medicines, and someone in the doctor's office advised them on the proper storage of the prescribed TIRF medicines.

The correct response rates from the 12-month KAB survey through the 60-month KAB survey are shown in Table 21. Knowledge and understanding of the key risk messages has generally remained stable over time including Items 10d, 10e, and 12b mentioned above, which have had lower correct response rates for all survey waves.). Question 11 had a notably improved correct response rate once the question was revised back to the original 36-month survey question for this survey as detailed below.

- Question 11 as presented in the 48-month survey: *TIRF medicines should only be taken by cancer patients who are opioid tolerant,* correct response "True"; correct response rate 43.5%.
- Question 11 as presented in the 60-month survey: *TIRF medicines should only be taken by patients who are opioid tolerant,* correct response "True"; correct response rate 89.4%.

Table 21 below includes key risk messages and questions/items within each key risk message as presented in the 60-month survey. It is important to note the question/item numbering, wording, and association with a specific key risk message may have changed across survey waves based on FDA feedback or other decisions made by the TRIG. A limitation to looking at correct response rates over time is that survey questions may have been modified. The primary focus of this table is to show general trends over time with a specific focus on changes from the 48-month survey to the 60-month survey.

Table 21. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response Rate % (95% CI)	24-Month Survey Correct/Desired Response Rate % (95% CI)	36-Month Survey Correct/Desired Response Rate % (95% CI)	48-Month Survey Correct/Desired Response Rate % (95% CI)	60-Month Survey Correct/Desired Response Rate % (95% CI)
Key Risk Message 1: TIRF Medicines Can Cause Life-threatening Breathing Problems That Can Lead to Death						
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.					
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death. (*Correct Response True*)	90.1 (85.0, 93.9)	90.1 (86.1, 93.2)	91.3 (86.8, 94.6)	91.9 (88.3 - 94.7)	91.6 (88.0 - 94.4)
Key Risk Message 2: Patients Should Not Take TIRF Medicines if They Are Not Opioid Tolerant						
11/12	Please answer True, False, or I don't know for the following statement:					
11	TIRF medicines should only be taken by patients who are opioid tolerant (*Correct Response True*)[1]	90.6 (85.6, 94.3)	91.7 (88.0, 94.6)	85.2 (79.9, 89.5)	43.5 (38.0 - 49.3)	89.4 (85.4 - 92.6)
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines. (*Correct Response True*)	91.7 (86.8, 95.2)	88.4 (84.3, 91.8)	81.7 (76.0, 86.5)	90.3 (86.5 - 93.4)	88.1 (83.9 - 91.5)

Table 21. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response Rate % (95% CI)	24-Month Survey Correct/Desired Response Rate % (95% CI)	36-Month Survey Correct/Desired Response Rate % (95% CI)	48-Month Survey Correct/Desired Response Rate % (95% CI)	60-Month Survey Correct/Desired Response Rate % (95% CI)
Key Risk Message 3: TIRF Medicines Should Be Taken Exactly as Prescribed By the Healthcare Provider						
10	For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.					
10a	Headache or migraine pain. (*Correct Response No*)	72.9[2]	77.5[2]	78.2[2]	80.6 (75.8 - 84.9)	78.1 (73.0 - 82.5)
10b	Breakthrough pain from cancer. (*Correct Response Yes*)	69.8[2]	64.2[2]	65.9[2]	68.4 (62.9 - 73.5)	72.6 (67.3 - 77.5)
10c	Dental pain. (*Correct Response No*)	89.6[2]	87.4[2]	87.3[2]	90.3 (86.5 - 93.4)	86.8 82.5 - 90.3]
10d	Pain after surgery. (*Correct Response No*)	67.7[2]	68.5[2]	70.3[2]	67.7 (62.2 - 72.9)	64.2 (58.6 - 69.5)
10e	Long-lasting pain not from cancer, like arthritis joint pain *(Correct Response No)*	24.5[2]	21.9[2]	25.3[2]	43.9 (38.3 - 49.6)	39.0 (33.6 - 44.7)
12	Please answer True, False, or I don't know for each of the following statements.					
12b	A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine. (*Correct Response True*)	42.7 (35.6, 50.0)	34.1 (28.8, 39.8)	36.7 (30.4, 43.3)	39.4 (33.9 - 45.0)	39.7 (34.2 - 45.4)
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.					

Table 21. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response Rate % (95% CI)	24-Month Survey Correct/Desired Response Rate % (95% CI)	36-Month Survey Correct/Desired Response Rate % (95% CI)	48-Month Survey Correct/Desired Response Rate % (95% CI)	60-Month Survey Correct/Desired Response Rate % (95% CI)
13b	It is OK for patients to take TIRF medicines for headache pain. (*Correct Response False*)	70.8 (63.9, 77.2)	68.2 (62.6, 73.4)	69.4 (63.0, 75.3)	74.8 (69.6 - 79.6)	67.4 (61.9 - 72.6)
13c	TIRF medicines should be taken exactly as prescribed by the doctor. (*Correct Response True*)	100.0 (98.1, 100.0)	99.7 (98.2, 100.0)	99.1 (96.9, 99.9)	100.0 (98.8 - 100.0)	99.7 (98.2 - 100.0)
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days. (*Correct Response False*)	82.3 (76.1, 87.4)	83.4 (78.8, 87.5)	83.0 (77.5, 87.6)	86.1 (81.8 - 89.8)	85.2 (80.7 - 88.9)
Key Risk Message 4: Patients Should Not Switch From One TIRF Medicine to Another Medicine That Contains Fentanyl Without Talking to a Healthcare Provider						
12	Please answer True, False, or I don't know for each of the following statements.					
12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first. (*Correct Response False*)	96.9 (93.3, 98.8)	94.4 (91.1, 96.7)	96.9 (93.8, 98.8)	95.2 (92.1 - 97.3)	95.8 (92.9 - 97.7)

Table 21. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response Rate % (95% CI)	24-Month Survey Correct/Desired Response Rate % (95% CI)	36-Month Survey Correct/Desired Response Rate % (95% CI)	48-Month Survey Correct/Desired Response Rate % (95% CI)	60-Month Survey Correct/Desired Response Rate % (95% CI)
Key Risk Message 5: Patients Should Never Give TIRF Medicines to Anyone Else Even if They Have the Same Symptoms						
12	Please answer True, False, or I don't know for each of the following statements.					
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient. *(Correct Response False)*	100.0 (98.1, 100.0)	98.0 (95.7, 99.3)	99.1 (96.9, 99.9)	99.4 (97.7 - 99.9)	97.7 (95.4 - 99.1)
17/18	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.					
17a	Selling or giving away TIRF medicines is against the law. *(Correct Response True)*	97.9 (94.8, 99.4)	98.3 (96.2, 99.5)	99.1 (96.9, 99.9)	98.7 (96.7 - 99.6)	99.4 (97.7 - 99.9)
18a	A side effect of TIRF medicines is the chance of abuse or addiction. *(Correct Response True)*	N/A[3]	N/A[3]	N/A[3]	N/A[3]	92.6 (89.1 - 95.2)
18b	TIRF medicines can be misused by people who abuse prescription medicines or street drugs. *(Correct Response True)*	N/A[3]	N/A[3]	N/A[3]	N/A[3]	97.4 (95.0 - 98.9)

Table 21. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response Rate % (95% CI)	24-Month Survey Correct/Desired Response Rate % (95% CI)	36-Month Survey Correct/Desired Response Rate % (95% CI)	48-Month Survey Correct/Desired Response Rate % (95% CI)	60-Month Survey Correct/Desired Response Rate % (95% CI)
18c	TIRF medicines should be kept in a safe place to prevent it from being stolen. *(Correct Response True)*	N/A[3]	N/A[3]	N/A[3]	N/A[3]	99.4 (97.7 - 99.9)
Key Risk Message 6: TIRF Medicines Should be Stored in a Safe Place Away From Children and Properly Disposed						
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.					
13a	TIRF medicines should be stored in a safe place out of the reach of children. *(Correct Response True)*	100.0 (98.1, 100.0)	100.0 (98.8, 100.0)	99.1 (96.9, 99.9)	99.7 (98.2 - 100.0)	100.0 (98.8 - 100.0)
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide. *(Correct Response True)*	95.8 (92.0, 98.2)	94.4 (91.1, 96.7)	93.9 (90.0, 96.6)	96.5 (93.7 - 98.2)	97.7 (95.4 - 99.1)
17e	A TIRF medicine can cause an overdose and death in any child who takes it. *(Correct Response True)*	90.6 (85.6, 94.3)	91.1 (87.3, 94.0)	90.4 (85.8, 93.9)	93.2 (89.8 - 95.8)	94.2 (91.0 - 96.5)

Table 21. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response Rate % (95% CI)	24-Month Survey Correct/Desired Response Rate % (95% CI)	36-Month Survey Correct/Desired Response Rate % (95% CI)	48-Month Survey Correct/Desired Response Rate % (95% CI)	60-Month Survey Correct/Desired Response Rate % (95% CI)
14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.) *(Correct Response: Get emergency help right away.)*	89.1 (83.8, 93.1)	87.4 (83.1, 90.9)	88.2 (83.3, 92.1)	88.1 (83.9 - 91.5)	89.0 (85.0 - 92.3)

[1] Question was revised for the 60-month survey.

[2] 95% confidence interval is not provided since the question/item was not part of a key risk message during reporting period.

[3] Question was not asked during the reporting period.

Conclusions

In general, knowledge and understanding of the key risk messages has remained stable over time (Table 21). Patients scored consistently low on 3 of 22 items: that TIRF medicines should not be taken for pain after surgery; that TIRF medicines should not be taken for long-lasting pain not from cancer, like arthritis joint pain; and that a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.

Overall, this 60-month survey shows a high level (greater than or equal to 65% for all but three items) of patient understanding of key risk messages based on the REMS goals. The TRIG acknowledges that there is room for improvement around patient knowledge related to conditions for use of a TIRF medicine and stopping a TIRF medicine when stopping their around-the-clock opioid pain medicine.

Appendix A Patient Survey Protocol Track Change Document: Comparison of 48-month Survey to 60-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Patient/Caregiver Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Actavis Laboratories FL, Inc.** **BioDelivery Sciences International, Inc. ~~(BDSI) *(replaced Meda Pharmaceuticals on March 11, 2015)*~~(BDSI)** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Depomed, Inc.** **~~Galena Biopharma, Inc.~~** **Insys Therapeutics, Inc.** **Mallinckrodt Pharmaceuticals** **Mylan~~,~~ Inc.** **Par ~~Pharmaceutical~~Pharmaceuticals, Inc.** **Sentynl Therapeutics, Inc.**
VERSION:	**~~1~~012.0**
DATE:	**~~13AUG2015~~04AUG2016**
APPROVED:	**~~FINAL~~Final**

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1. LIST OF ABBREVIATIONS

BDSI	BioDelivery Sciences International, Inc.
CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
IRB	Institutional Review Board
KAB	Knowledge, Attitudes, and Behavior
~~PBM~~	~~Pharmacy Benefits Management~~
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access ~~Program~~program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics, which are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. ~~(BDSI) (replaced Meda Pharmaceuticals on March 11, 2015~~(BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; ~~Galena Biopharma, Inc.;~~ Insys Therapeutics, Inc; Mallinckrodt Pharmaceuticals; Mylan Inc.; Par Pharmaceuticals, Inc.; and ~~Par Pharmaceutical,~~Sentynl Therapeutics. Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the risks of misuse, abuse, addiction, overdose and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access ~~Program~~program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the ~~risk~~risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which include use only in opioid-tolerant patients

2. Preventing inappropriate conversion between TIRF medicines

3. Preventing accidental exposure to children and others for whom it was not prescribed

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess patients' and caregivers' knowledge, attitudes, and behavior (KAB) regarding the safe use of TIRF medicines as described in the product-specific Medication Guide. This protocol will describe the administration of the surveys that will be conducted among patients who are treated with TIRF medicines, or their caregivers. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes and/or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE PATIENT EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of patients around the following key information and risk messages communicated through the REMS:

1) TIRF medicines can cause life-threatening breathing problems that can lead to death.
2) Patients should not take TIRF medicines if they are not opioid tolerant.
3) TIRF medicines should be taken exactly as prescribed by the healthcare provider.
4) Patients should not switch from one TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.
5) Patients should never give TIRF medicines to anyone else even if they have the same symptoms.
6) TIRF medicines should be stored in a safe place away from children and properly disposed.

The survey will also include questions about whether patients received, read, and understood the product-specific Medication Guide and Patient-Prescriber Agreement Form (PPAF).

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Qualitative Research on the Survey

Qualitative research to test patient comprehension was performed on the patient survey in 2012. Findings were incorporated into the survey prior to implementation of Wave 1.

4.2 Survey Design

This survey will be conducted among a sample of patients or their caregivers who have filled a prescription for a TIRF medicine within the past 4 months (120 days) prior to survey launch. Respondents who have participated in a previous wave of the TIRF REMS KAB Survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered, online through a secure website
- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix ~~B~~ A is written to reflect wording for both methods of survey administration: Internet-based and telephone administration.

All respondents who complete the survey and who provide their contact information will be mailed a $50 gift card for their time.

4.2.1 Questions and Statements on REMS Goals

The questionnaire is made up of multiple-choice, closed-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and open-ended questions. These questions will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3. The survey is written to follow principles of health literacy and readability.

~~Questionnaire items will be~~Questions are presented in several formats:

- Statements or questions asking the respondent to indicate whether the statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes," "no," or "I don't know" as potential response options);
- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and
- Questions allowing for the respondent to provide information about when, where and from whom they obtained a Medication Guide, as well as to list questions they have about information in the Medication Guides.

Questionnaires will be analyzed to determine patient understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for the key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A). For better readability, the patient questions, only, are presented in the key risk messages tables. Caregiver questions are presented in Appendix A.

Key Risk Message 1: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
Question No.	**Question**	**Desired Response**
13	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d	TIRF medicines can cause life-threatening breathing problems that can lead to death.	**TRUE**

Key Risk Message 2: Patients should not take TIRF medicines if they are not opioid tolerant.		
Question No.	**Question**	**Desired Response**
11	Please answer True, False, or I don't know for the following statement:	
	TIRF medicines should only be taken by ~~cancer~~ patients who are opioid tolerant.	**TRUE**
12	Please answer True, False, or I don't know for each of the following statements.	
12a	Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	**TRUE**

Key Risk Message 3: TIRF medicines should be taken exactly as prescribed by the healthcare provider.		
Question No.	**Question**	**Desired Response**
10	For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.	
10a	Headache or migraine pain	**NO**
10b	Breakthrough pain from cancer	**YES**
10c	Dental pain	**NO**
10d	Pain after surgery	**NO**
10e	Long-lasting pain not from cancer, like arthritis joint pain	**NO**
12	Please answer True, False, or I don't know for each of the following statements.	
12b	A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	**TRUE**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13b	It is OK for patients to take TIRF medicines for headache pain.	**FALSE**
13c	TIRF medicines should be taken exactly as prescribed by the doctor.	**TRUE**
~~**13b**~~	~~It is OK for patients to take TIRF medicines for headache pain.~~	~~**FALSE**~~
17b	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	**FALSE**

Key Risk Message 4: Patients should not switch from one TIRF medicine to another medicine that contains fentanyl without talking to a healthcare provider.		
Question No.	**Question**	**Desired Response**
12	Please answer True, False, or I don't know for each of the following statements.	

12c	It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	**FALSE**

Key Risk Message 5: Patients should never give TIRF medicines to anyone else even if they have the same symptoms.		
Question No.	**Question**	**Desired Response**
12	Please answer True, False, or I don't know for each of the following statements.	
12d	A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	**FALSE**
17/18	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a	Selling or giving away TIRF medicines is against the law.	**TRUE**
18a	A side effect of TIRF medicines is the chance of abuse or addiction.	**TRUE**
18b	TIRF medicines can be misused by people who abuse prescription medicines or street drugs.	**TRUE**
18c	TIRF medicines should be kept in a safe place to prevent it from being stolen.	**TRUE**

Key Risk Message 6: TIRF medicines should be stored in a safe place away from children and properly disposed.		
Question No.	**Question**	**Desired Response**
13/17	Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a	TIRF medicines should be stored in a safe place out of the reach of children.	**TRUE**
14	What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	**GET EMERGENCY HELP RIGHT AWAY.**
17c	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	**TRUE**
17e	A TIRF medicine can cause an overdose and death in any child who takes it.	**TRUE**

~~14~~	~~What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)~~	~~Get emergency help right away.~~

4.2.2 Additional Questions

Questions about the requirements of the TIRF REMS, and receipt and understanding of the Medication Guides and PPAF will be asked after the key risk message questions, and will be followed by the collection of demographic information at the completion of the survey.

4.3 ~~Subject~~Participant Recruitment

A random sample of patients who are passively enrolled in the TIRF REMS Access ~~Program~~program and have received a TIRF medicine in the previous 4 months (120 days) will be invited to participate via an invitation letter. Address verification is required on these data due to the limited data points collected through the PPAF. In order to obtain this additional information a public records database will be used and those data combined with the TIRF REMS Access ~~Program~~program data will be used to distribute those invitations to the select patient population. ~~Additional patients will be identified for participation through a pharmacy benefits management (PBM) partner, which will provide a broad demographic coverage and include patients in 49 states.~~ Through use of these sources, a list will be created of patients who have filled a prescription for a TIRF medicine within 4 months (120 days) prior to survey launch (first prescriptions and refills). Patients in this list will be invited to participate in the survey through an invitation letter (Appendix B). The letter will be sent from the Survey Coordinating Center and mailed directly to the patients on UBC letterhead ~~(for the patients being invited by way of the TIRF REMS Access Program database and the public record database) or the PBM's letterhead at the corporate level (for those patients being recruited through the PBM). Both invitation letters will be mailed via the United States (US) Postal Service.~~ via the United States (US) Postal Service.

The invitation will indicate that participants will receive a $50 gift card for completing the survey. Each invitation will also include a unique code and directions for accessing the survey either via the Internet or by telephone through an interviewer at the Survey Coordinating Center. ~~The unique code will be used to identify the manufacturer of the most recent TIRF prescription that the patient filled.~~

A sample of patients who have filled a prescription for a TIRF medicine within the 4 months (120 days) prior to survey launch will be chosen from the TIRF REMS Access ~~Program database and/or PBM's~~program database. This sampling approach will be used to create several batches of survey invitations. The overall number of unique patients and the duration of the survey period will dictate the size and number of invitation batches. If the required number of completed surveys is not achieved within a reasonable time frame, a second mailing will be sent to non-respondents from the original batch mailing and initial invitations will be sent to patients in the second batch. If the required number of completed surveys is still not achieved within a reasonable time frame, reminder letters will be sent to the patients in the second batch and initial invitations will be sent to the third batch of patients. If these efforts do not result in the required number of surveys within a reasonable time frame, then a new sample of patients may be selected if available. The intervals for sending reminder invitations to non-responders and for selecting a new sample will be condensed as necessary based on the actual rate of survey accrual relative to the proximity of the target survey close date.

All respondents who complete the survey and who provide their contact information will be mailed a $50 gift card to thank them for their participation. The mailing will include a thank

you letter, a copy of the product-specific Medication Guide, and a copy of the correct answers to the key risk message questions.

4.3.1 Measures to Minimize Bias in the Sample

The sample of participating patients will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of patients for participation.

Respondents will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

~~5. STUDY POPULATION~~

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 patients treated with TIRF medicines is proposed for the survey wave. The size of the sample was determined based on both practical and statistical considerations. ~~There is no target comprehension rate specified *a priori*.~~ A sample of 300 completed surveys will allow estimation of the comprehension rate for each key risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

The following respondents are eligible to participate in the survey:

- Patients who are 18 years of age or older who have filled a prescription for at least one of the TIRF medicines within 4 months (120 days) prior to survey launch
- Caregivers 18 years of age or older who care for patients who have filled a TIRF medicine prescription within the past 4 months (120 days) prior to survey launch and are unable to take the survey for themselves

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Patients who have previously participated in the TIRF REMS KAB survey (this exclusion applies to the second and subsequent waves only)
- Patients or their immediate family members who have ever worked for Actavis Laboratories FL, Inc~~.~~,.; Anesta LLC~~,~~; BioDelivery Sciences International, Inc. (BDSI~~),~~); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma; Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan~~,~~ Inc.; Par ~~Pharmaceutical~~Pharmaceuticals, Inc.; Teva Pharmaceuticals, Ltd.; Sentynl Therapeutics. Inc.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

~~6. SURVEY PROCESS~~

6. SURVEY PROCESS

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm patient eligibility. ~~The entire survey is expected to take approximately 20 minutes to complete.~~ Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, respondents are immediately notified with a thank you message that survey participation has ended. If eligible, respondents are allowed to continue survey participation.

The electronic data capture (EDC) system that is used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Patient-identifying information will be stored separately from survey data.

The entire survey is expected to take approximately 20 minutes to complete.

6.1.1 Telephone

The telephone survey is facilitated by a trained interviewer from the Survey Coordinating Center using a CATI program. The respondent will be required to provide a unique code to access the survey. Working from a CATI script, the interviewer will read questions or statements to the respondent and enter the responses into the EDC system. Screening and main elements of the questionnaire will be administered sequentially during the same telephone call. Telephone interviewing allows participation of respondents who do not have Internet access, or prefer to complete the survey in this manner.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If respondents select to participate in the survey online, they will be directed to a secured website and instructed to enter a unique code to access the survey. An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified survey time period.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question

once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. Any free text fields will be grouped into applicable categories. Verbatim text from open-ended questions will be displayed when appropriate. The following will be reported as part of this analysis:

- The number of invitations issued
- The number of invitations returned as undeliverable
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents who completed all questions presented to them
- Description of survey participants, including:
  - Type of respondent (patient/caregiver)
  - Age (patient/caregiver)
  - Gender (respondent)
  - Educational level (respondent)
  - Main language spoken at home (respondent)
  - Ethnicity (respondent)
  - Race (respondent)
  - Geographic region (respondent)
- Data from all respondents who completed all questions presented to them in the survey ("completers") will be analyzed, including:

- Frequency distribution of responses to each key risk message question.
- Percent of completers selecting desired response to each question relating to each key risk message and 95% CI.

Measurement of understanding will be computed for each question of the key risk message individually. A secondary analysis will be conducted to determine the number of completers who answered all items correctly for the key risk message. Behavior questions will be summarized on a question-by-question basis and are not included in the analysis by key risk message.

Mean knowledge scores will be computed for each key risk message; an overall knowledge score will be computed for each respondent as well.

Additional analyses may be performed as needed.

8. SAFETY EVENT REPORTING

The survey will be conducted via the Internet and by telephone. It is possible that a respondent may report an adverse event or other safety event experienced while taking TIRF medicines either in free text fields of the survey or while in conversation with the Survey Coordinating Center. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. The respondent will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact him/her if there are questions about the survey. The Internet-based questionnaires will be monitored for any comments recorded in free text fields. Information on all comments that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The EDC system used for data collection encrypts all identifiable information and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail a $50 gift card, a Thank You Letter, a product-specific Medication Guide, and correct survey responses to key risk message questions after the survey is completed. Respondent contact information is also requested in the event a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information. A respondent may be contacted only if clarification or follow-up is needed regarding a possible safety event that was mentioned to the interviewer or recorded in free text fields of the online survey.

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to receive TIRF medicines.

This protocol and survey will be reviewed and approved by a central Institutional Review Board (IRB) before administration of the survey.

APPENDIX A Screening and Main Questionnaire

Survey Legend

[PROGRAMMER] is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

[PATIENT] indicates text applicable to a patient when it differs from survey text for caregivers, parents and legal guardians.

[OTHER] indicates text applicable to parents, caregivers, and legal guardians when it differs from survey text for patients.

(INTERVIEWER) is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

[ONLINE] indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

[BEGIN SURVEY CONTENT] and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

[TERMINATE] is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

> *Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.*

[RANDOMIZE LIST] is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as “I don’t know,” “Prefer not to answer” or “None of the above” will always appear at the end of the randomized responses.

[GO TO Qx] (Skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

Response options for questions that allow multiple responses must be indicated with check

Survey Legend

boxes (□). At least one option must be selected for the question to be considered answered.

If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option~~.~~, if applicable.

Response options for questions that allow only one response must be indicated with radio buttons (○).

If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option, if applicable.

[FREE TEXT] indicates to the programmer that one line should be provided for data entry.

[MULTILINE INPUT] indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines).

[DROP-DOWN LIST INPUT WITH STATES TABLE] indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Survey Legend

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS
- West South Central Division - AR, LA, OK, TX

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[BEGIN ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by UBC on behalf of the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access ~~Program (“~~program (TIRF REMS Access ~~Program”~~program or Program), sponsors of which include the makers of Abstral®, Actiq®, Fentora®, Lazanda®, Subsys® and the generic versions of any of these brands. These TIRF Medicines are also known as rapid onset opioids ~~(~~and sometimes called ~~“~~fast acting fentanyls~~”).~~. Please note that references to the TIRF REMS Access ~~Program~~program in this introduction include the sponsors of the Program, as well as its retained agents or contractors, including UBC.

The information collected will help the makers of TIRF Medicines know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF Medicines.

How We Use Your Information

The terms of the TIRF REMS Access ~~Program~~program Patient-Prescriber Agreement Form (PPAF) on file and the Patient Privacy Notice contained therein, provide that the TIRF REMS Access ~~Program~~program may receive, use, and share your health information, using a unique identifier instead of your name, in order to evaluate the proper use of TIRF Medicines and report to the Food and Drug Administration (FDA) about the effectiveness of the Program. Should you choose to participate in the survey, you agree that any information you provide during the course of the survey may be used or shared with the TIRF REMS Access ~~Program~~program according to these terms.

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be collected by UBC, compiled, and reported in anonymous form to the TIRF REMS Access ~~Program~~program and the FDA. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 gift card for your time.

Your name and address will be received only by UBC and will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. The TIRF REMS Access ~~Program~~program will not sell, transfer (except in connection with reporting to the FDA), or rent your information. Your privacy will be protected; however, research survey records may be inspected by the FDA and a company called Sterling Independent Services, Inc., which is the Institutional Review Board (IRB) that looks out for the interest of survey participants. Your choice to allow the TIRF REMS Access ~~Program~~program to use your information is entirely voluntary, but necessary to take part in this survey.

Please be assured that your contact information and your individual responses will be kept strictly confidential. As noted above, however, information you provide will be combined with information and survey responses provided by others and shared or reported in anonymous form. By participating in the survey, you acknowledge and agree that such combined anonymous data may be used by the TIRF REMS Access ~~Program~~program and disclosed to the FDA. By participating, you also acknowledge that the FDA and/or IRB, may inspect the records related to this survey which may include your individual responses.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at 1-888-636-1062. Be sure to write down this telephone number; it will not be displayed again.

How to Learn More About This Survey

If you have questions about the survey, or have any problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297.

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF Medicines, talk to your doctor, pharmacist, or other health care professional.

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[BEGIN PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The survey is being conducted by UBC on behalf of the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access ~~Program (“~~program (TIRF REMS Access ~~Program”~~program or Program) sponsors of which include the makers of Abstral®, Actiq®, Fentora®, Lazanda®, Subsys® and the generic versions of any of these brands. These TIRF **(INTERVIEWER: Pronounce “TIRF,” then spell out T-I-R-F)** Medicines~~,~~ are also known as rapid onset opioids **(INTERVIEWER: Please pause briefly)** ~~(~~and sometimes called ~~“~~fast acting fentanyls~~”) or TIRF Medicines.~~. Please note that references to the TIRF REMS Access ~~Program~~program in this introduction include the sponsors of the Program, as well as its retained agents or contractors, including UBC.

~~**(INTERVIEWER: Pronounce “TIRF,” then spell out T-I-R-F).**~~

The information collected will help the makers of TIRF Medicines know if patients and their caregivers understand important information about taking these medicines. The survey will take about 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time without penalty or loss of benefits to which you are otherwise entitled. Your answers to the questions or your decision to take part in the survey will not affect your ability to receive or take TIRF Medicines.

Now I would like to tell you about how your contact information will be used.

The terms of the TIRF REMS Access ~~Program~~program Patient-Prescriber Agreement Form (PPAF) on file and the Patient Privacy Notice contained therein, provide that the TIRF REMS Access ~~Program~~program may receive, use, and share your health information, using a unique identifier instead of your name, in order to evaluate the proper use of TIRF Medicines and report to the Food and Drug Administration (FDA) about the effectiveness of the Program. Should you choose to participate in the survey, you agree that any information you provide during the course of the survey may be used or shared with the TIRF REMS Access ~~Program~~program according to these terms.

Your answers to the survey questions will be combined with answers given by other people taking the survey. All answers will be collected by UBC, compiled, and reported in anonymous form to the TIRF REMS Access ~~Program~~program and the FDA. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 gift card for your time.

Your name and address will be received only by UBC and will be used only to send you the gift card, a Thank You Letter, a product-specific Medication Guide, and a copy of the correct answers to key risk message questions, after you complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your answers.

Now I would like to tell you about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. The TIRF REMS Access ~~Program~~program will not sell, transfer (except in connection with reporting to the FDA), or rent your information. Your privacy will be protected; however, research survey records may be inspected by the FDA and a company called Sterling Independent Services, Inc., which is the Institutional Review Board (IRB) that looks out for the interest of survey participants. Your choice to allow the TIRF REMS Access ~~Program~~program to use your information is entirely voluntary, but necessary to take part in this survey.

Please be assured that your contact information~~,~~ and your individual responses will be kept strictly confidential. As noted above, however, information you provide will be combined with information and survey responses provided by others and shared or reported in anonymous form. By participating in the survey, you acknowledge and agree that such combined anonymous data may be used by the TIRF REMS Access ~~Program~~program and disclosed to the FDA. By participating, you also acknowledge that the FDA and/or IRB~~,~~ may inspect the records related to this survey which may include your individual responses.

If you have questions about your rights as a research participant or related concerns, you may contact the IRB at 1-888-636-1062.

The information in this survey should not take the place of talking with your doctor or health care professional. If you have any questions about your condition or treatment or that of the person you care for, or if you would like more information about TIRF Medicines, talk to your doctor, pharmacist, or other health care professional.

Please feel free to ask me to repeat any questions or statements as we go through the survey.

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Do you agree to take part in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Within the last 4 months (120 days), have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of any of these brands.

   - ○ Yes **[GO TO Q4]**
   - ○ No
   - ○ I don't know

3. Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months (120 days)? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys® and the generic versions of any of these brands.

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. **[PATIENT]** For which TIRF medicines have you filled a prescription in the last 4 months (120 days)? Please select all that apply.

[CAREGIVER] For which TIRF medicines has the person you care for filled a prescription in the last 4 months (120 days)? Please select all that apply.

- ☐ Abstral
- ☐ Actiq, including generic versions of Actiq
- ☐ Fentora
- ☐ Lazanda
- ☐ Subsys
- ☐ Other
- ☐ I don't know **[CLEAR ALL OTHER SELECTIONS]**

5. Have you ever taken part in a survey about a TIRF medicine before?

- ○ Yes **[TERMINATE]**
- ○ No
- ○ I don't know **[TERMINATE]**

6. Which of the following groups best describes your age?

- ○ Under 18 **[TERMINATE]**
- ○ 18 29
- ○ 30 39
- ○ 40 49
- ○ 50 59
- ○ 60 69
- ○ 70 or older
- ○ Prefer not to answer **[TERMINATE]**

7. **[CAREGIVER]** Which of the following groups best describes the patient's age?

- ○ Under 16
- ○ 16 29
- ○ 30 39
- ○ 40 49
- ○ 50 59
- ○ 60 69
- ○ 70 or older
- ○ Prefer not to answer **[TERMINATE]**

8. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

- ☐ Actavis Laboratories FL, Inc. **[TERMINATE]**
- ☐ Anesta LLC **[TERMINATE]**
- ☐ BioDelivery Services International (BDSI) **[TERMINATE]**
- ☐ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
- ☐ Depomed, Inc. **[TERMINATE]**
- ☐ Galena Biopharma, Inc. **[TERMINATE]**
- ☐ Insys Therapeutics, Inc. **[TERMINATE]**
- ☐ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Mylan~~,~~ Inc. **[TERMINATE]**
- ☐ Par ~~Pharmaceutical~~Pharmaceuticals, Inc. **[TERMINATE]**
- ☐ RelayHealth**[TERMINATE]**
- ☐ Sentynl Therapeutics. Inc. **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA (Food and Drug Administration) **[TERMINATE]**
- ☐ No **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

[BEGIN PREAMBLE 2 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

[BEGIN PATIENT] Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for you. TIRF medicines include

Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of these brands. Please think of the information that you read or that was provided to you by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

[END PATIENT]

[BEGIN CAREGIVER] Please answer the following questions based on information about the TIRF medicine that was most recently prescribed for the patient. TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of these brands. Please think of the information that you read or that was provided to you or to the patient by a doctor, nurse, or other healthcare professional. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

[END CAREGIVER]

[END PREAMBLE 2]

9. **[PATIENT]** Did ~~the~~a doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of these brands.

[CAREGIVER] Did ~~the~~a doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed to the patient? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of these brands.

- o Yes
- o No
- o I don't know

10. **[PATIENT]** For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.

[CAREGIVER] For which of the following conditions should the person you take care of use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.

[RANDOMIZE LIST]	**Yes**	**No**	**I don't know**
10a. Headache or migraine pain	○	○	○
10b. Breakthrough pain from cancer	○	○	○
10c. Dental pain	○	○	○
10d. Pain after surgery	○	○	○
10e. Long-lasting pain not from cancer, like arthritis joint pain	○	○	○

11. Please answer True, False, or I don't know for the following statement:

TIRF medicines should only be taken by ~~cancer~~ patients who are opioid tolerant.

- ○ True
- ○ False
- ○ I don't know

12. Please answer True, False, or I don't know for each of the following statements.

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
12a. Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	○	○	○
12b. A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	○	○	○
12c. It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	○	○	○
12d. A patient may give TIRF medicines to another person if	○	○	○

they have the same symptoms as the patient.

13. **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
13a.	TIRF medicines should be stored in a safe place out of the reach of children.	○	○	○
13b.	It is OK for patients to take TIRF medicines for headache pain.	○	○	○
13c.	TIRF medicines should be taken exactly as prescribed by the doctor.	○	○	○
13d.	TIRF medicines can cause life-threatening breathing problems that can lead to death.	○	○	○

14. What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)

[RANDOMIZE LIST]

- ○ Wait an hour and see if the person is OK.
- ○ Get emergency help right away.
- ○ Do nothing.
- ○ I don't know.

15. **[PATIENT]** Did ~~the~~a doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did ~~the~~a doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for the patient?

- Yes
- No
- I don't know

16. **[PATIENT]** Did ~~the~~a doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?

[CAREGIVER] Did ~~the~~a doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for the patient?

- Yes
- No
- I don't know

17. **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
17a.	Selling or giving away TIRF medicines is against the law.	○	○	○
17b.	It is OK to take TIRF medicines for short-term pain that will go away in a few days.	○	○	○
17c.	TIRF medicines must be disposed of as described in the specific product's Medication Guide.	○	○	○
17d.	TIRF medicines are only available to patients through a pharmacy enrolled in a special program (called the TIRF REMS Access ~~Program~~program).	○	○	○
17e.	A TIRF medicine can cause an overdose and death in any child who takes it.	○	○	○

18. **[PATIENT]** Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

[CAREGIVER] Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for the patient.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
18a.	A side effect of TIRF medicines is the chance of abuse or addiction.	○	○	○
18b.	TIRF medicines can be misused by people who abuse prescription medicines or street drugs.	○	○	○
18c.	TIRF medicines should be kept in a safe place to prevent it from being stolen.	○	○	○

[BEGIN PREAMBLE 3 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

[BEGIN PATIENT] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for you.

[END PATIENT]

[BEGIN CAREGIVER] The next set of questions is about the Medication Guide for the TIRF medicine that was most recently prescribed for the patient.

[END CAREGIVER]

A Medication Guide is a paper handout that contains important information about the risks associated with the use of a TIRF medicine and how to use it safely. Medication Guides always include the title "Medication Guide" followed by the name of the medicine and its pronunciation. The Medication Guide usually has a section titled "What is the most important information I should know?" The Medication Guide is in a question-and-answer format and may be given to you by your pharmacist, doctor, or other healthcare professional.

[END PREAMBLE 3]

~~18.~~19 **[PATIENT]** Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?

[CAREGIVER] Have you or the patient ever received a Medication Guide for the TIRF medicine that was prescribed for the patient?

- ○ Yes
- ○ No -**[GO TO PREAMBLE 4]**
- ○ I don't know **[GO TO PREAMBLE 4]**

~~19.~~20 **[PATIENT]** Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

[CAREGIVER] Did you or the patient receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?

- ○ Yes
- ○ No -**[GO TO ~~Q21~~Q22]**
- ○ I don't know **[GO TO ~~Q21~~Q22]**

~~20.~~21 **[PATIENT]** When was the Medication Guide given to you? Please select all that apply.

[CAREGIVER] When was the Medication Guide given to you or the patient? Please select all that apply.

- □ At the first appointment with the doctor who prescribed the TIRF medicine
- □ At the last appointment with the doctor who prescribed the TIRF medicine
- □ I don't remember **[CLEAR ALL OTHER SELECTIONS]**

~~21.~~22 **[PATIENT]** Did you receive the Medication Guide for the TIRF medicine from the pharmacy?

[CAREGIVER] Did you or the patient receive the Medication Guide for the TIRF medicine from the pharmacy?

- Yes
- No -**[GO TO ~~Q23~~Q24]**
- I don't know **[GO TO ~~Q23~~Q24]**

~~22.~~23 **[PATIENT]** How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?

[CAREGIVER] How frequently do you or the patient receive a Medication Guide for the TIRF medicine at the pharmacy?

- Only with the first filled prescription
- Each time a prescription is filled
- Other (please specify): **[FREE TEXT]**
- I don't know

~~23.~~24 Did you read the Medication Guide?

- Yes
- No **[GO TO ~~Q26~~Q27]**
- I don't know **[GO TO ~~Q26~~Q27]**

~~24.~~25 How much did you read?

- All of it
- Most of it
- Some of it
- I don't know

~~25.~~26. How much of the Medication Guide did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

~~26.~~27. Did someone offer to explain the Medication Guide to you?

- ○ Yes
- ○ No **[GO TO ~~Q30~~Q31]**
- ○ I don't know **[GO TO ~~Q30~~Q31]**

~~27.~~28. Who offered to explain the Medication Guide to you? Please select all that apply.

- ☐ The doctor or another healthcare professional in the doctor's office
- ☐ The pharmacist where the TIRF medicine prescription was filled
- ☐ Someone else **[IF SELECTED, SHOW THE FOLLOWING ON THE SAME PAGE:]**

  Specify the type of person but not his/her name:

  [FREE TEXT]

~~28.~~29. Did you accept the offer to have the Medication Guide explained to you?

- ○ Yes
- ○ No **[GO TO ~~Q30~~Q31]**
- ○ I don't know **[GO TO ~~Q30~~Q31]**

~~29.~~30. How much of the explanation did you understand?

- All of it
- Most of it
- Some of it
- None of it
- I don't know

~~30.~~31. Did you or do you have any questions about the information in the Medication Guide?

- Yes
- No **[GO TO PREAMBLE 4]**
- I don't know **[GO TO PREAMBLE 4]**

[IF QUESTION ~~30~~31 YES, DISPLAY ~~Q31~~Q32 ON SAME PAGE]

~~31.~~32. What are your questions? **[MULTILINE INPUT]**

[BEGIN PREAMBLE 4 – DISPLAY ON SAME PAGE AS NEXT QUESTION]

The next set of questions is about the Patient-Prescriber Agreement Form for TIRF medicines. As a reminder, TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of any of these brands. The Patient-Prescriber Agreement is a form that is signed by the doctor and the patient or their caregiver. This form may also be referred to as the Prescriber-Patient Agreement.

[END PREAMBLE 4]

~~32.~~33. Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?

- ○ Yes
- ○ No **[GO TO ~~Q34~~Q35]**
- ○ I don't know **[GO TO ~~Q34~~Q35]**

~~33.~~34. How much of the explanation did you understand?

- ○ All of it
- ○ Most of it
- ○ Some of it
- ○ None of it
- ○ I don't know

~~34.~~35. **[PATIENT]** Did you sign a Patient-Prescriber Agreement Form?

[CAREGIVER] Did you or the person you are caring for sign a Patient-Prescriber Agreement Form?

- ○ Yes
- ○ No **[GO TO ~~DEMOGRAPHICS~~ PREAMBLE 5]**
- ○ I don't know **[GO TO ~~DEMOGRAPHICS~~ PREAMBLE 5]**

~~35.~~36. Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?

- ○ Yes
- ○ No
- ○ I don't know

[BEGIN PREAMBLE 5 – DISPLAY ON SAME PAGE AS NEXT QUESTION]

[BEGIN PATIENT] Please answer the following questions based on the conversation you had with your doctor, nurse, or other healthcare professional in your doctor's office. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

[END PATIENT]

[BEGIN CAREGIVER] Please answer the following questions based on the conversation you had with the patient's doctor, nurse, or other healthcare professional in the doctor's office. If you don't know the answers to any of the following questions please respond "I don't know" instead of guessing the correct responses.

[END CAREGIVER]

[END PREAMBLE 5]

37. **[PATIENT]** Did a doctor, nurse, or other healthcare professional in the doctor's office ever ask you about the presence of children in your home?

[CAREGIVER] Did a doctor, nurse, or other healthcare professional in the doctor's office ever ask you about the presence of children in the patient's home?

- ○ Yes
- ○ No
- ○ I don't know

38. **[PATIENT]** Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you not to share the TIRF medicines with anyone else?

[CAREGIVER] Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you and the patient not to share the TIRF medicines with anyone else ?

- ○ Yes
- ○ No
- ○ I don't know

39. **[PATIENT]** Did a doctor, nurse, or other healthcare professional in the doctor's office ever counsel you that accidental exposure to TIRF medicines by a child may be fatal ?

[CAREGIVER] Did a doctor, nurse, or other healthcare professional in the doctor's office ever counsel you and the patient that accidental exposure to TIRF medicines by a child may be fatal ?

- ○ Yes
- ○ No
- ○ I don't know

40. **[PATIENT]** Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you to keep TIRF medicines out of reach of children to prevent accidental exposure?

[CAREGIVER] Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you and the patient to keep TIRF medicines out of reach of children to prevent accidental exposure ?

- ○ Yes
- ○ No
- ○ I don't know

41. **[PATIENT]** Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you about proper disposal of any unused or partially used TIRF medicines?

[CAREGIVER] Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you and the patient about proper disposal of any unused or partially used TIRF medicine?

- ○ Yes
- ○ No
- ○ I don't know

[BEGIN DEMOGRAPHICS PREAMBLE - DISPLAY ON SAME PAGE AS NEXT QUESTION]

There are just a few more questions to help us combine your answers with other answers we have received.

[END DEMOGRAPHICS PREAMBLE]

~~36.~~42. What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

~~37.~~43. What is the highest level of education you have completed?

- ○ Less than high school
- ○ Some high school
- ○ High school graduate/GED
- ○ Some college
- ○ ~~Some college~~/Associate's degree
- ○ Bachelor's degree
- ○ Master's degree
- ○ Professional or Doctoral degree
- ○ Prefer not to answer

~~38.~~44. What is the main language you speak at home?

- English
- French
- Spanish
- Portuguese
- Italian
- German
- Chinese
- Japanese
- Korean
- Other
- Prefer not to answer

~~39.~~45. Are you Hispanic or Latino?

- Yes
- No
- Prefer not to answer

~~40.~~46. For informational purposes only, which of the following U.S. census categories best describes your race?

- American Indian or Alaska Native
- Asian (origins of Far East, Southeast Asia or the Indian subcontinent)
- Black or African American
- Native Hawaiian or Other Pacific Islander
- White
- Two or more races
- Other
- Prefer not to answer

~~41.~~47. In which state do you live?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE - BEGIN ADVERSE EVENT/PRODUCT COMPLAINT – KEEP ON ONE PAGE]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- Yes
- No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[BEGIN CLOSING 1 – KEEP ON ONE PAGE]

You are eligible to receive a $50 gift card for your time completing the survey. In order to receive the gift card, we need to collect your name and address so that we can mail it to you. If you do not provide your name and address you will not receive the gift card for your time taking the survey.

Do you agree to give us your name and mailing address so we can send your payment?

- Yes
- No **[GO TO CLOSING 2]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: **[MUST BE 5 DIGIT NUMERIC-ONLY CHARACTERS]**

[END CLOSING 1]

[BEGIN CLOSING 2 – KEEP ON ONE PAGE]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

○ Yes

○ No **[GO TO CLOSING 3]**

Telephone: **[MUST BE 10-DIGIT NUMERIC-ONLY CHARACTERS]**

[END CLOSING 2]

[BEGIN CLOSING 3]

This is the end of the survey. If you have questions about the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Thank you again for your help.

[END CLOSING 3]

[END SURVEY CONTENT]

APPENDIX B ~~SAMPLE Patient Letter of Invitation~~ Recruitment Letters

INVITATION LETTER

[CURR_DATE]
[PAT_FIRST_NAME] [PAT_LAST_NAME
] ~~[CURR_DATE]~~
[PAT_STREET_ADDR]
[PAT_CITY], [PAT_STATE] [PAT_ZIP]

Dear [PAT_FULL_NAME]:

~~Thank you for choosing [pharmacy partner or PBM name] for your prescription needs. The purpose of this letter is to inform you about a voluntary research survey being conducted by [COMPANY], the maker of [BRAND_GENERIC].~~
We are contacting you in connection with managing your participation in the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program (TIRF REMS Access program or the Program). As you know, the TIRF REMS Access program is an FDA (Food and Drug Administration) required program designed to ensure appropriate use of TIRF medicines and to mitigate the risk of misuse, abuse, addiction, overdose and serious complications with the use of certain TIRF Medicines (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys® and the generic versions of any of these brands). *References in this letter to the TIRF REMS Access program (Program) include the sponsors of the Program, as well as agents or contractors retained by the Program.*

As part of your participation in the TIRF REMS Access program, we would like to inform you of a voluntary research survey being conducted by the Program. The survey is part of an FDA requirement to find out if patients and/or their caregivers understand important safety information about ~~[BRAND]~~TIRF Medicines. Express Scripts and ~~other medicines like it. The first~~its subsidiary UBC have been retained by the Program to identify 300 people ~~who~~to complete this 20-minute survey ~~and provide their contact information~~. Eligible individuals who complete the survey will ~~receive~~be sent a $50 ~~[pharmacy partner or PBM name]~~ gift card ~~from [COMPANY]~~ to thank them for their time.

The terms of the TIRF REMS Access program Patient-Prescriber Agreement Form (PPAF) on file and the Patient Privacy Notice contained therein, provide that the TIRF REMS Access program may receive, use, and share your health information, using a unique identifier instead of your name, in order to evaluate the proper use of TIRF Medicines and report to the FDA about the effectiveness of the Program. Should you choose to participate in the survey, you agree that any information you provide during the course of the survey may be used by or shared with the TIRF REMS Access program according to these terms. You acknowledge, however, that should you choose to provide UBC with your name and contact information so that you may receive the $50 gift card for your time, UBC may use your name and contact

information for that purpose. Please be assured that your contact information and your individual responses will be kept strictly confidential. Any information you provide may, however, be combined with information and survey responses provided by others and shared or reported in anonymous form. By participating in the survey, you acknowledge and agree that such combined anonymous data may be used by the TIRF REMS Access program and disclosed to the FDA. By participating, you also acknowledge that the FDA as well as a company called Sterling Independent Services, Inc., which is the Institutional Review Board (IRB) that looks out for the interest of survey participants, may inspect the records related to this survey which may include your individual responses.

You may be eligible to take part in the survey if you have taken ~~[BRAND]~~a TIRF Medicine and are 18 years of age or older. If you are unable to take the survey yourself, a caregiver who is 18 or older may be eligible to take the survey for you. The survey asks questions about the type of information you received about ~~[BRAND]~~the TIRF Medicine you have taken and where and how you ~~get~~receive your medical information.

If you are interested in participating and to find out if you are eligible:

- Go online* to www~~.TIRFREMSsurvey.com~~.TIRFREMSsurvey.com any time or
- ~~Call 877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday~~

~~Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.~~

- ~~***It is recommended***~~Call toll-free 1-877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.

***Please note** that you **should** take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.*

~~(over, please)~~

You are not required to take part in this survey. If you choose to ~~take part, please be assured that your contact information and your individual responses will be kept strictly confidential. You~~ participate in the survey, you will not be ~~asked~~required to identify yourself ~~to participate in the survey.~~. However, if you wish to receive the $50 gift card from ~~[COMPANY],~~the TIRF REMS Access program, you must provide your name and contact information for delivery. ~~Your answers to the survey questions will be combined with answers given by others, and your name will not be used in any written report or publication.~~ Neither taking the survey nor your answers to the questions will affect your ability to receive or take ~~[BRAND].~~a TIRF Medicine.

~~Sincerely,~~

~~[Pharmacy partner or PBM name]~~

~~[COMPANY] funded the cost of the gift card, the cost of mailing this letter and paid a fee to [pharmacy partner or PBM name]. The research study is not being conducted by [pharmacy partner or PBM name]. No information that can identify you, your medication, or your health condition will be provided by [pharmacy partner or PBM name] to [COMPANY]. This letter provides information about a drug prescribed by your doctor and is not a recommendation by [pharmacy partner or PBM name] to use a particular drug for your condition. Call [pharmacy partner or PBM name] toll free at xxx-xxx-xxxx if you do not wish to continue receiving mailings about [BRAND] from [pharmacy partner or PBM name].~~

Sincerely,
The TIRF REMS Survey Team
1-877-379-3297
www.TIRFREMSsurvey.com

REMINDER LETTER

[CURR_DATE]

[PAT_FIRST_NAME] [PAT_LAST_NAME]
[PAT_STREET_ADDR]
[PAT_CITY], [PAT_STATE] [PAT_ZIP]

Dear [PAT_FULL_NAME]:

We recently sent you a letter in connection with managing your participation in the Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access program (TIRF REMS Access Program or the Program). As you know, the TIRF REMS Access program is an FDA (Food and Drug Administration) required program designed to ensure appropriate use of TIRF medicines and to mitigate the risk of misuse, abuse, addiction, overdose and serious complications with the use of certain TIRF Medicines (Abstral®, Actiq®, Fentora®, Lazanda®, Subsys® and the generic versions of any of these brands). *References in this letter to the TIRF REMS Access program or Program include the sponsors of the Program, as well as agents or contractors retained by the Program.*

As part of your participation in the TIRF REMS Access program, we would like to inform you of a voluntary research survey being conducted by the Program. The survey is part of an FDA requirement to find out if patients and/or their caregivers understand important safety information about TIRF Medicines. Express Scripts and its subsidiary UBC have been retained by the Program to identify 300 people to complete this 20-minute survey. Eligible individuals who complete the survey will be sent a $50 gift card to thank them for their time.

The terms of the TIRF REMS Access program Patient-Prescriber Agreement Form (PPAF) on file and the Patient Privacy Notice contained therein, provide that the TIRF REMS Access program may receive, use, and share your health information, using a unique identifier instead of your name, in order to evaluate the proper use of TIRF Medicines and report to the FDA about the effectiveness of the Program. Should you choose to participate in the survey, you agree that any information you provide during the course of the survey may be used by or shared with the TIRF REMS Access program according to these terms. You acknowledge, however, that should you choose to provide UBC with your name and contact information so that you may receive the $50 gift card for your time, UBC may use your name and contact information for that purpose. Please be assured that your contact information and your individual responses will be kept strictly confidential. Any information you provide may, however, be combined with information and survey responses provided by others and shared or reported in anonymous form. By participating in the survey, you acknowledge and agree that such combined anonymous data may be used by the TIRF REMS Access program and disclosed to the FDA. By participating, you also acknowledge that the FDA as well as a company called Sterling Independent Services, Inc., which is the Institutional Review Board

(IRB) that looks out for the interest of survey participants, may inspect the records related to this survey which may include your individual responses.

You may be eligible to take part in the survey if you have taken a TIRF Medicine and are 18 years of age or older. If you are unable to take the survey yourself, a caregiver who is 18 or older may be eligible to take the survey for you. The survey asks questions about the type of information you received about the TIRF Medicine you have taken and where and how you receive your medical information.

If you are interested in participating and to find out if you are eligible:

- Go online* to www.TIRFREMSsurvey.com any time or
- Call toll-free 1-877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.

Please note that you should take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

You are not required to take part in this survey. If you choose to participate in the survey, you will not be required to identify yourself. However, if you wish to receive the $50 gift card from TIRF REMS Access program, you must provide your name and contact information for delivery. Neither taking the survey nor your answers to the questions will affect your ability to receive or take a TIRF Medicine.

Sincerely,
The TIRF REMS Survey Team
1-877-379-3297
www.TIRFREMSsurvey.com

THANK YOU LETTER

[CURR_DATE]

[PAT_FIRST_NAME] [PAT_LAST_NAME]
[PAT_STREET_ADDR]
[PAT_CITY], [PAT_STATE] [PAT_ZIP]

Dear [PAT_FULL_NAME],

On behalf of the TIRF REMS Industry Group, we would like to thank you for taking the time to complete the TIRF Medicines Survey. Your participation helps us to meet the requirements from the FDA (Food and Drug Administration). To thank you for your time and participation, we have enclosed a $50 gift card.

Card Activation Instructions:
To prevent loss, the enclosed card is not activated. Prior to using your card, please call the TIRF Medicines Survey Team 1-877-379-3297 between 8:00 a.m. and 8:00 p.m. Eastern Time Monday through Friday to activate your card. Please have your card available when you make the call. Also, please read the enclosed Terms and Conditions document before using your gift card as well as the privacy policy that can be found at:
http://www.ctpayer.com/downloads/privacy_policy.pdf

Please note the enclosed gift card needs to be activated on or before **XX XXX XXXX**.

Additionally, for your information, we have enclosed the following two documents:

1. Medication Guide for [BRAND® (generic)]

2. The correct answers to survey questions about your medicine's key risks.

Sincerely,
The TIRF REMS Survey Team
1-877-379-3297

www.TIRFREMSsurvey.com

Enclosures: Gift Card with Terms and Conditions Document
Medication Guide for TIRF Medicines
Correct Answers to Important Survey Questions

APPENDIX C Correct Answer Document

Correct Responses to Select PATIENT Survey Questions about Important Safety Messages for Transmucosal Immediate Release Fentanyl (TIRF) medicines (TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands)

Q: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.

STATEMENT	DESIRED RESPONSE
TIRF medicines can cause life-threatening breathing problems that can lead to death.	**TRUE**
It is OK for patients to take TIRF medicines for headache pain.	**FALSE**
TIRF medicines should be taken exactly as prescribed by the doctor.	**TRUE**
It is OK to take TIRF medicines for short-term pain that will go away in a few days.	**FALSE**
Selling or giving away TIRF medicines is against the law.	**TRUE**
TIRF medicines should be stored in a safe place out of the reach of children.	**TRUE**
TIRF medicines must be disposed of as described in the specific product's Medication Guide.	**TRUE**
A TIRF medicine can cause an overdose and death in any child who takes it.	**TRUE**

Q: For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.

STATEMENT	DESIRED RESPONSE
Headache or migraine pain	**NO**
Breakthrough pain from cancer	**YES**
Dental pain	**NO**
Pain after surgery	**NO**
Long-lasting pain not from cancer, like arthritis joint pain	**NO**

Q: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)

A: Get emergency help right away.

Q: Please answer True, False, or I don't know for each of the following statements:

STATEMENT	DESIRED RESPONSE
TIRF medicines should only be taken by patients who are opioid tolerant.	**TRUE**
Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	**TRUE**
A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	**TRUE**
It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	**FALSE**
A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	**FALSE**
A side effect of TIRF medicines is the chance of abuse or addiction.	**TRUE**
TIRF medicines can be misused by people who abuse prescription medicines or street drugs.	**TRUE**
TIRF medicines should be kept in a safe place to prevent it from being stolen.	**TRUE**

If you have any questions about these survey responses, please discuss your questions with your healthcare provider and refer to the Medication Guide(s) for the TIRF medicine(s) that you take.

Appendix B Survey Tables

Table 1.1: Survey Administration Statistics	
Parameter, n (%)	
Number of invitations distributed	2945
Number of invitations returned as undeliverable	399
Number of reminder letters distributed	5397
All Respondents[1]	394 (15.5)
Eligible Respondents[2]	321 (81.5)
Completed survey[3]	310 (96.6)
Did not complete the survey[3]	11 (3.4)
Respondents not eligible[2], [4]	73 (18.5)

Source: Appendix B: Survey Tables, Table 1.1
[1] Number of respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[2] Percentage is based on the number of all respondents.
[3] Percentage is based on the number of eligible respondents.
[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

Table 1.2: Survey Participant Eligibility Results - All Respondents	
Question	**Patients/Caregivers (N=394) n (%)**
Question 1: Do you agree to take part in this survey?	
Yes	376 (95.4)
No[1]	2 (0.5)
Discontinued	16 (4.1)
Question 2: Within the last 4 months (120 days), have you filled a prescription for yourself for a transmucosal immediate release fentanyl medicine (known as "TIRF medicines")? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of any of these brands.	
Yes	357 (90.6)
No	15 (3.8)
I don't know	3 (0.8)
Question not asked [2]	2 (0.5)
Discontinued	17 (4.3)
Question 3: Are you a caregiver for someone who has filled a prescription for a TIRF medicine within the last 4 months (120 days)? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys® and the generic versions of any of these brands.	
Yes	5 (1.3)
No[1]	13 (3.3)
I don't know[1]	0
N/A *(Answered "Yes" to Question 2)*	357 (90.6)
Question not asked [2]	2 (0.5)
Discontinued	17 (4.3)
Question 4: For which TIRF medicines have you filled a prescription in the last 4 months (120 days)? Please select all that apply.[3], [5]	
Abstral	15 (3.8)
Actiq, including generic versions of Actiq	92 (23.4)
Fentora	69 (17.5)
Lazanda	17 (4.3)
Subsys	162 (41.1)
Other	23 (5.8)
I don't know	7 (1.8)

Table 1.2: Survey Participant Eligibility Results - All Respondents	
Question	**Patients/Caregivers (N=394) n (%)**
Question not asked [2]	15 (3.8)
Discontinued	17 (4.3)
Question 5: Have you ever taken part in a survey about a TIRF medicine before?	
Yes[1]	26 (6.6)
No	323 (82.0)
I don't know[1]	12 (3.0)
Question not asked [2]	15 (3.8)
Discontinued	18 (4.6)
Question 6: Which of the following groups best describes your age?	
Under 18[1]	0
18 - 29	8 (2.0)
30 - 39	23 (5.8)
40 - 49	60 (15.2)
50 - 59	123 (31.2)
60 - 69	92 (23.4)
70 or older	17 (4.3)
Prefer not to answer[1]	0
Question not asked [2]	53 (13.5)
Discontinued	18 (4.6)
Question 7: Which of the following groups best describes the patient's age?[4]	
Under 16	0
16 - 29	0
30 - 39	0
40 - 49	1 (0.3)
50 - 59	1 (0.3)
60 - 69	3 (0.8)
70 or older	0
Prefer not to answer[1]	0
Question not asked [2]	372 (94.4)

Table 1.2: Survey Participant Eligibility Results - All Respondents	
Question	**Patients/Caregivers (N=394) n (%)**
Discontinued	17 (4.3)
Question 8: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[5]	
Actavis Laboratories FL, Inc.[1]	0
Anesta LLC[1]	0
BioDelivery Services International (BDSI)[1]	0
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	0
Depomed, Inc.[1]	0
Galena Biopharma, Inc.[1]	0
Insys Therapeutics, Inc.[1]	0
Mallinckrodt Pharmaceuticals[1]	1 (0.3)
McKesson Specialty Care Solutions[1]	0
Mylan Inc.[1]	0
Par Pharmaceuticals, Inc.[1]	0
RelayHealth[1]	0
Sentynl Therapeutics. Inc.[1]	0
Teva Pharmaceuticals, Ltd.[1]	0
United BioSource Corporation[1]	0
FDA (Food and Drug Administration)[1]	0
No[6]	321 (81.5)
I don't know[1]	0
Question not asked [2]	53 (13.5)

Table 1.2: Survey Participant Eligibility Results - All Respondents	
Question	**Patients/Caregivers (N=394) n (%)**
Discontinued	19 (4.8)

Source: Appendix B: Survey Tables, Table 1.2
Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.
[1] Ineligible to participate in the survey.
[2] Question not asked due to termination response from a previous question or skip pattern.
[3] Question does not dictate eligibility for survey completion but is asked of all respondents who did not terminate prior to question presentation.
[4] Only caregivers are asked this question.
[5] More than one response can be selected, so percentages may not sum to 100%.
[6] Ineligible to participate in the survey if selected additionally to another response.

Table 1.3: Time to Complete Survey - Completed Surveys			
	Telephone	**Internet**	**Total[1]**
Summary Statistic (minutes)			
N	103	207	310
Mean (SD)	22.44 (6.012)	16.49 (7.987)	18.47 (7.895)
Minimum	15.7	6.1	6.1
Median	21.10	14.65	17.66
Maximum	46.3	49.2	49.2
Category, n			
0 to <5 Minutes	0	0	0
5 to <10 Minutes	0	39	39
10 to <15 Minutes	0	71	71
15 to <20 Minutes	39	47	86
20 to <25 Minutes	47	27	74
25 to <30 Minutes	10	8	18
30 Minutes or more	7	15	22

Source: Appendix B: Survey Tables, Table 1.3
[1] Total number of eligible respondents completing the survey.

Table 2: Description of Eligible Patients/Caregivers - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
Respondent's age based on Question 6: Which of the following groups best describes your age?	
18 - 29	8 (2.6)
30 - 39	21 (6.8)
40 - 49	59 (19.0)
50 - 59	118 (38.1)
60 - 69	88 (28.4)
70 or older	16 (5.2)
Patient's age based on Question 6/7: Which of the following groups best describes your age/the patient's age?	
Under 16	0
16 - 29	8 (2.6)
30 - 39	21 (6.8)
40 - 49	60 (19.4)
50 - 59	116 (37.4)
60 - 69	89 (28.7)
70 or older	16 (5.2)
Question 42: What is your gender?	
Male	110 (35.5)
Female	198 (63.9)
Prefer not to answer	2 (0.6)
Question 43: What is the highest level of education you have completed?	
Less than high school	1 (0.3)
Some high school	4 (1.3)
High school graduate/GED	52 (16.8)
Some college	97 (31.3)
Associate's degree	41 (13.2)
Bachelor's degree	72 (23.2)
Master's degree	25 (8.1)
Professional or Doctoral degree	15 (4.8)

Table 2: Description of Eligible Patients/Caregivers - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
Prefer not to answer	3 (1.0)
Question 44: What is the main language you speak at home?	
English	305 (98.4)
French	0
Spanish	2 (0.6)
Portuguese	0
Italian	0
German	0
Chinese	0
Japanese	0
Korean	0
Other	1 (0.3)
Prefer not to answer	2 (0.6)
Question 45: Are you Hispanic or Latino?	
Yes	16 (5.2)
No	289 (93.2)
Prefer not to answer	5 (1.6)
Question 46: For informational purposes only, which of the following U.S. census categories best describes your race?	
American Indian or Alaska Native	5 (1.6)
Asian (origins of Far East, Southeast Asia or the Indian subcontinent)	1 (0.3)
Black or African American	13 (4.2)
Native Hawaiian or Other Pacific Islander	1 (0.3)
White	267 (86.1)
Other	7 (2.3)
Prefer not to answer	9 (2.9)
Two or more races	7 (2.3)
Geographic Distribution (based on Question 47 - In which state do you live?)[2]	
Northeast	56 (18.1)

Table 2: Description of Eligible Patients/Caregivers - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
Midwest	50 (16.1)
South	109 (35.2)
West	95 (30.6)
Other	0
Prefer not to answer	0

Source: Appendix B: Survey Tables, Table 2
[1] Total number of eligible respondents completing the survey.
[2] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.

Table 2a: Comparison of Survey Respondents to General Population of TIRF Users			
Question	**Patients Completing Survey n (%)**	**Patients Who Have Received a TIRF Medicine Prescription in the Last 4 Months (120 days)[1] n (%)**	**p-value**
	(N=310)	**(N=3134)**	
TIRF Medicine Prescription(s) Filled in the last 4 Months (120 days)[2]			
Abstral	15 (4.8)	66 (2.1)	
Actiq, including generic versions of Actiq	71 (22.9)	1125 (35.9)	
Fentora	56 (18.1)	606 (19.3)	
Lazanda	16 (5.2)	174 (5.6)	
Subsys	146 (47.1)	1247 (39.8)	
Other	20 (6.5)	*N/A*	
I don't know	5 (1.6)	*N/A*	
Age Group[3]			
Under 16	0	16 (0.5)	
16 - 29	8 (2.6)	90 (2.9)	
30 - 39	21 (6.8)	272 (8.8)	
40 - 49	60 (19.4)	588 (18.9)	
50 - 59	116 (37.4)	1127 (36.3)	
60 - 69	89 (28.7)	782 (25.2)	
70 or older	16 (5.2)	233 (7.5)	0.3579
Unknown	*N/A*	26	
Gender[4]			
Male	110 (35.5)	1225 (39.1)	
Female	198 (63.9)	1904 (60.8)	0.2379
Prefer not to answer/Unknown	2 (0.6)	5 (0.2)	
Geographic Distribution[5]			
Northeast	56 (18.1)	527 (16.8)	
Midwest	50 (16.1)	449 (14.3)	
South	109 (35.2)	1062 (33.9)	
West	95 (30.6)	1096 (35.0)	0.4656

Table 2a: Comparison of Survey Respondents to General Population of TIRF Users			
Question	**Patients Completing Survey n (%)**	**Patients Who Have Received a TIRF Medicine Prescription in the Last 4 Months (120 days)[1] n (%)**	**p-value**
Other[6]	0	*N/A*	
Prefer not to answer[6]	0	*N/A*	
	(N=310)	**(N=1671)**	
Highest Level of Education Completed[7]			
Less than high school diploma	5 (1.6)	93 (5.6)	
High school	52 (16.8)	526 (31.5)	
Some college	138 (44.5)	454 (27.2)	
Completed college	72 (23.2)	379 (22.7)	
Graduate school	40 (12.9)	219 (13.1)	<.0001
Prefer not to answer	3 (1.0)	0	
Main Language Spoken at Home[8]			
English	305 (98.4)	1600 (95.8)	
French	0	*	
Spanish	2 (0.6)	49 (2.9)	
Portuguese	0	*	
Italian	0	*	
German	0	5 (0.3)	
Chinese	0	0	
Japanese	0	0	
Korean	0	0	
Other	1 (0.3)	12 (0.7)	0.0914
Prefer not to answer	2 (0.6)	0	
Hispanic or Latino[9]			
Yes	16 (5.2)	113 (6.8)	
No	289 (93.2)	1558 (93.2)	0.3242
Prefer not to answer	5 (1.6)	0	
Race According to US Census Categories[10]			

Table 2a: Comparison of Survey Respondents to General Population of TIRF Users			
Question	**Patients Completing Survey n (%)**	**Patients Who Have Received a TIRF Medicine Prescription in the Last 4 Months (120 days)[1] n (%)**	**p-value**
American Indian or Alaska Native[6]	5 (1.6)		
Asian (origins of Far East, Southeast Asia or the Indian subcontinent)	1 (0.3)	22 (1.3)	
Black or African American	13 (4.2)	115 (6.9)	
Native Hawaiian or Other Pacific Islander[6]	1 (0.3)		
White	267 (86.1)	1492 (89.3)	
Two or more races[6]	7 (2.3)		
Other[6]	7 (2.3)		<.0001

Table 2a: Comparison of Survey Respondents to General Population of TIRF Users			
Question	Patients Completing Survey n (%)	Patients Who Have Received a TIRF Medicine Prescription in the Last 4 Months (120 days)[1] n (%)	p-value
Prefer not to answer/Unknown	9 (2.9)	42 (2.5)	

Source: Appendix B: Survey Tables, Table 2a
Note: Race/Ethnicity, language spoken in the home, and education level are only available for 1671 patients with a Consumer Profile. P-values are calculated by a chi-square test excluding prefer not to answer, other, and comparable categories.
N/A = Not available.
[1] Based on data from IMS provided on 01Dec2016. Data covered period of 05May2016 to 02Sep2016.
[2] Based on Question 4; More than one type of TIRF medicine could be selected.
[3] Based on Question 6/7; Percentages for the IMS data are calculated based on the sum of available counts, minus the count for "Unknown."
[4] Based on Question 42.
[5] Based on Question 47; U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.
[6] Level not provided and/or collected by the IMS data.
[7] Based on Question 43; Less than high school diploma includes "Less than high school" and "Some high school"; Some college includes "Some college" and "Associate's degree"; Completed college includes "Bachelor's degree"; Graduate school includes "Master's degree" and "Professional or Doctoral degree."
[8] Based on Question 44; "English" for the IMS data is calculated using the total of 1671 patients with a Consumer Profile, minus the sum of other available counts. In the IMS data, French, German, Italian, and Portuguese are reported as combined with a total of 10 patients, and individually as 5 patients for German, and 1-4 patients for French, Italian, and Portuguese. The count of 5 for German and the total of 5 for French, Italian, and Portuguese are used in the "English" calculation.
[9] Based on Question 45; "No" for the IMS data is calculated using the total of 1671 patients with a Consumer Profile, minus the count for "Yes."
[10] Based on Question 46; "White" for the IMS data is calculated by combining the individual categories of Caucasian (1379 patients) and Hispanic/Latino (113 patients) as reported in the IMS data.
* represents 1-4 patients.

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
Question 9: Did a doctor, nurse, or other healthcare professional in the doctor's office ever talk to you about the risks and possible side effects of the TIRF medicine that was most recently prescribed for you? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and the generic versions of these brands.	
Yes	265 (85.5)
No	37 (11.9)
I don't know	8 (2.6)
Question 10: For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.	
10a: Headache or migraine pain	
Yes	34 (11.0)
No[2]	242 (78.1)
I don't know	34 (11.0)
10b: Breakthrough pain from cancer	
Yes[2]	225 (72.6)
No	81 (26.1)
I don't know	4 (1.3)
10c: Dental pain	
Yes	5 (1.6)
No[2]	269 (86.8)
I don't know	36 (11.6)
10d: Pain after surgery	
Yes	69 (22.3)
No[2]	199 (64.2)
I don't know	42 (13.5)
10e: Long-lasting pain not from cancer, like arthritis joint pain	
Yes	148 (47.7)
No[2]	121 (39.0)
I don't know	41 (13.2)
Question 11: Please answer True, False, or I don't know for the following statement:	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
TIRF medicines should only be taken by patients who are opioid tolerant.	
True[2]	277 (89.4)
False	8 (2.6)
I don't know	25 (8.1)
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	
True[2]	273 (88.1)
False	14 (4.5)
I don't know	23 (7.4)
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	
True[2]	123 (39.7)
False	88 (28.4)
I don't know	99 (31.9)
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	
True	6 (1.9)
False[2]	297 (95.8)
I don't know	7 (2.3)
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	
True	6 (1.9)
False[2]	303 (97.7)
I don't know	1 (0.3)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a: TIRF medicines should be stored in a safe place out of the reach of children.	
True[2]	310 (100.0)
False	0
I don't know	0

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
13b: It is OK for patients to take TIRF medicines for headache pain.	
True	20 (6.5)
False[2]	209 (67.4)
I don't know	81 (26.1)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.	
True[2]	309 (99.7)
False	1 (0.3)
I don't know	0
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.	
True[2]	284 (91.6)
False	8 (2.6)
I don't know	18 (5.8)
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	
Wait an hour and see if the person is OK.	10 (3.2)
Get emergency help right away.[2]	276 (89.0)
Do nothing.	0
I don't know.	24 (7.7)
Question 15: Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to use the TIRF medicine that was most recently prescribed for you?	
Yes	294 (94.8)
No	15 (4.8)
I don't know	1 (0.3)
Question 16: Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you how to store or keep the TIRF medicine that was most recently prescribed for you?	
Yes	270 (87.1)
No	35 (11.3)
I don't know	5 (1.6)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
17a: Selling or giving away TIRF medicines is against the law.	
True[2]	308 (99.4)
False	1 (0.3)
I don't know	1 (0.3)
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.	
True	9 (2.9)
False[2]	264 (85.2)
I don't know	37 (11.9)
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.	
True[2]	303 (97.7)
False	2 (0.6)
I don't know	5 (1.6)
17d: TIRF medicines are only available to patients through a pharmacy enrolled in a special program (called the TIRF REMS Access program).	
True[2]	238 (76.8)
False	10 (3.2)
I don't know	62 (20.0)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.	
True[2]	292 (94.2)
False	5 (1.6)
I don't know	13 (4.2)
Question 18: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
18a: A side effect of TIRF medicines is the chance of abuse or addiction.	
True[2]	287 (92.6)
False	5 (1.6)
I don't know	18 (5.8)
18b: TIRF medicines can be misused by people who abuse prescription medicines or street drugs.	
True[2]	302 (97.4)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
False	0
I don't know	8 (2.6)
18c: TIRF medicines should be kept in a safe place to prevent it from being stolen.	
True[2]	308 (99.4)
False	1 (0.3)
I don't know	1 (0.3)
Question 37: Did a doctor, nurse, or other healthcare professional in the doctor's office ever ask you about the presence of children in your home?	
Yes	191 (61.6)
No	89 (28.7)
I don't know	30 (9.7)
Question 38: Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you not to share the TIRF medicines with anyone else?	
Yes	268 (86.5)
No	34 (11.0)
I don't know	8 (2.6)
Question 39: Did a doctor, nurse, or other healthcare professional in the doctor's office ever counsel you that accidental exposure to TIRF medicines by a child may be fatal?	
Yes	237 (76.5)
No	48 (15.5)
I don't know	25 (8.1)
Question 40: Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you to keep TIRF medicines out of reach of children to prevent accidental exposure?	
Yes	264 (85.2)
No	35 (11.3)
I don't know	11 (3.5)
Question 41: Did a doctor, nurse, or other healthcare professional in the doctor's office ever tell you about proper disposal of any unused or partially used TIRF medicines?	
Yes	237 (76.5)
No	48 (15.5)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
I don't know	25 (8.1)

Source: Appendix B: Survey Tables, Table 3
[1] Total number of eligible respondents completing the survey.
[2] Correct response.

Table 4: Responses to Questions about TIRF Educational Materials - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
Question 19: Have you ever received a Medication Guide for the TIRF medicine that was prescribed for you?	
Yes	288 (92.9)
No	5 (1.6)
I don't know	17 (5.5)
Question 20: Did you receive the Medication Guide from the doctor who prescribed the TIRF medicine or someone in the doctor's office?[2]	
Yes	164 (56.9)
No	104 (36.1)
I don't know	20 (6.9)
N/A (Answered "No" or "I don't know" to Question 19)	22
Question 21: When was the Medication Guide given to you? Please select all that apply.[2], [3]	
At the first appointment with the doctor who prescribed the TIRF medicine	134 (81.7)
At the last appointment with the doctor who prescribed the TIRF medicine	26 (15.9)
I don't remember	23 (14.0)
N/A (Answered "No" or "I don't know" to Question 19 or 20)	146
Question 22: Did you receive the Medication Guide for the TIRF medicine from the pharmacy?[2]	
Yes	265 (92.0)
No	16 (5.6)
I don't know	7 (2.4)
N/A (Answered "No" or "I don't know" to Question 19)	22
Question 23: How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?[2], [4]	
Only with the first filled prescription	10 (3.8)
Each time a prescription is filled	242 (91.3)
Other (please specify):	8 (3.0)
I don't know	5 (1.9)
N/A (Answered "No" or "I don't know" to Question 19 or 22)	45
Question 24: Did you read the Medication Guide?[2]	
Yes	278 (96.5)

Table 4: Responses to Questions about TIRF Educational Materials - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
No	7 (2.4)
I don't know	3 (1.0)
N/A (Answered "No" or "I don't know" to Question 19)	22
Question 25: How much did you read?[2]	
All of it	168 (60.4)
Most of it	90 (32.4)
Some of it	20 (7.2)
I don't know	0
N/A (Answered "No" or "I don't know" to Question 19 or 24)	32
Question 26: How much of the Medication Guide did you understand?[2]	
All of it	144 (51.8)
Most of it	109 (39.2)
Some of it	25 (9.0)
None of it	0
I don't know	0
N/A (Answered "No" or "I don't know" to Question 19 or 24)	32
Question 27: Did someone offer to explain the Medication Guide to you?[2]	
Yes	194 (67.4)
No	79 (27.4)
I don't know	15 (5.2)
N/A (Answered "No" or "I don't know" to Question 19)	22
Question 28: Who offered to explain the Medication Guide to you? Please select all that apply.[2], [3], [5]	
The doctor or another healthcare professional in the doctor's office	131 (67.5)
The pharmacist where the TIRF medicine prescription was filled	161 (83.0)
Someone else	16 (8.2)
N/A (Answered "No" or "I don't know" to Question 19 or 27)	116
Question 29: Did you accept the offer to have the Medication Guide explained to you?[2]	
Yes	125 (64.4)
No	66 (34.0)

Table 4: Responses to Questions about TIRF Educational Materials - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
I don't know	3 (1.5)
N/A (Answered "No" or "I don't know" to Question 19 or 27)	116
Question 30: How much of the explanation did you understand?[2]	
All of it	91 (72.8)
Most of it	29 (23.2)
Some of it	5 (4.0)
None of it	0
I don't know	0
N/A (Answered "No" or "I don't know" to Question 19, 27 or 29)	185
Question 31: Did you or do you have any questions about the information in the Medication Guide?[2], [6]	
Yes	10 (3.5)
No	275 (95.5)
I don't know	3 (1.0)
N/A (Answered "No" or "I don't know" to Question 19)	22

Source: Appendix B: Survey Tables, Table 4
[1] Total number of eligible respondents completing the survey.
[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[3] More than one response can be selected, so percentages may not sum to 100%.
[4] Verbatim text for Question 23 (Other frequency of receiving a Medication Guide in the pharmacy) is presented in Listing 1.
[5] Verbatim text for Question 28 (Other type of person explaining Medication Guide) is presented in Listing 2.
[6] Verbatim text for question about the Medication Guide (Question 32) is presented in Listing 3.

Table 5: Responses to Questions about the Patient-Prescriber Agreement Form - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%)**
Question 33: Did the doctor or someone in the doctor's office explain the Patient-Prescriber Agreement Form to you?	
Yes	239 (77.1)
No	32 (10.3)
I don't know	39 (12.6)
Question 34: How much of the explanation did you understand?[2]	
All of it	200 (83.7)
Most of it	36 (15.1)
Some of it	3 (1.3)
None of it	0
I don't know	0
N/A (Answered "No" or "I don't know" to Question 33)	71
Question 35: Did you sign a Patient-Prescriber Agreement Form?	
Yes	237 (76.5)
No	15 (4.8)
I don't know	58 (18.7)
Question 36: Did the doctor or someone in the doctor's office give you a copy of the signed Patient-Prescriber Agreement Form?[2]	
Yes	182 (76.8)
No	16 (6.8)
I don't know	39 (16.5)
N/A (Answered "No" or "I don't know" to Question 35)	73

Source: Appendix B: Survey Tables, Table 5
[1] Total number of eligible respondents completing the survey.
[2] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

Table 6.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%) [95% CI][2]**
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.	
True[3]	284 (91.6) [88.0 - 94.4]
False	8 (2.6)
I don't know	18 (5.8)

Source: Appendix B: Survey Tables, Table 6.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

Table 6.1.1: Responses to Questions Linked to Key Risk Message #1 by Reading Medication Guide - Completed Surveys

Question	Reading Medication Guide: Received and read Med Guide (N=258) n (%) [95% CI][1]	Reading Medication Guide: Not received or not read Med Guide (N=52) n (%) [95% CI][1]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
True[2]	238 (92.2) [88.3 - 95.2]	46 (88.5) [76.6 - 95.6]
False	7 (2.7)	1 (1.9)
I don't know	13 (5.0)	5 (9.6)

Source: Appendix B: Survey Tables, Table 6.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.2: Responses to Questions Linked to Key Risk Message #1 by Understanding of the Medication Guide - Completed Surveys				
	Understanding of the Medication Guide			
Question	Understood most or all (N=253) n (%) [95% CI][1]	Understood some (N=25) n (%) [95% CI][1]	Did not understand (N=0) n (%) [95% CI][1]	Did not receive or read (N=32) n (%) [95% CI][1]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
True[2]	234 (92.5) [88.5 - 95.4]	22 (88.0) [68.8 - 97.5]	0	28 (87.5) [71.0 - 96.5]
False	5 (2.0)	2 (8.0)	0	1 (3.1)
I don't know	14 (5.5)	1 (4.0)	0	3 (9.4)

Source: Appendix B: Survey Tables, Table 6.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.3: Responses to Questions Linked to Key Risk Message #1 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=207) n (%) [95% CI][1]	Telephone (N=103) n (%) [95% CI][1]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.		
True[2]	191 (92.3) [87.8 - 95.5]	93 (90.3) [82.9 - 95.2]
False	7 (3.4)	1 (1.0)
I don't know	9 (4.3)	9 (8.7)

Source: Appendix B: Survey Tables, Table 6.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.4: Responses to Questions Linked to Key Risk Message #1 by Highest Level of Education - Completed Surveys				
	Highest Level of Education			
Question	GED or less (N=60) n (%) [95% CI][1]	College (N=138) n (%) [95% CI][1]	BA/BS or MS/MA (N=97) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
True[2]	51 (85.0) [73.4 - 92.9]	133 (96.4) [91.7 - 98.8]	85 (87.6) [79.4 - 93.4]	15 (100.0) [78.2 - 100.0]
False	4 (6.7)	1 (0.7)	3 (3.1)	0
I don't know	5 (8.3)	4 (2.9)	9 (9.3)	0

Source: Appendix B: Survey Tables, Table 6.1.4
Note: GED or less includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." College includes "Some college" and "Associate's degree." BA/BS or MS/MA includes "Bachelor's degree" and "Master's degree." Professional or Doctoral degree includes "Professional or Doctoral degree."
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.5: Responses to Questions Linked to Key Risk Message #1 by Age Group of Respondent - Completed Surveys				
	Age Group of Respondent			
Question	18 - 39 (N=29) n (%) [95% CI][1]	40 - 49 (N=59) n (%) [95% CI][1]	50 - 59 (N=118) n (%) [95% CI][1]	60 or older (N=104) n (%) [95% CI][1]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13d: TIRF medicines can cause life-threatening breathing problems that can lead to death.				
True[2]	27 (93.1) [77.2 - 99.2]	58 (98.3) [90.9 - 100.0]	108 (91.5) [85.0 - 95.9]	91 (87.5) [79.6 - 93.2]
False	1 (3.4)	0	5 (4.2)	2 (1.9)
I don't know	1 (3.4)	1 (1.7)	5 (4.2)	11 (10.6)

Source: Appendix B: Survey Tables, Table 6.1.5
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%) [95% CI][2]**
Question 11: Please answer True, False, or I don't know for the following statement:	
TIRF medicines should only be taken by patients who are opioid tolerant.	
True[3]	277 (89.4) [85.4 - 92.6]
False	8 (2.6)
I don't know	25 (8.1)
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.	
True[3]	273 (88.1) [83.9 - 91.5]
False	14 (4.5)
I don't know	23 (7.4)

Source: Appendix B: Survey Tables, Table 7.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

Table 7.1.1: Responses to Questions Linked to Key Risk Message #2 by Reading Medication Guide - Completed Surveys

Question	Reading Medication Guide: Received and read Med Guide (N=258) n (%) [95% CI][1]	Reading Medication Guide: Not received or not read Med Guide (N=52) n (%) [95% CI][1]
Question 11: Please answer True, False, or I don't know for the following statement:		
TIRF medicines should only be taken by patients who are opioid tolerant.		
True[2]	234 (90.7) [86.5 - 93.9]	43 (82.7) [69.7 - 91.8]
False	6 (2.3)	2 (3.8)
I don't know	18 (7.0)	7 (13.5)
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.		
True[2]	228 (88.4) [83.8 - 92.0]	45 (86.5) [74.2 - 94.4]
False	12 (4.7)	2 (3.8)
I don't know	18 (7.0)	5 (9.6)

Source: Appendix B: Survey Tables, Table 7.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.2: Responses to Questions Linked to Key Risk Message #2 by Understanding of the Medication Guide - Completed Surveys

Question	Understanding of the Medication Guide			
	Understood most or all (N=253) n (%) [95% CI][1]	Understood some (N=25) n (%) [95% CI][1]	Did not understand (N=0) n (%) [95% CI][1]	Did not receive or read (N=32) n (%) [95% CI][1]
Question 11: Please answer True, False, or I don't know for the following statement:				
TIRF medicines should only be taken by patients who are opioid tolerant.				
True[2]	228 (90.1) [85.8 - 93.5]	19 (76.0) [54.9 - 90.6]	0	30 (93.8) [79.2 - 99.2]
False	6 (2.4)	2 (8.0)	0	0
I don't know	19 (7.5)	4 (16.0)	0	2 (6.3)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.				
True[2]	225 (88.9) [84.4 - 92.5]	21 (84.0) [63.9 - 95.5]	0	27 (84.4) [67.2 - 94.7]
False	12 (4.7)	1 (4.0)	0	1 (3.1)
I don't know	16 (6.3)	3 (12.0)	0	4 (12.5)

Source: Appendix B: Survey Tables, Table 7.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.3: Responses to Questions Linked to Key Risk Message #2 by Modality to Complete Survey - Completed Surveys

Question	Modality to Complete Survey	
	Internet (N=207) n (%) [95% CI][1]	Telephone (N=103) n (%) [95% CI][1]
Question 11: Please answer True, False, or I don't know for the following statement:		
TIRF medicines should only be taken by patients who are opioid tolerant.		
True[2]	189 (91.3) [86.6 - 94.8]	88 (85.4) [77.1 - 91.6]
False	6 (2.9)	2 (1.9)
I don't know	12 (5.8)	13 (12.6)
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.		
True[2]	185 (89.4) [84.4 - 93.2]	88 (85.4) [77.1 - 91.6]
False	7 (3.4)	7 (6.8)
I don't know	15 (7.2)	8 (7.8)

Source: Appendix B: Survey Tables, Table 7.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.4: Responses to Questions Linked to Key Risk Message #2 by Highest Level of Education - Completed Surveys				
	Highest Level of Education			
Question	GED or less (N=60) n (%) [95% CI][1]	College (N=138) n (%) [95% CI][1]	BA/BS or MS/MA (N=97) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
Question 11: Please answer True, False, or I don't know for the following statement:				
TIRF medicines should only be taken by patients who are opioid tolerant.				
True[2]	51 (85.0) [73.4 - 92.9]	124 (89.9) [83.6 - 94.3]	89 (91.8) [84.4 - 96.4]	13 (86.7) [59.5 - 98.3]
False	0	4 (2.9)	2 (2.1)	2 (13.3)
I don't know	9 (15.0)	10 (7.2)	6 (6.2)	0
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.				
True[2]	53 (88.3) [77.4 - 95.2]	121 (87.7) [81.0 - 92.7]	86 (88.7) [80.6 - 94.2]	13 (86.7) [59.5 - 98.3]
False	2 (3.3)	7 (5.1)	5 (5.2)	0
I don't know	5 (8.3)	10 (7.2)	6 (6.2)	2 (13.3)

Source: Appendix B: Survey Tables, Table 7.1.4
Note: GED or less includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." College includes "Some college" and "Associate's degree." BA/BS or MS/MA includes "Bachelor's degree" and "Master's degree." Professional or Doctoral degree includes "Professional or Doctoral degree."
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.5: Responses to Questions Linked to Key Risk Message #2 by Age Group of Respondent - Completed Surveys				
	Age Group of Respondent			
Question	18 - 39 (N=29) n (%) [95% CI][1]	40 - 49 (N=59) n (%) [95% CI][1]	50 - 59 (N=118) n (%) [95% CI][1]	60 or older (N=104) n (%) [95% CI][1]
Question 11: Please answer True, False, or I don't know for the following statement:				
TIRF medicines should only be taken by patients who are opioid tolerant.				
True[2]	26 (89.7) [72.6 - 97.8]	52 (88.1) [77.1 - 95.1]	107 (90.7) [83.9 - 95.3]	92 (88.5) [80.7 - 93.9]
False	2 (6.9)	5 (8.5)	1 (0.8)	0
I don't know	1 (3.4)	2 (3.4)	10 (8.5)	12 (11.5)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12a: Opioid tolerant means that a patient is already taking other opioid pain medicines around-the-clock and their body is used to these medicines.				
True[2]	28 (96.6) [82.2 - 99.9]	54 (91.5) [81.3 - 97.2]	106 (89.8) [82.9 - 94.6]	85 (81.7) [72.9 - 88.6]
False	1 (3.4)	2 (3.4)	4 (3.4)	7 (6.7)
I don't know	0	3 (5.1)	8 (6.8)	12 (11.5)

Source: Appendix B: Survey Tables, Table 7.1.5
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Correct Responses	Patients/Caregivers (N=310)[1] n (%)
0 correct responses	17 (5.5)
1 correct response	36 (11.6)
2 correct responses	257 (82.9)

Source: Appendix B: Survey Tables, Table 7.2
[1] Total number of eligible respondents completing the survey.

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%) [95% CI][2]**
Question 10: For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.	
10a: Headache or migraine pain	
Yes	34 (11.0)
No[3]	242 (78.1) [73.0 - 82.5]
I don't know	34 (11.0)
10b: Breakthrough pain from cancer	
Yes[3]	225 (72.6) [67.3 - 77.5]
No	81 (26.1)
I don't know	4 (1.3)
10c: Dental pain	
Yes	5 (1.6)
No[3]	269 (86.8) [82.5 - 90.3]
I don't know	36 (11.6)
10d: Pain after surgery	
Yes	69 (22.3)
No[3]	199 (64.2) [58.6 - 69.5]
I don't know	42 (13.5)
10e: Long-lasting pain not from cancer, like arthritis joint pain	
Yes	148 (47.7)
No[3]	121 (39.0) [33.6 - 44.7]
I don't know	41 (13.2)
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	
True[3]	123 (39.7) [34.2 - 45.4]
False	88 (28.4)
I don't know	99 (31.9)

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%) [95% CI][2]**
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13b: It is OK for patients to take TIRF medicines for headache pain.	
True	20 (6.5)
False[3]	209 (67.4) [61.9 - 72.6]
I don't know	81 (26.1)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.	
True[3]	309 (99.7) [98.2 - 100.0]
False	1 (0.3)
I don't know	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.	
True	9 (2.9)
False[3]	264 (85.2) [80.7 - 88.9]
I don't know	37 (11.9)

Source: Appendix B: Survey Tables, Table 8.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

Table 8.1.1: Responses to Questions Linked to Key Risk Message #3 by Reading Medication Guide - Completed Surveys

Question	Reading Medication Guide: Received and read Med Guide (N=258) n (%) [95% CI][1]	Reading Medication Guide: Not received or not read Med Guide (N=52) n (%) [95% CI][1]
Question 10: For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.		
10a: Headache or migraine pain		
Yes	30 (11.6)	4 (7.7)
No[2]	202 (78.3) [72.8 - 83.2]	40 (76.9) [63.2 - 87.5]
I don't know	26 (10.1)	8 (15.4)
10b: Breakthrough pain from cancer		
Yes[2]	189 (73.3) [67.4 - 78.6]	36 (69.2) [54.9 - 81.3]
No	65 (25.2)	16 (30.8)
I don't know	4 (1.6)	0
10c: Dental pain		
Yes	4 (1.6)	1 (1.9)
No[2]	226 (87.6) [82.9 - 91.4]	43 (82.7) [69.7 - 91.8]
I don't know	28 (10.9)	8 (15.4)
10d: Pain after surgery		
Yes	55 (21.3)	14 (26.9)
No[2]	170 (65.9) [59.8 - 71.7]	29 (55.8) [41.3 - 69.5]
I don't know	33 (12.8)	9 (17.3)
10e: Long-lasting pain not from cancer, like arthritis joint pain		
Yes	122 (47.3)	26 (50.0)
No[2]	103 (39.9) [33.9 - 46.2]	18 (34.6) [22.0 - 49.1]
I don't know	33 (12.8)	8 (15.4)
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.		
True[2]	110 (42.6) [36.5 - 48.9]	13 (25.0) [14.0 - 38.9]
False	71 (27.5)	17 (32.7)

Table 8.1.1: Responses to Questions Linked to Key Risk Message #3 by Reading Medication Guide - Completed Surveys		
	Reading Medication Guide	
Question	Received and read Med Guide (N=258) n (%) [95% CI][1]	Not received or not read Med Guide (N=52) n (%) [95% CI][1]
I don't know	77 (29.8)	22 (42.3)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
13b: It is OK for patients to take TIRF medicines for headache pain.		
True	18 (7.0)	2 (3.8)
False[2]	180 (69.8) [63.8 - 75.3]	29 (55.8) [41.3 - 69.5]
I don't know	60 (23.3)	21 (40.4)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.		
True[2]	258 (100.0) [98.6 - 100.0]	51 (98.1) [89.7 - 100.0]
False	0	1 (1.9)
I don't know	0	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.		
True	6 (2.3)	3 (5.8)
False[2]	229 (88.8) [84.3 - 92.3]	35 (67.3) [52.9 - 79.7]
I don't know	23 (8.9)	14 (26.9)

Source: Appendix B: Survey Tables, Table 8.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.2: Responses to Questions Linked to Key Risk Message #3 by Understanding of the Medication Guide - Completed Surveys				
	Understanding of the Medication Guide			
Question	Understood most or all (N=253) n (%) [95% CI][1]	Understood some (N=25) n (%) [95% CI][1]	Did not understand (N=0) n (%) [95% CI][1]	Did not receive or read (N=32) n (%) [95% CI][1]
Question 10: For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.				
10a: Headache or migraine pain				
Yes	30 (11.9)	3 (12.0)	0	1 (3.1)
No[2]	198 (78.3) [72.7 - 83.2]	19 (76.0) [54.9 - 90.6]	0	25 (78.1) [60.0 - 90.7]
I don't know	25 (9.9)	3 (12.0)	0	6 (18.8)
10b: Breakthrough pain from cancer				
Yes[2]	186 (73.5) [67.6 - 78.8]	17 (68.0) [46.5 - 85.1]	0	22 (68.8) [50.0 - 83.9]
No	63 (24.9)	8 (32.0)	0	10 (31.3)
I don't know	4 (1.6)	0	0	0
10c: Dental pain				
Yes	4 (1.6)	0	0	1 (3.1)
No[2]	223 (88.1) [83.5 - 91.9]	22 (88.0) [68.8 - 97.5]	0	24 (75.0) [56.6 - 88.5]
I don't know	26 (10.3)	3 (12.0)	0	7 (21.9)
10d: Pain after surgery				
Yes	54 (21.3)	5 (20.0)	0	10 (31.3)
No[2]	169 (66.8) [60.6 - 72.6]	13 (52.0) [31.3 - 72.2]	0	17 (53.1) [34.7 - 70.9]
I don't know	30 (11.9)	7 (28.0)	0	5 (15.6)
10e: Long-lasting pain not from cancer, like arthritis joint pain				

Table 8.1.2: Responses to Questions Linked to Key Risk Message #3 by Understanding of the Medication Guide - Completed Surveys				
	Understanding of the Medication Guide			
Question	Understood most or all (N=253) n (%) [95% CI][1]	Understood some (N=25) n (%) [95% CI][1]	Did not understand (N=0) n (%) [95% CI][1]	Did not receive or read (N=32) n (%) [95% CI][1]
Yes	119 (47.0)	15 (60.0)	0	14 (43.8)
No[2]	98 (38.7) [32.7 - 45.0]	9 (36.0) [18.0 - 57.5]	0	14 (43.8) [26.4 - 62.3]
I don't know	36 (14.2)	1 (4.0)	0	4 (12.5)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.				
True[2]	105 (41.5) [35.4 - 47.8]	10 (40.0) [21.1 - 61.3]	0	8 (25.0) [11.5 - 43.4]
False	74 (29.2)	5 (20.0)	0	9 (28.1)
I don't know	74 (29.2)	10 (40.0)	0	15 (46.9)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13b: It is OK for patients to take TIRF medicines for headache pain.				
True	18 (7.1)	1 (4.0)	0	1 (3.1)
False[2]	178 (70.4) [64.3 - 75.9]	15 (60.0) [38.7 - 78.9]	0	16 (50.0) [31.9 - 68.1]
I don't know	57 (22.5)	9 (36.0)	0	15 (46.9)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.				
True[2]	253 (100.0) [98.6 - 100.0]	25 (100.0) [86.3 - 100.0]	0	31 (96.9) [83.8 - 99.9]
False	0	0	0	1 (3.1)
I don't know	0	0	0	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				

Table 8.1.2: Responses to Questions Linked to Key Risk Message #3 by Understanding of the Medication Guide - Completed Surveys

Question	Understanding of the Medication Guide			
	Understood most or all (N=253) n (%) [95% CI][1]	Understood some (N=25) n (%) [95% CI][1]	Did not understand (N=0) n (%) [95% CI][1]	Did not receive or read (N=32) n (%) [95% CI][1]
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.				
True	6 (2.4)	1 (4.0)	0	2 (6.3)
False[2]	227 (89.7) [85.3 - 93.2]	18 (72.0) [50.6 - 87.9]	0	19 (59.4) [40.6 - 76.3]
I don't know	20 (7.9)	6 (24.0)	0	11 (34.4)

Source: Appendix B: Survey Tables, Table 8.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.3: Responses to Questions Linked to Key Risk Message #3 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=207) n (%) [95% CI][1]	Telephone (N=103) n (%) [95% CI][1]
Question 10: For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.		
10a: Headache or migraine pain		
Yes	20 (9.7)	14 (13.6)
No[2]	164 (79.2) [73.1 - 84.5]	78 (75.7) [66.3 - 83.6]
I don't know	23 (11.1)	11 (10.7)
10b: Breakthrough pain from cancer		
Yes[2]	142 (68.6) [61.8 - 74.9]	83 (80.6) [71.6 - 87.7]
No	62 (30.0)	19 (18.4)
I don't know	3 (1.4)	1 (1.0)
10c: Dental pain		
Yes	2 (1.0)	3 (2.9)
No[2]	181 (87.4) [82.1 - 91.6]	88 (85.4) [77.1 - 91.6]
I don't know	24 (11.6)	12 (11.7)
10d: Pain after surgery		
Yes	35 (16.9)	34 (33.0)
No[2]	141 (68.1) [61.3 - 74.4]	58 (56.3) [46.2 - 66.1]
I don't know	31 (15.0)	11 (10.7)
10e: Long-lasting pain not from cancer, like arthritis joint pain		
Yes	102 (49.3)	46 (44.7)
No[2]	78 (37.7) [31.1 - 44.7]	43 (41.7) [32.1 - 51.9]
I don't know	27 (13.0)	14 (13.6)
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.		
True[2]	94 (45.4) [38.5 - 52.5]	29 (28.2) [19.7 - 37.9]
False	55 (26.6)	33 (32.0)
I don't know	58 (28.0)	41 (39.8)

Table 8.1.3: Responses to Questions Linked to Key Risk Message #3 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=207) n (%) [95% CI][1]	Telephone (N=103) n (%) [95% CI][1]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
13b: It is OK for patients to take TIRF medicines for headache pain.		
True	14 (6.8)	6 (5.8)
False[2]	141 (68.1) [61.3 - 74.4]	68 (66.0) [56.0 - 75.1]
I don't know	52 (25.1)	29 (28.2)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.		
True[2]	206 (99.5) [97.3 - 100.0]	103 (100.0) [96.5 - 100.0]
False	1 (0.5)	0
I don't know	0	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.		
True	5 (2.4)	4 (3.9)
False[2]	176 (85.0) [79.4 - 89.6]	88 (85.4) [77.1 - 91.6]
I don't know	26 (12.6)	11 (10.7)

Source: Appendix B: Survey Tables, Table 8.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.4: Responses to Questions Linked to Key Risk Message #3 by Highest Level of Education - Completed Surveys				
	Highest Level of Education			
Question	GED or less (N=60) n (%) [95% CI][1]	College (N=138) n (%) [95% CI][1]	BA/BS or MS/MA (N=97) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
Question 10: For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.				
10a: Headache or migraine pain				
Yes	4 (6.7)	18 (13.0)	11 (11.3)	1 (6.7)
No[2]	48 (80.0) [67.7 - 89.2]	105 (76.1) [68.1 - 82.9]	77 (79.4) [70.0 - 86.9]	12 (80.0) [51.9 - 95.7]
I don't know	8 (13.3)	15 (10.9)	9 (9.3)	2 (13.3)
10b: Breakthrough pain from cancer				
Yes[2]	46 (76.7) [64.0 - 86.6]	95 (68.8) [60.4 - 76.4]	73 (75.3) [65.5 - 83.5]	11 (73.3) [44.9 - 92.2]
No	13 (21.7)	43 (31.2)	22 (22.7)	3 (20.0)
I don't know	1 (1.7)	0	2 (2.1)	1 (6.7)
10c: Dental pain				
Yes	0	2 (1.4)	3 (3.1)	0
No[2]	50 (83.3) [71.5 - 91.7]	120 (87.0) [80.2 - 92.1]	85 (87.6) [79.4 - 93.4]	14 (93.3) [68.1 - 99.8]
I don't know	10 (16.7)	16 (11.6)	9 (9.3)	1 (6.7)
10d: Pain after surgery				
Yes	16 (26.7)	28 (20.3)	22 (22.7)	3 (20.0)
No[2]	35 (58.3) [44.9 - 70.9]	96 (69.6) [61.2 - 77.1]	60 (61.9) [51.4 - 71.5]	8 (53.3) [26.6 - 78.7]
I don't know	9 (15.0)	14 (10.1)	15 (15.5)	4 (26.7)

Table 8.1.4: Responses to Questions Linked to Key Risk Message #3 by Highest Level of Education - Completed Surveys				
	Highest Level of Education			
Question	GED or less (N=60) n (%) [95% CI][1]	College (N=138) n (%) [95% CI][1]	BA/BS or MS/MA (N=97) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
10e: Long-lasting pain not from cancer, like arthritis joint pain				
Yes	34 (56.7)	74 (53.6)	36 (37.1)	4 (26.7)
No[2]	18 (30.0) [18.8 - 43.2]	46 (33.3) [25.5 - 41.9]	47 (48.5) [38.2 - 58.8]	10 (66.7) [38.4 - 88.2]
I don't know	8 (13.3)	18 (13.0)	14 (14.4)	1 (6.7)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.				
True[2]	21 (35.0) [23.1 - 48.4]	54 (39.1) [30.9 - 47.8]	39 (40.2) [30.4 - 50.7]	9 (60.0) [32.3 - 83.7]
False	17 (28.3)	44 (31.9)	24 (24.7)	3 (20.0)
I don't know	22 (36.7)	40 (29.0)	34 (35.1)	3 (20.0)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13b: It is OK for patients to take TIRF medicines for headache pain.				
True	3 (5.0)	11 (8.0)	6 (6.2)	0
False[2]	38 (63.3) [49.9 - 75.4]	89 (64.5) [55.9 - 72.4]	71 (73.2) [63.2 - 81.7]	11 (73.3) [44.9 - 92.2]
I don't know	19 (31.7)	38 (27.5)	20 (20.6)	4 (26.7)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.				
True[2]	60 (100.0) [94.0 - 100.0]	138 (100.0) [97.4 - 100.0]	96 (99.0) [94.4 - 100.0]	15 (100.0) [78.2 - 100.0]
False	0	0	1 (1.0)	0

Table 8.1.4: Responses to Questions Linked to Key Risk Message #3 by Highest Level of Education - Completed Surveys				
	Highest Level of Education			
Question	GED or less (N=60) n (%) [95% CI][1]	College (N=138) n (%) [95% CI][1]	BA/BS or MS/MA (N=97) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
I don't know	0	0	0	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.				
True	4 (6.7)	3 (2.2)	2 (2.1)	0
False[2]	48 (80.0) [67.7 - 89.2]	120 (87.0) [80.2 - 92.1]	85 (87.6) [79.4 - 93.4]	11 (73.3) [44.9 - 92.2]
I don't know	8 (13.3)	15 (10.9)	10 (10.3)	4 (26.7)

Source: Appendix B: Survey Tables, Table 8.1.4
Note: GED or less includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." College includes "Some college" and "Associate's degree." BA/BS or MS/MA includes "Bachelor's degree" and "Master's degree." Professional or Doctoral degree includes "Professional or Doctoral degree."
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.5: Responses to Questions Linked to Key Risk Message #3 by Age Group of Respondent - Completed Surveys				
	Age Group of Respondent			
Question	18 - 39 (N=29) n (%) [95% CI][1]	40 - 49 (N=59) n (%) [95% CI][1]	50 - 59 (N=118) n (%) [95% CI][1]	60 or older (N=104) n (%) [95% CI][1]
Question 10: For which of the following conditions should you use a TIRF medicine? Please answer Yes, No, or I don't know for each statement.				
10a: Headache or migraine pain				
Yes	5 (17.2)	9 (15.3)	10 (8.5)	10 (9.6)
No[2]	19 (65.5) [45.7 - 82.1]	47 (79.7) [67.2 - 89.0]	93 (78.8) [70.3 - 85.8]	83 (79.8) [70.8 - 87.0]
I don't know	5 (17.2)	3 (5.1)	15 (12.7)	11 (10.6)
10b: Breakthrough pain from cancer				
Yes[2]	22 (75.9) [56.5 - 89.7]	40 (67.8) [54.4 - 79.4]	91 (77.1) [68.5 - 84.3]	72 (69.2) [59.4 - 77.9]
No	6 (20.7)	18 (30.5)	25 (21.2)	32 (30.8)
I don't know	1 (3.4)	1 (1.7)	2 (1.7)	0
10c: Dental pain				
Yes	0	0	2 (1.7)	3 (2.9)
No[2]	24 (82.8) [64.2 - 94.2]	57 (96.6) [88.3 - 99.6]	103 (87.3) [79.9 - 92.7]	85 (81.7) [72.9 - 88.6]
I don't know	5 (17.2)	2 (3.4)	13 (11.0)	16 (15.4)
10d: Pain after surgery				
Yes	5 (17.2)	5 (8.5)	29 (24.6)	30 (28.8)
No[2]	18 (62.1) [42.3 - 79.3]	49 (83.1) [71.0 - 91.6]	72 (61.0) [51.6 - 69.9]	60 (57.7) [47.6 - 67.3]
I don't know	6 (20.7)	5 (8.5)	17 (14.4)	14 (13.5)
10e: Long-lasting pain not from cancer, like arthritis joint pain				

Table 8.1.5: Responses to Questions Linked to Key Risk Message #3 by Age Group of Respondent - Completed Surveys				
	Age Group of Respondent			
Question	18 - 39 (N=29) n (%) [95% CI][1]	40 - 49 (N=59) n (%) [95% CI][1]	50 - 59 (N=118) n (%) [95% CI][1]	60 or older (N=104) n (%) [95% CI][1]
Yes	10 (34.5)	32 (54.2)	54 (45.8)	52 (50.0)
No[2]	13 (44.8) [26.4 - 64.3]	21 (35.6) [23.6 - 49.1]	47 (39.8) [30.9 - 49.3]	40 (38.5) [29.1 - 48.5]
I don't know	6 (20.7)	6 (10.2)	17 (14.4)	12 (11.5)
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12b: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.				
True[2]	17 (58.6) [38.9 - 76.5]	25 (42.4) [29.6 - 55.9]	45 (38.1) [29.4 - 47.5]	36 (34.6) [25.6 - 44.6]
False	4 (13.8)	23 (39.0)	32 (27.1)	29 (27.9)
I don't know	8 (27.6)	11 (18.6)	41 (34.7)	39 (37.5)
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13b: It is OK for patients to take TIRF medicines for headache pain.				
True	4 (13.8)	5 (8.5)	5 (4.2)	6 (5.8)
False[2]	22 (75.9) [56.5 - 89.7]	45 (76.3) [63.4 - 86.4]	76 (64.4) [55.1 - 73.0]	66 (63.5) [53.4 - 72.7]
I don't know	3 (10.3)	9 (15.3)	37 (31.4)	32 (30.8)
13c: TIRF medicines should be taken exactly as prescribed by the doctor.				
True[2]	29 (100.0) [88.1 - 100.0]	59 (100.0) [93.9 - 100.0]	117 (99.2) [95.4 - 100.0]	104 (100.0) [96.5 - 100.0]
False	0	0	1 (0.8)	0
I don't know	0	0	0	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				

Table 8.1.5: Responses to Questions Linked to Key Risk Message #3 by Age Group of Respondent - Completed Surveys				
	Age Group of Respondent			
Question	18 - 39 (N=29) n (%) [95% CI][1]	40 - 49 (N=59) n (%) [95% CI][1]	50 - 59 (N=118) n (%) [95% CI][1]	60 or older (N=104) n (%) [95% CI][1]
17b: It is OK to take TIRF medicines for short-term pain that will go away in a few days.				
True	1 (3.4)	2 (3.4)	2 (1.7)	4 (3.8)
False[2]	26 (89.7) [72.6 - 97.8]	51 (86.4) [75.0 - 94.0]	101 (85.6) [77.9 - 91.4]	86 (82.7) [74.0 - 89.4]
I don't know	2 (6.9)	6 (10.2)	15 (12.7)	14 (13.5)

Source: Appendix B: Survey Tables, Table 8.1.5
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Correct Responses	Patients/Caregivers (N=310)[1] n (%)
0 correct responses	0
1 correct response	0
2 correct responses	9 (2.9)
3 correct responses	13 (4.2)
4 correct responses	29 (9.4)
5 correct responses	45 (14.5)
6 correct responses	64 (20.6)
7 correct responses	55 (17.7)
8 correct responses	61 (19.7)
9 correct responses	34 (11.0)

Source: Appendix B: Survey Tables, Table 8.2
[1] Total number of eligible respondents completing the survey.

Table 9.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%) [95% CI][2]**
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.	
True	6 (1.9)
False[3]	297 (95.8) [92.9 - 97.7]
I don't know	7 (2.3)

Source: Appendix B: Survey Tables, Table 9.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

Table 9.1.1: Responses to Questions Linked to Key Risk Message #4 by Reading Medication Guide - Completed Surveys

Question	Reading Medication Guide: Received and read Med Guide (N=258) n (%) [95% CI][1]	Reading Medication Guide: Not received or not read Med Guide (N=52) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.		
True	5 (1.9)	1 (1.9)
False[2]	247 (95.7) [92.5 - 97.9]	50 (96.2) [86.8 - 99.5]
I don't know	6 (2.3)	1 (1.9)

Source: Appendix B: Survey Tables, Table 9.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.2: Responses to Questions Linked to Key Risk Message #4 by Understanding of the Medication Guide - Completed Surveys				
	Understanding of the Medication Guide			
Question	Understood most or all (N=253) n (%) [95% CI][1]	Understood some (N=25) n (%) [95% CI][1]	Did not understand (N=0) n (%) [95% CI][1]	Did not receive or read (N=32) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.				
True	4 (1.6)	1 (4.0)	0	1 (3.1)
False[2]	243 (96.0) [92.9 - 98.1]	24 (96.0) [79.6 - 99.9]	0	30 (93.8) [79.2 - 99.2]
I don't know	6 (2.4)	0	0	1 (3.1)

Source: Appendix B: Survey Tables, Table 9.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.3: Responses to Questions Linked to Key Risk Message #4 by Modality to Complete Survey - Completed Surveys

Question	Modality to Complete Survey	
	Internet (N=207) n (%) [95% CI][1]	Telephone (N=103) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.		
True	2 (1.0)	4 (3.9)
False[2]	201 (97.1) [93.8 - 98.9]	96 (93.2) [86.5 - 97.2]
I don't know	4 (1.9)	3 (2.9)

Source: Appendix B: Survey Tables, Table 9.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.4: Responses to Questions Linked to Key Risk Message #4 by Highest Level of Education - Completed Surveys				
	Highest Level of Education			
Question	GED or less (N=60) n (%) [95% CI][1]	College (N=138) n (%) [95% CI][1]	BA/BS or MS/MA (N=97) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.				
True	2 (3.3)	1 (0.7)	3 (3.1)	0
False[2]	55 (91.7) [81.6 - 97.2]	134 (97.1) [92.7 - 99.2]	93 (95.9) [89.8 - 98.9]	15 (100.0) [78.2 - 100.0]
I don't know	3 (5.0)	3 (2.2)	1 (1.0)	0

Source: Appendix B: Survey Tables, Table 9.1.4
Note: GED or less includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." College includes "Some college" and "Associate's degree." BA/BS or MS/MA includes "Bachelor's degree" and "Master's degree." Professional or Doctoral degree includes "Professional or Doctoral degree."
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.5: Responses to Questions Linked to Key Risk Message #4 by Age Group of Respondent - Completed Surveys				
	Age Group of Respondent			
Question	18 - 39 (N=29) n (%) [95% CI][1]	40 - 49 (N=59) n (%) [95% CI][1]	50 - 59 (N=118) n (%) [95% CI][1]	60 or older (N=104) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12c: It is safe to switch to another medicine that contains fentanyl without talking to a healthcare provider first.				
True	0	2 (3.4)	2 (1.7)	2 (1.9)
False[2]	29 (100.0) [88.1 - 100.0]	57 (96.6) [88.3 - 99.6]	112 (94.9) [89.3 - 98.1]	99 (95.2) [89.1 - 98.4]
I don't know	0	0	4 (3.4)	3 (2.9)

Source: Appendix B: Survey Tables, Table 9.1.5
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #5 - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%) [95% CI][2]**
Question 12: Please answer True, False, or I don't know for each of the following statements.	
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.	
True	6 (1.9)
False[3]	303 (97.7) [95.4 - 99.1]
I don't know	1 (0.3)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17a: Selling or giving away TIRF medicines is against the law.	
True[3]	308 (99.4) [97.7 - 99.9]
False	1 (0.3)
I don't know	1 (0.3)
Question 18: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
18a: A side effect of TIRF medicines is the chance of abuse or addiction.	
True[3]	287 (92.6) [89.1 - 95.2]
False	5 (1.6)
I don't know	18 (5.8)
18b: TIRF medicines can be misused by people who abuse prescription medicines or street drugs.	
True[3]	302 (97.4) [95.0 - 98.9]
False	0
I don't know	8 (2.6)
18c: TIRF medicines should be kept in a safe place to prevent it from being stolen.	
True[3]	308 (99.4) [97.7 - 99.9]
False	1 (0.3)
I don't know	1 (0.3)

Source: Appendix B: Survey Tables, Table 10.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

Table 10.1.1: Responses to Questions Linked to Key Risk Message #5 by Reading Medication Guide - Completed Surveys

Question	Reading Medication Guide: Received and read Med Guide (N=258) n (%) [95% CI][1]	Reading Medication Guide: Not received or not read Med Guide (N=52) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.		
True	4 (1.6)	2 (3.8)
False[2]	253 (98.1) [95.5 - 99.4]	50 (96.2) [86.8 - 99.5]
I don't know	1 (0.4)	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17a: Selling or giving away TIRF medicines is against the law.		
True[2]	256 (99.2) [97.2 - 99.9]	52 (100.0) [93.2 - 100.0]
False	1 (0.4)	0
I don't know	1 (0.4)	0
Question 18: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
18a: A side effect of TIRF medicines is the chance of abuse or addiction.		
True[2]	240 (93.0) [89.2 - 95.8]	47 (90.4) [79.0 - 96.8]
False	3 (1.2)	2 (3.8)
I don't know	15 (5.8)	3 (5.8)
18b: TIRF medicines can be misused by people who abuse prescription medicines or street drugs.		
True[2]	252 (97.7) [95.0 - 99.1]	50 (96.2) [86.8 - 99.5]
False	0	0
I don't know	6 (2.3)	2 (3.8)
18c: TIRF medicines should be kept in a safe place to prevent it from being stolen.		
True[2]	256 (99.2) [97.2 - 99.9]	52 (100.0) [93.2 - 100.0]
False	1 (0.4)	0
I don't know	1 (0.4)	0

Source: Appendix B: Survey Tables, Table 10.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.2: Responses to Questions Linked to Key Risk Message #5 by Understanding of the Medication Guide - Completed Surveys				
	Understanding of the Medication Guide			
Question	Understood most or all (N=253) n (%) [95% CI][1]	Understood some (N=25) n (%) [95% CI][1]	Did not understand (N=0) n (%) [95% CI][1]	Did not receive or read (N=32) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.				
True	4 (1.6)	1 (4.0)	0	1 (3.1)
False[2]	248 (98.0) [95.4 - 99.4]	24 (96.0) [79.6 - 99.9]	0	31 (96.9) [83.8 - 99.9]
I don't know	1 (0.4)	0	0	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17a: Selling or giving away TIRF medicines is against the law.				
True[2]	252 (99.6) [97.8 - 100.0]	24 (96.0) [79.6 - 99.9]	0	32 (100.0) [89.1 - 100.0]
False	0	1 (4.0)	0	0
I don't know	1 (0.4)	0	0	0
Question 18: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
18a: A side effect of TIRF medicines is the chance of abuse or addiction.				
True[2]	238 (94.1) [90.4 - 96.6]	19 (76.0) [54.9 - 90.6]	0	30 (93.8) [79.2 - 99.2]
False	3 (1.2)	2 (8.0)	0	0
I don't know	12 (4.7)	4 (16.0)	0	2 (6.3)
18b: TIRF medicines can be misused by people who abuse prescription medicines or street drugs.				
True[2]	249 (98.4) [96.0 - 99.6]	23 (92.0) [74.0 - 99.0]	0	30 (93.8) [79.2 - 99.2]
False	0	0	0	0

Table 10.1.2: Responses to Questions Linked to Key Risk Message #5 by Understanding of the Medication Guide - Completed Surveys				
	Understanding of the Medication Guide			
Question	Understood most or all (N=253) n (%) [95% CI][1]	Understood some (N=25) n (%) [95% CI][1]	Did not understand (N=0) n (%) [95% CI][1]	Did not receive or read (N=32) n (%) [95% CI][1]
I don't know	4 (1.6)	2 (8.0)	0	2 (6.3)
18c: TIRF medicines should be kept in a safe place to prevent it from being stolen.				
True[2]	251 (99.2) [97.2 - 99.9]	25 (100.0) [86.3 - 100.0]	0	32 (100.0) [89.1 - 100.0]
False	1 (0.4)	0	0	0
I don't know	1 (0.4)	0	0	0

Source: Appendix B: Survey Tables, Table 10.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.3: Responses to Questions Linked to Key Risk Message #5 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=207) n (%) [95% CI][1]	Telephone (N=103) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.		
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.		
True	1 (0.5)	5 (4.9)
False[2]	206 (99.5) [97.3 - 100.0]	97 (94.2) [87.8 - 97.8]
I don't know	0	1 (1.0)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17a: Selling or giving away TIRF medicines is against the law.		
True[2]	205 (99.0) [96.6 - 99.9]	103 (100.0) [96.5 - 100.0]
False	1 (0.5)	0
I don't know	1 (0.5)	0
Question 18: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
18a: A side effect of TIRF medicines is the chance of abuse or addiction.		
True[2]	193 (93.2) [88.9 - 96.3]	94 (91.3) [84.1 - 95.9]
False	3 (1.4)	2 (1.9)
I don't know	11 (5.3)	7 (6.8)
18b: TIRF medicines can be misused by people who abuse prescription medicines or street drugs.		
True[2]	201 (97.1) [93.8 - 98.9]	101 (98.1) [93.2 - 99.8]
False	0	0
I don't know	6 (2.9)	2 (1.9)
18c: TIRF medicines should be kept in a safe place to prevent it from being stolen.		
True[2]	206 (99.5) [97.3 - 100.0]	102 (99.0) [94.7 - 100.0]
False	0	1 (1.0)
I don't know	1 (0.5)	0

Source: Appendix B: Survey Tables, Table 10.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.4: Responses to Questions Linked to Key Risk Message #5 by Highest Level of Education - Completed Surveys				
	Highest Level of Education			
Question	GED or less (N=60) n (%) [95% CI][1]	College (N=138) n (%) [95% CI][1]	BA/BS or MS/MA (N=97) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.				
True	0	1 (0.7)	5 (5.2)	0
False[2]	59 (98.3) [91.1 - 100.0]	137 (99.3) [96.0 - 100.0]	92 (94.8) [88.4 - 98.3]	15 (100.0) [78.2 - 100.0]
I don't know	1 (1.7)	0	0	0
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17a: Selling or giving away TIRF medicines is against the law.				
True[2]	60 (100.0) [94.0 - 100.0]	137 (99.3) [96.0 - 100.0]	97 (100.0) [96.3 - 100.0]	14 (93.3) [68.1 - 99.8]
False	0	1 (0.7)	0	0
I don't know	0	0	0	1 (6.7)
Question 18: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
18a: A side effect of TIRF medicines is the chance of abuse or addiction.				
True[2]	51 (85.0) [73.4 - 92.9]	131 (94.9) [89.8 - 97.9]	90 (92.8) [85.7 - 97.0]	15 (100.0) [78.2 - 100.0]
False	2 (3.3)	2 (1.4)	1 (1.0)	0
I don't know	7 (11.7)	5 (3.6)	6 (6.2)	0
18b: TIRF medicines can be misused by people who abuse prescription medicines or street drugs.				
True[2]	57 (95.0) [86.1 - 99.0]	136 (98.6) [94.9 - 99.8]	94 (96.9) [91.2 - 99.4]	15 (100.0) [78.2 - 100.0]

Table 10.1.4: Responses to Questions Linked to Key Risk Message #5 by Highest Level of Education - Completed Surveys				
	Highest Level of Education			
Question	GED or less (N=60) n (%) [95% CI][1]	College (N=138) n (%) [95% CI][1]	BA/BS or MS/MA (N=97) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
False	0	0	0	0
I don't know	3 (5.0)	2 (1.4)	3 (3.1)	0
18c: TIRF medicines should be kept in a safe place to prevent it from being stolen.				
True[2]	60 (100.0) [94.0 - 100.0]	136 (98.6) [94.9 - 99.8]	97 (100.0) [96.3 - 100.0]	15 (100.0) [78.2 - 100.0]
False	0	1 (0.7)	0	0
I don't know	0	1 (0.7)	0	0

Source: Appendix B: Survey Tables, Table 10.1.4
Note: GED or less includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." College includes "Some college" and "Associate's degree." BA/BS or MS/MA includes "Bachelor's degree" and "Master's degree." Professional or Doctoral degree includes "Professional or Doctoral degree."
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.5: Responses to Questions Linked to Key Risk Message #5 by Age Group of Respondent - Completed Surveys				
	Age Group of Respondent			
Question	18 - 39 (N=29) n (%) [95% CI][1]	40 - 49 (N=59) n (%) [95% CI][1]	50 - 59 (N=118) n (%) [95% CI][1]	60 or older (N=104) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each of the following statements.				
12d: A patient may give TIRF medicines to another person if they have the same symptoms as the patient.				
True	0	0	3 (2.5)	3 (2.9)
False[2]	29 (100.0) [88.1 - 100.0]	59 (100.0) [93.9 - 100.0]	115 (97.5) [92.7 - 99.5]	100 (96.2) [90.4 - 98.9]
I don't know	0	0	0	1 (1.0)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17a: Selling or giving away TIRF medicines is against the law.				
True[2]	29 (100.0) [88.1 - 100.0]	59 (100.0) [93.9 - 100.0]	118 (100.0) [96.9 - 100.0]	102 (98.1) [93.2 - 99.8]
False	0	0	0	1 (1.0)
I don't know	0	0	0	1 (1.0)
Question 18: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
18a: A side effect of TIRF medicines is the chance of abuse or addiction.				
True[2]	28 (96.6) [82.2 - 99.9]	56 (94.9) [85.9 - 98.9]	108 (91.5) [85.0 - 95.9]	95 (91.3) [84.2 - 96.0]
False	1 (3.4)	0	2 (1.7)	2 (1.9)
I don't know	0	3 (5.1)	8 (6.8)	7 (6.7)
18b: TIRF medicines can be misused by people who abuse prescription medicines or street drugs.				
True[2]	28 (96.6) [82.2 - 99.9]	58 (98.3) [90.9 - 100.0]	114 (96.6) [91.5 - 99.1]	102 (98.1) [93.2 - 99.8]
False	0	0	0	0

Table 10.1.5: Responses to Questions Linked to Key Risk Message #5 by Age Group of Respondent - Completed Surveys				
	Age Group of Respondent			
Question	18 - 39 (N=29) n (%) [95% CI][1]	40 - 49 (N=59) n (%) [95% CI][1]	50 - 59 (N=118) n (%) [95% CI][1]	60 or older (N=104) n (%) [95% CI][1]
I don't know	1 (3.4)	1 (1.7)	4 (3.4)	2 (1.9)
18c: TIRF medicines should be kept in a safe place to prevent it from being stolen.				
True[2]	29 (100.0) [88.1 - 100.0]	58 (98.3) [90.9 - 100.0]	118 (100.0) [96.9 - 100.0]	103 (99.0) [94.8 - 100.0]
False	0	0	0	1 (1.0)
I don't know	0	1 (1.7)	0	0

Source: Appendix B: Survey Tables, Table 10.1.5
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #5 - Completed Surveys

Correct Responses	Patients/Caregivers (N=310)[1] n (%)
0 correct responses	0
1 correct response	0
2 correct responses	1 (0.3)
3 correct responses	2 (0.6)
4 correct responses	35 (11.3)
5 correct responses	272 (87.7)

Source: Appendix B: Survey Tables, Table 10.2
[1] Total number of eligible respondents completing the survey.

Table 11.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #6 - Completed Surveys	
Question	**Patients/Caregivers (N=310)[1] n (%) [95% CI][2]**
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
13a: TIRF medicines should be stored in a safe place out of the reach of children.	
True[3]	310 (100.0) [98.8 - 100.0]
False	0
I don't know	0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)	
Wait an hour and see if the person is OK.	10 (3.2)
Get emergency help right away.[3]	276 (89.0) [85.0 - 92.3]
Do nothing.	0
I don't know.	24 (7.7)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.	
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.	
True[3]	303 (97.7) [95.4 - 99.1]
False	2 (0.6)
I don't know	5 (1.6)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.	
True[3]	292 (94.2) [91.0 - 96.5]
False	5 (1.6)
I don't know	13 (4.2)

Source: Appendix B: Survey Tables, Table 11.1
[1] Total number of eligible respondents completing the survey.
[2] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[3] Correct response.

Table 11.1.1: Responses to Questions Linked to Key Risk Message #6 by Reading Medication Guide - Completed Surveys

Question	Reading Medication Guide: Received and read Med Guide (N=258) n (%) [95% CI][1]	Reading Medication Guide: Not received or not read Med Guide (N=52) n (%) [95% CI][1]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
13a: TIRF medicines should be stored in a safe place out of the reach of children.		
True[2]	258 (100.0) [98.6 - 100.0]	52 (100.0) [93.2 - 100.0]
False	0	0
I don't know	0	0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)		
Wait an hour and see if the person is OK.	6 (2.3)	4 (7.7)
Get emergency help right away.[2]	235 (91.1) [86.9 - 94.3]	41 (78.8) [65.3 - 88.9]
Do nothing.	0	0
I don't know.	17 (6.6)	7 (13.5)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.		
True[2]	252 (97.7) [95.0 - 99.1]	51 (98.1) [89.7 - 100.0]
False	2 (0.8)	0
I don't know	4 (1.6)	1 (1.9)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.		
True[2]	245 (95.0) [91.5 - 97.3]	47 (90.4) [79.0 - 96.8]
False	4 (1.6)	1 (1.9)
I don't know	9 (3.5)	4 (7.7)

Source: Appendix B: Survey Tables, Table 11.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 11.1.2: Responses to Questions Linked to Key Risk Message #6 by Understanding of the Medication Guide - Completed Surveys				
	Understanding of the Medication Guide			
Question	Understood most or all (N=253) n (%) [95% CI][1]	Understood some (N=25) n (%) [95% CI][1]	Did not understand (N=0) n (%) [95% CI][1]	Did not receive or read (N=32) n (%) [95% CI][1]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13a: TIRF medicines should be stored in a safe place out of the reach of children.				
True[2]	253 (100.0) [98.6 - 100.0]	25 (100.0) [86.3 - 100.0]	0	32 (100.0) [89.1 - 100.0]
False	0	0	0	0
I don't know	0	0	0	0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)				
Wait an hour and see if the person is OK.	7 (2.8)	1 (4.0)	0	2 (6.3)
Get emergency help right away.[2]	230 (90.9) [86.7 - 94.1]	22 (88.0) [68.8 - 97.5]	0	24 (75.0) [56.6 - 88.5]
Do nothing.	0	0	0	0
I don't know.	16 (6.3)	2 (8.0)	0	6 (18.8)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.				
True[2]	247 (97.6) [94.9 - 99.1]	25 (100.0) [86.3 - 100.0]	0	31 (96.9) [83.8 - 99.9]
False	2 (0.8)	0	0	0
I don't know	4 (1.6)	0	0	1 (3.1)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.				
True[2]	241 (95.3) [91.9 - 97.5]	22 (88.0) [68.8 - 97.5]	0	29 (90.6) [75.0 - 98.0]
False	4 (1.6)	0	0	1 (3.1)

Table 11.1.2: Responses to Questions Linked to Key Risk Message #6 by Understanding of the Medication Guide - Completed Surveys

Question	Understanding of the Medication Guide			
	Understood most or all (N=253) n (%) [95% CI][1]	Understood some (N=25) n (%) [95% CI][1]	Did not understand (N=0) n (%) [95% CI][1]	Did not receive or read (N=32) n (%) [95% CI][1]
I don't know	8 (3.2)	3 (12.0)	0	2 (6.3)

Source: Appendix B: Survey Tables, Table 11.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 11.1.3: Responses to Questions Linked to Key Risk Message #6 by Modality to Complete Survey - Completed Surveys

Question	Modality to Complete Survey	
	Internet (N=207) n (%) [95% CI][1]	Telephone (N=103) n (%) [95% CI][1]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
13a: TIRF medicines should be stored in a safe place out of the reach of children.		
True[2]	207 (100.0) [98.2 - 100.0]	103 (100.0) [96.5 - 100.0]
False	0	0
I don't know	0	0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)		
Wait an hour and see if the person is OK.	5 (2.4)	5 (4.9)
Get emergency help right away.[2]	188 (90.8) [86.0 - 94.4]	88 (85.4) [77.1 - 91.6]
Do nothing.	0	0
I don't know.	14 (6.8)	10 (9.7)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.		
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.		
True[2]	204 (98.6) [95.8 - 99.7]	99 (96.1) [90.4 - 98.9]
False	1 (0.5)	1 (1.0)
I don't know	2 (1.0)	3 (2.9)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.		
True[2]	196 (94.7) [90.7 - 97.3]	96 (93.2) [86.5 - 97.2]
False	3 (1.4)	2 (1.9)
I don't know	8 (3.9)	5 (4.9)

Source: Appendix B: Survey Tables, Table 11.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 11.1.4: Responses to Questions Linked to Key Risk Message #6 by Highest Level of Education - Completed Surveys				
	Highest Level of Education			
Question	GED or less (N=60) n (%) [95% CI][1]	College (N=138) n (%) [95% CI][1]	BA/BS or MS/MA (N=97) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13a: TIRF medicines should be stored in a safe place out of the reach of children.				
True[2]	60 (100.0) [94.0 - 100.0]	138 (100.0) [97.4 - 100.0]	97 (100.0) [96.3 - 100.0]	15 (100.0) [78.2 - 100.0]
False	0	0	0	0
I don't know	0	0	0	0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)				
Wait an hour and see if the person is OK.	1 (1.7)	5 (3.6)	4 (4.1)	0
Get emergency help right away.[2]	56 (93.3) [83.8 - 98.2]	125 (90.6) [84.4 - 94.9]	81 (83.5) [74.6 - 90.3]	14 (93.3) [68.1 - 99.8]
Do nothing.	0	0	0	0
I don't know.	3 (5.0)	8 (5.8)	12 (12.4)	1 (6.7)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.				
True[2]	59 (98.3) [91.1 - 100.0]	134 (97.1) [92.7 - 99.2]	96 (99.0) [94.4 - 100.0]	14 (93.3) [68.1 - 99.8]
False	0	1 (0.7)	1 (1.0)	0
I don't know	1 (1.7)	3 (2.2)	0	1 (6.7)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.				
True[2]	58 (96.7) [88.5 - 99.6]	130 (94.2) [88.9 - 97.5]	90 (92.8) [85.7 - 97.0]	14 (93.3) [68.1 - 99.8]

Table 11.1.4: Responses to Questions Linked to Key Risk Message #6 by Highest Level of Education - Completed Surveys				
	Highest Level of Education			
Question	GED or less (N=60) n (%) [95% CI][1]	College (N=138) n (%) [95% CI][1]	BA/BS or MS/MA (N=97) n (%) [95% CI][1]	Professional or Doctoral Degree (N=15) n (%) [95% CI][1]
False	0	3 (2.2)	2 (2.1)	0
I don't know	2 (3.3)	5 (3.6)	5 (5.2)	1 (6.7)

Source: Appendix B: Survey Tables, Table 11.1.4
Note: GED or less includes "Less than high school," "Some high school," "High school graduate/GED," or "Prefer not to answer." College includes "Some college" and "Associate's degree." BA/BS or MS/MA includes "Bachelor's degree" and "Master's degree." Professional or Doctoral degree includes "Professional or Doctoral degree."
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 11.1.5: Responses to Questions Linked to Key Risk Message #6 by Age Group of Respondent - Completed Surveys				
	Age Group of Respondent			
Question	18 - 39 (N=29) n (%) [95% CI][1]	40 - 49 (N=59) n (%) [95% CI][1]	50 - 59 (N=118) n (%) [95% CI][1]	60 or older (N=104) n (%) [95% CI][1]
Question 13: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
13a: TIRF medicines should be stored in a safe place out of the reach of children.				
True[2]	29 (100.0) [88.1 - 100.0]	59 (100.0) [93.9 - 100.0]	118 (100.0) [96.9 - 100.0]	104 (100.0) [96.5 - 100.0]
False	0	0	0	0
I don't know	0	0	0	0
Question 14: What should you do if an adult who has not been prescribed a TIRF medicine takes a TIRF medicine? (Please select one.)				
Wait an hour and see if the person is OK.	0	3 (5.1)	5 (4.2)	2 (1.9)
Get emergency help right away.[2]	27 (93.1) [77.2 - 99.2]	54 (91.5) [81.3 - 97.2]	110 (93.2) [87.1 - 97.0]	85 (81.7) [72.9 - 88.6]
Do nothing.	0	0	0	0
I don't know.	2 (6.9)	2 (3.4)	3 (2.5)	17 (16.3)
Question 17: Please answer True, False, or I don't know for each statement about the TIRF medicine that was most recently prescribed for you.				
17c: TIRF medicines must be disposed of as described in the specific product's Medication Guide.				
True[2]	29 (100.0) [88.1 - 100.0]	58 (98.3) [90.9 - 100.0]	115 (97.5) [92.7 - 99.5]	101 (97.1) [91.8 - 99.4]
False	0	0	1 (0.8)	1 (1.0)
I don't know	0	1 (1.7)	2 (1.7)	2 (1.9)
17e: A TIRF medicine can cause an overdose and death in any child who takes it.				
True[2]	29 (100.0) [88.1 - 100.0]	54 (91.5) [81.3 - 97.2]	116 (98.3) [94.0 - 99.8]	93 (89.4) [81.9 - 94.6]
False	0	2 (3.4)	1 (0.8)	2 (1.9)

Table 11.1.5: Responses to Questions Linked to Key Risk Message #6 by Age Group of Respondent - Completed Surveys				
	Age Group of Respondent			
Question	18 - 39 (N=29) n (%) [95% CI][1]	40 - 49 (N=59) n (%) [95% CI][1]	50 - 59 (N=118) n (%) [95% CI][1]	60 or older (N=104) n (%) [95% CI][1]
I don't know	0	3 (5.1)	1 (0.8)	9 (8.7)

Source: Appendix B: Survey Tables, Table 11.1.5
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 11.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #6 - Completed Surveys

Correct Responses	Patients/Caregivers (N=310)[1] n (%)
0 correct responses	0
1 correct response	1 (0.3)
2 correct responses	7 (2.3)
3 correct responses	42 (13.5)
4 correct responses	260 (83.9)

Source: Appendix B: Survey Tables, Table 11.2
[1] Total number of eligible respondents completing the survey.

Table 12: Average Knowledge Scores - Completed Surveys	
	Score [95% CI][1]
KRM #1	91.6 [88.5, 94.7]
KRM #2	88.7 [85.7, 91.7]
KRM #3	70.3 [68.1, 72.5]
KRM #4	95.8 [93.6, 98.1]
KRM #5	97.3 [96.4, 98.2]
KRM #6	95.2 [93.9, 96.6]
Overall Knowledge Score	84.8 [83.5, 86.0]

Source: Appendix B: Survey Tables, Table 12
[1] 95% CIs are constructed based on normal distribution function.

Listing 1: Listing of Verbatim Responses to Question #23 (How frequently do you receive a Medication Guide for the TIRF medicine at the pharmacy?) - Completed Surveys
Verbatim Responses
each bx of medicine
Each new box of TIRF (Subsys) has a new guide inside, on top after you open the box.
i have used actiq for over15 years now.i have seen a zillion medication guides.i no longer have the pharmacy hand me the medication literature anymore,as i already know what is in the guide by heart
If I ask for it, and when they switch medicines
In every box
in every box
Once The last time I received it at a different pharmacy
upon request

Listing 2: Listing of Verbatim Responses to Question #28 (Who offered to explain the Medication Guide to you?) - Completed Surveys
Verbatim Responses
Drug Representative
husband
Husband/Caregiver
I am a doctor
manufacturer of subsys
My Mom
My significant other is an experienced RN
My wife
nurse
Parent...a RN
Pharmaceutical Rep
SERVICE CENTER FOR PATIENTS AT INSYS
Someone from Subsys
Subsys Representative
The company
wife

Listing 3: Listing of Verbatim Responses to Question #32 (Questions about the Medication Guide) - Completed Surveys
Verbatim Responses
Does it cause seizures?
How Long can I use this medication before it is harmful to me ? As in How Many Years ?
I did when I first began taking Aciq,to make sure I under the information my doctor had provided to me.
I had questions about what I didn't understand.
I have been taking the medication for some time and I don't remember.
It states you can use the medication under the tongue, however it also states it is to dissolve within (I think its 14-28 minutes) but when I put it under my tongue, I salivate alot and its dissolved within a minute or two and does not seem to work at all (it seems to only work specific to that intended breakdown timeframe). Then I have to wait for next dose and am miserable. I don't use under tongue anymore. So this is confusing to me as guide shows under tongue as a site for use. A doctor also said I could use it on lower gum/cheek but directions do not state this. I've not tried it - so again, it seems to make sense you could use it at that site, but directions only show using it between upper cheek and gum. (I have an oral cancer - tongue cancer so it has been tricky to use in mouth at times which is why it would be good to know this information- esp after surgery when swelling was worst and as mouth becomes ulcerated from radiation).
The question is the disposal of it, because if it's, I'm kind of, I don't agree with how they say to dispose of the medication. The way I was told to do, what it says in the pamphlet, I don't agree with. They tell you to fold them over and flush them in the toilet. That is polluting. I put it in red bag trash, like at the hospital, and I take them to a center. Like what they use in a doctors office or a hospital for used needles. How did they come up with that as a viable solution to get rid of the drug that's so dangerous.
What are the long-term effects of the many TIRF-REMS medications? Oral damage, organ failure, etc..
Why does it have to be in medical terminology instead of easy to understand terms?
WHY IS a drug such as fentora and aqtiq, after over 10 years of use for patients with extreme pain for SCI injuries. Suddenly only prescribed to people with cancer ?

Listing 4: Listing of Adverse Events and/or Product Complaints Reported by Modality	
Verbatim Text	**Modality of Report**
I have a hard time getting up. Even if you take it the way you are supposed to take it it's highly addictive. I need to be able to get up out the bed sometimes. I'm on hydrocodone, oxycodone, and fentanyl and the amount of pain the angioedema gives me none of those medications help. It took the doctors 6 years to diagnose they thought it was gout, arthritis, rheumatoid arthritis, bone cancer. My problem is there is no medication for it.	Telephone
It states you can use the medication under the tongue, however it also states it is to dissolve within (I think its 14-28 minutes) but when I put it under my tongue, I salivate alot and its dissolved within a minute or two and does not seem to work at all (it seems to only work specific to that intended breakdown timeframe). Then I have to wait for next dose and am miserable. I don't use under tongue anymore. So this is confusing to me as guide shows under tongue as a site for use. A doctor also said I could use it on lower gum/cheek but directions do not state this. I've not tried it - so again, it seems to make sense you could use it at that site, but directions only show using it between upper cheek and gum. (I have an oral cancer - tongue cancer so it has been tricky to use in mouth at times which is why it would be good to know this information- esp after surgery when swelling was worst and as mouth becomes ulcerated from radiation).	Internet
He has passed. He did in the hospital. Once we found the correct dosage, the drug was very beneficial.	Telephone
Its chronic pain but not arthritis	Telephone
No, they gave it to me for chronic pain. I suffer from chronic pain, and doctors tried other medicines but they gave me bad reactions.	Telephone
He passed away. He was still taking the Subsys when he passed away on (b) (6) and I received this letter in the mail so I'm calling to let you know.	Telephone
What are the long-term effects of the many TIRF-REMS medications? Oral damage, organ failure, etc..	Internet
I get one sucker at a time for the procedures that I get, the injections in my back.	Telephone
They are much weaker than you would think.	Telephone
I was on Abstral for almost two years, but then they told me they wouldn't cover it anymore because it's only for cancer patients.	Telephone
Arizona recently legalized marijuana but my doctor won't prescribe it because it is not approved by the FDA...this is frustrating because i was recently diagnosed with cancer	Telephone
He has a little trouble speaking. Yes, but it has been a awhile since his surgery.	Telephone
Patient, XXXXX, passed away on (b) (6). Mother is unsure what product he was taking, if any.	Telephone

Listing 4: Listing of Adverse Events and/or Product Complaints Reported by Modality	
Verbatim Text	**Modality of Report**
I was in a car accident in 91'. Broke my back, my whole lower back was fuzzed, Degenerative Bone Disease, my Sacram Sack failed and I had to have multiple surgeries, there was a 95% chance I'd end up in a wheel chair, Sciatica, Sciatica issues, I have nerve problems and nerve damage, and I have severe arthritis as well. I know there are other issues that I just don't know the name for, I just don't know what they are called. There all just technical names that, there was all stuff that was found out with a Mila gram/spinal tape they drain all your spinal fluid out and they fill it with Radioactive fluid. There are four of five other issues I just don't know what they're called. This was a last resort.	Telephone
I have a hard time concentrating.	Telephone
Why does it have to be in medical terminology instead of easy to understand terms?	Internet
I have been using the Fentanyl patch for some time and I also used the Subsys, now they want me to use the HCT1Q. I am still using the Fentanyl the duragesic Mylan brand. I was taking the Subsys and they were working great. I suffer from chronic hepatitis its not nice to have pain. I used it for 1 year and then they took it away from me because I didn't have cancer.	Telephone
I'm getting a headache.	Telephone
My hand is gimpy. I have dialysis.	Telephone
This Subsys is what I was taking was not good for me- not good for me at all.	Telephone
I've been using it for almost 3 years. I am 63 years old. I know how to control my prescription. My memory is not so good. I did the chemo the worst somebody can have when I had the colon cancer, I take chemo on the nerves on my feet so I don't feel my feet after I get up in the morning it takes 5-10 minutes I touch my feet to the ground it's like you put nails inside of them it's painful. The only medicine to make me feel like a normal person. Sometimes the medicine comes half filled, or completely empty. I already spoke with the company and gave them some of the empty containers.	Telephone
You'll have to excuse me, I have a bad cold.	Telephone
I'm sorry, I'm hard of hearing	Telephone
Patient, XXXXX has passed away.	Telephone
Patient, XXXXX, passed away on (b) (6) .	Telephone
The patient, XXXXX, passed away.	Telephone
This would be helpful because I'm sick so it would be nice to get $50. I have a lot of actual issues with it. I don't think it works properly that well like a lot of it doesn't work sometimes.	Telephone

Listing 4: Listing of Adverse Events and/or Product Complaints Reported by Modality	
Verbatim Text	**Modality of Report**
The question is the disposal of it, because if it's, I'm kind of, I don't agree with how they say to dispose of the medication. The way I was told to do, what it says in the pamphlet, I don't agree with. They tell you to fold them over and flush them in the toilet. That is polluting. I put it in red bag trash, like at the hospital, and I take them to a center. Like what they use in a doctors office or a hospital for used needles. How did they come up with that as a viable solution to get rid of the drug that's so dangerous.	Telephone
how long can I use this medication before it is harmful to me? As in How Many Years?	Internet
Patient, XXXXX, passed away on (b) (6) .	Telephone
The patient, XXXXX, has passed away.	Telephone
Patient, XXXXX, passed away on (b) (6)	Telephone
My memory is not so good.	Telephone
It's breakthrough pain, but it's not from cancer.	Telephone
I'm going through withdraws. If I would have taken it, it would have killed me. I'll call back, I have to put my oxygen on.	Telephone
My husband is now deceased.	Telephone
I had a cancer tumor removed. My doctor is trying different medications for all of my problems: neuropathy, back, vertabrate, fractures, numerous health issues I have. I have been HIV+ for 30 years.	Telephone
I was just hoping that by doing this survey it would show- because the people that have abused the medication that don't need it for pain have made it very hard for those of us in pain that really need it. My goal is to answer questions so people that really need it not taken away from them, that's what my doctors trying to do. They aren't looking at the people that genuinely need it. I'm suffering tor it, it's so unfair. I wish I was never put on it then I wouldn't know there is something to get me through part of the day.	Telephone
In response to survey question Pain after surgery Verbatim Response: He did have it in the hospital.	Telephone
I know it came out for cancer, I'm not a cancer patient.	Telephone
Does it cause seizures?	Internet
I've been taking Fentora for my back. The pharmacy said I can't take it anymore because I don't have bone cancer, but another pharmacy told me that they'd dispense it.	Telephone
Its for retractable back pain. Its back pain.	Telephone
A big old gash on my head, a big old cut on my head. With this brain injury, I don't want to choose wrong. I found mistake with medicine. Medicine was being radiating, and stored in UPS trucks.	Telephone
You're sending these letters to my my brother XXXXX. This is my brother. He has been deceased since July.	Telephone

Listing 4: Listing of Adverse Events and/or Product Complaints Reported by Modality	
Verbatim Text	**Modality of Report**
This is ridiculous – well getting calls every other day when you're sick and there is a reason you are on this medicine is just wrong, very, very, wrong!	Telephone
I take it for a migraine. I take it to prevent my headaches. I take it if I know my headache is going south.	Telephone
WHY IS a drug such as fentora and aqtiq, after over 10 years of use for patients with extreme pain for SCI injuries. Suddenly only prescribed to people with cancer ?	Internet
When I use the dose and it feels like I'm not getting anything out of it. I used to feel it going inside me. Now, I don't feel it at all. The medicine isn't working properly because I don't feel it. They increased my dose and the pharmacy won't feel it because I have to finish something that isn't working for me. What I'm feeling now isn't like what I was feeling.	Telephone
I just had surgery and I was using it	Telephone
I wasn't feeling well when I called before and I was dealing with cancer and things. I have a nephew who went to jail for abusing it. I have been sick for so long on so many different medications.	Telephone
Patient, XXXXX, died in July	Telephone
I'm a bit hearing impaired, so I might ask you to repeat things.	Telephone
He passed away in August. (XXXXX) He tried the fentanyl one time, and it sent him into a grand mal seizure, and I lost him two weeks later.	Telephone
I take it for chronic pain.	Telephone
I just had all my teeth pulled, so I can't talk real clear.	Telephone
I've had different issues.	Telephone
He's in a nursing home.	Telephone
He was on fentanyl patches. They were worthless, they didn't relieve the pain at all. He switched to methadone, so that gives you an idea of how worthless they were. Patient, XXXXX, passed away.	Telephone
Pt: XXXXX Pt passed away as per her husband XXXXX.	Telephone
Pt: XXXXX Per pt's wife XXXXX is deceased.	Telephone
Patient, XXXXX, passed away at the end of August.	Telephone
PT: XXXXX Per pt's mother, XXXXX patient has passed away and he was on a fentanyl spray	Telephone
It's been a lifesaver for me XXXXX he's in severe pain all the time he suffered an aneurysm at 47 and like they say once the air hits the brain its never the same the pain he suffers- and accordance with all that he can get up and move around he can have some quality of life.	Telephone

Listing 4: Listing of Adverse Events and/or Product Complaints Reported by Modality	
Verbatim Text	**Modality of Report**
She has short term memory loss too. She's not very copacetic. She takes two things, she takes Actiq 1200mcg, and the patch. The only thing I would potentially disagree with, in my wife's case she has severe migraines. She has almost constant severe migraines. That's the reason she takes it opposed to cancer. She takes it actually because she has chronic, really bad migraines.	Telephone
I'm so sick I have nausea I have degenerative bone disease and I hurt so bad and I don't feel like filling it out- I just let me be. I might do it later I'll never get over this pain bones breakin and this pain and everything. I'll get back to you when I can think clear. I'm just in so much pain.	Telephone
I was on hospice. - When I was on hospice they told us, but its okay because I lived. I'm alive!	Telephone
Hold on, I'm handicapped. I'm blind, I can hardly see.	Telephone
XXXXX deceased (b) (6)	Mail
The patient,XXXXX, passed away in July.	Telephone
This letter is to inform you that XXXXX passed away on (b) (6). This forwarding address is solely for informational notification only. Do not send any mail this address in the future. Thank you for your kind attention. Sincerely, XXXXX	Mail
I've been doing chemo.	Telephone
He died in February	Telephone
On 11/29/2016 received a letter stating the following: "XXXXX passed away (b) (6) & was in the hospital from (b) (6) until that day. He is not able to do your survey & he hasn't had meds from you in months."	Telephone
This was sent to my sister, she's sick	Telephone
I'm not taking this for cancer, my total body was crushed 10 years ago. I had a 2000lb wall crush me.	Telephone
Remove from mailing list, XXXXX died (b) (6).	Mail
I actually slipped in my backyard and ended up breaking all kinds of bones in my foot and ankle.	Telephone
I've been getting these letters addressed to my husband. He passed away.. Is there any way I can get him taken off of this list?	Telephone

Listing 4: Listing of Adverse Events and/or Product Complaints Reported by Modality	
Verbatim Text	**Modality of Report**
The medication worked fantastic, she's on workers comp and it's way too expensive we went on and on with the court. You guys price this stuff way out of the ball park. She has had 8 back surgeries, 2 in the throat, and 6 in the lower back- its way too expensive- sorry. They cut her off. Now we have been playing. Now we have been playing around with other stuff for the last 6 months it doesn't work quite as well- welcome to America I guess. You can tell your guys its way too expensive.	Telephone

XXXXX = Patient information removed to preserve confidentiality.

4.3 Pharmacy KAB Report

Title:	**Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment** **Quantitative Testing of Pharmacist Knowledge, Attitudes, and Behavior (KAB) about TIRF Products Safety and Use Information**
Document Number:	Wave 5, 60-Month REMS Assessment Report Version 1.0
Survey Time Period:	26 September 2016 to 13 December 2016
Product Name:	Transmucosal Immediate Release Fentanyl
Sponsor:	**TIRF REMS Industry Group (TRIG) of Companies:** Actavis Laboratories FL, Inc. BioDelivery Sciences International, Inc. (BDSI) Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) Depomed, Inc. Insys Therapeutics, Inc. Mallinckrodt Pharmaceuticals Mylan, Inc. Par Pharmaceutical, Inc. Sentynl Therapeutics, Inc.
Date:	10 February 2017

Confidentiality Statement

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LIST OF ABBREVIATIONS

BDSI	BioDelivery Sciences International, Inc.
CI	Confidence Interval
CSP	Closed System Pharmacy
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
ISI	Important Safety Information
KAB	Knowledge, Attitudes, and Behavior
KRM	Key Risk Message
N/A	Not Applicable or Not Available
REMS	Risk Evaluation and Mitigation Strategy
SCC	Survey Coordinating Center
SD	Standard Deviation
TIRF	Transmucosal Immediate Release Fentanyl
TIRF medicines	Transmucosal Immediate Release Fentanyl products
TIRF REMS Access program	REMS program for TIRF medicines
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service

EXECUTIVE SUMMARY

The 60-month Knowledge, Attitudes, and Behavior (KAB) survey for pharmacists who dispense Transmucosal Immediate Release Fentanyl (TIRF) medicines was conducted as part of the 60-Month TIRF Risk Evaluation and Mitigation Strategy (REMS) Access program assessment. On 21 July 2016, the Food and Drug Administration (FDA) provided feedback on the pharmacist survey. After careful review of the requested changes, the TIRF REMS Industry Group (TRIG) notified FDA that in order to incorporate all changes, an extension for report submission would be required. As proposed by the FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month KAB survey results were planned for a separate submission from the overall assessment report on or before 17 February 2017. The survey launched on 26 September 2016 and closed on 13 December 2016.

Subjects to complete the pharmacist survey were recruited from pharmacies enrolled in the TIRF REMS Access program as of 02 September 2016 who had dispensed a TIRF medicine in the last 6 months. Out of the total of 561 pharmacists who accessed the survey, 333 (59.4%) pharmacists met eligibility criteria, and of those who met eligibility criteria, 318 (95.5%) completed the survey, exceeding the target of 300 completed surveys.

On 21 July 2016, FDA provided feedback on the KAB survey for pharmacists. Changes to the 60-month KAB survey for pharmacists based on FDA feedback included the addition of 3 survey questions and a change to the recruitment strategy to limit the survey to pharmacists who had dispensed TIRF medicines in the past 6 months and attempt to recruit more closed system pharmacists and non-supervisory pharmacists. The addition of Question 12 (*TIRF medicines should only be taken by patients who are opioid tolerant [True/False]*) and Question 13 (*Which of the following risks are associated with the use of TIRF medicines? [True/False for each of the following: misuse, abuse, addiction, overdose, hypothyroidism, and infection]*) is discussed below with the key risk message results. Question 15 (*How frequently do you perform the following activities when dispensing TIRF medicines?*) included 3 response items about pharmacist-reported activity. For each item, most respondents selected *always* or *only with the first prescription*; and few respondents selected *sometimes*, *never*, or *I don't know*. Changes to recruitment efforts included a revised invitation letter addressed to the "pharmacist-in-charge" including 3 letters with unique codes; the pharmacist-in-charge was asked to distribute these letters to non-supervisory staff involved in the dispensing of TIRF medicines. This strategy was successful, with 74.8% of respondents indicating they were not the pharmacist-in-charge.

The overall knowledge score of 85.7 (95% confidence interval [CI]: 84.4 87.0) for the survey indicates most respondents demonstrated understanding of the key risk messages (KRMs). The average knowledge score was ≥83.8 for 3 of the 4 key risk messages and was 75.4 for Key Risk Message 2 (TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older [16 years of age and older for Actiq® brand and generic equivalents] who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain); the lower average knowledge score for Key Risk Message 2 reflected 3 linked questions/items (described below) with correct response rates <65%. Of the 36 questions/items included as part of key risk messages, 27 items of the key risk messages had a correct response rate

>80%, and 6 items had correct response rates from 65.1% to 79.6%. Three questions/items of Key Risk Message 2 had a correct response rate below the desired threshold of 65% (Items 6a, 6c, and 9e). The correct response rate for Item 6a (*According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time*) was 61.9%. The correct response rate for Item 6c (*A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine*) was 41.2%. This item was added to the 48-month survey based on feedback provided by FDA in the 24-month and the 36-month FDA REMS Acknowledgement Letter. The correct response rate for Item 9e (*Chronic non-cancer pain is not an indication for which TIRF medicines can be prescribed*) was 43.4% for this 60-month survey. Item 9e has also had a low correct response rate across all previous pharmacist KAB surveys conducted (12-month, 24-month, 36-month, and 48-month surveys). The survey score for Item 9e may indicate that some respondents are dispensing TIRF medicines for non-cancer associated indications.

When comparing correct response rates from the 12-month KAB survey through the 60-month KAB survey, no trend was evident for this 60-month survey in knowledge and understanding of the key risk messages. As described above, 2 new survey questions (Question 12 and Question 13 [6 separate response items]) were added as part of key risk messages for the 60-month survey. Correct response rates for the new questions/items were ≥95.6% for Question 12 and 4 items of Question 13 and 84.0%-89.3% for the 2 false items of Question 13 (hypothyroidism and infection).

1. PHARMACIST SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate release opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The FDA has determined that a shared system REMS is required to mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access program was approved by the FDA on 28 December 2011. This report describes the results from the pharmacist surveys conducted for the 60-month TIRF REMS Access program assessment, and reflects the REMS reporting period of 29 October 2015 to 28 October 2016. The 60-month KAB survey launched on 26 September 2016 and closed on 13 December 2016.

The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and (where applicable) their respective generic equivalents. The TRIG includes Actavis Laboratories FL, Inc., BioDelivery Sciences International, Inc. (BDSI), Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc., Insys Therapeutics, Inc., Mallinckrodt Pharmaceuticals, Mylan, Inc., Par Pharmaceutical, Inc., and Sentynl Therapeutics, Inc. One company joined the TRIG during the reporting period: Sentynl Therapeutics, Inc. replaced Galena Biopharm, Inc. on 09 January 2016.

The TIRF REMS Access program consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments. The goals of the TIRF REMS Access program are to mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2. Preventing inappropriate conversion between TIRF medicines.

3. Preventing accidental exposure to children and others for whom it was not prescribed.

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS Access program assessment is the conduct of quantitative evaluation surveys to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS Access program educational materials, TIRF REMS Access program Pharmacy Enrollment Form, and Prescribing Information of each product. Administration of the surveys conducted among pharmacies enrolled in the TIRF REMS Access program is described in the protocol (See Appendix A). Note: Protocol and survey question revisions from the 48-month assessment report are identified as tracked changes.

Data from the surveys, together with other TIRF REMS Access program evaluation metrics, will be used to determine whether changes need to be made to the TIRF REMS Access program processes or educational materials to make them more effective in achieving the goals of the TIRF REMS Access program.

1.1 Changes to the KAB Survey for Pharmacists Based on FDA Feedback

On 21 July 2016, FDA provided feedback on the pharmacist survey. After careful review of the requested changes, the TRIG notified FDA that in order to incorporate all changes, an extension for report submission would be required. As proposed by FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month KAB survey results were planned for a separate submission from the overall assessment report on or before 17 February 2017.

Specific updates made to the protocol and survey included:

- Changes to recruitment strategy to:
    - Limit the survey to pharmacists who had dispensed TIRF medicines in the past 6 months
    - Attempt to recruit more closed system pharmacists and non-supervisory pharmacists.

- Addition of the following questions:
    - Question 15 *How frequently do you perform the following activities when dispensing TIRF medicines?*
        - *Item 15a Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed.*
        - *Item 15b Instruct the patient on how to use the TIRF medicine that was most recently prescribed.*
        - *Item 15c Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed.*
    - Question 12 *TIRF medicines should only be taken by patients who are opioid tolerant (True/False)*
    - Question 13 *Which of the following risks are associated with the use of TIRF medicines?*
        - *13a Misuse*
        - *13b Abuse*
        - *13c Addiction*
        - *13d Overdose*
        - *13e Hypothyroidism*
        - *13f Infection*
- Changes to the KAB survey reporting to include:
    - A description of how pharmacies that dispense TIRF medicines compare to the pharmacies represented by survey respondents.
    - The percentage of orders from outpatient versus inpatient versus closed system pharmacies (if possible)

Additional information was requested as follows:

- If multiple regions were represented by pharmacies represented in the survey
- How many pharmacists were from the same pharmacies
- How many pharmacies were represented in the survey

All of the above requested changes were incorporated prior to survey launch on 26 September 2016.

2. PHARMACIST SURVEY OBJECTIVES

The evaluation survey used a questionnaire to document the level of knowledge and assess the attitudes and behavior of pharmacists regarding the following key information and risk messages communicated through the REMS:

1. TIRF medicines are only contraindicated in opioid non-tolerant patients.
2. TIRF medicines are indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
3. TIRF medicines contain fentanyl, an opioid agonist, and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.
4. TIRF medicines are not interchangeable with each other, regardless of route of administration.
5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions developed to test pharmacist understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, which can be found in Appendix A.

3.1 Survey Sample

A sample of 300 pharmacists who were enrolled in the TIRF REMS Access program and had dispensed a TIRF medicine in the last 6 months was planned for this fifth KAB survey, which was expected to be open from 26 September 2016 to 13 December 2016. The survey sample size was determined based on both practical and statistical considerations. The survey was written to reflect wording for both methods of survey administration: Internet-based and telephone.

3.1.1 Eligibility

Subjects were recruited from pharmacies enrolled in the TIRF REMS Access program as of 02 September 2016 and that had dispensed a TIRF medicine in the last 6 months. Note: The 6-month time period was at the pharmacy level as pharmacist level data was not collected by the REMS. All pharmacists who worked at the enrolled pharmacy were eligible to participate, which could have resulted in multiple completed surveys per pharmacy. Respondents or respondents with immediate family members who had ever worked for any of the TRIG companies, McKesson Specialty Care Solutions, RelayHealth, United BioSource Corporation (UBC), or the FDA were not eligible to participate nor were respondents who participated in the previous waves of the survey (the 12-month TIRF REMS Access program assessment, the 24-month TIRF REMS Access program assessment, the 36-month TIRF REMS Access program assessment, or the 48-month TIRF REMS Access program assessment).

3.1.2 Recruitment

Subjects were recruited via an invitation letter sent through the United States Postal Service (USPS) or via fax (see Section 5.1.1 for more detail). In an effort to ensure that a higher percentage of non-supervisory dispensing pharmacists were included for this reporting period per FDA request, the invitation letter was revised and addressed to the "pharmacist-in-charge" and disseminated to those pharmacies enrolled in the TIRF REMS Access program. To increase the number of non-supervisory staff participants, a total of 3 letters with unique codes were provided to each pharmacy. The pharmacist-in-charge was asked to distribute these letters to non-supervisory staff involved in the dispensing of TIRF medicines.

If the required number of completed surveys was not achieved within a reasonable time frame, second and third mailings to non-respondents, as well as initial invitations to new samples of pharmacies, if the data were available, were sent as necessary based on the actual rate of survey accrual relative to the proximity of the target survey close date.

Each letter of invitation included a unique code needed to access the survey. Three categories of pharmacies were randomly sampled: Closed System Pharmacy (CSP), Inpatient Pharmacy, and Outpatient Pharmacy. Each pharmacy was provided a unique access code based on their pharmacy type because some questions in the survey were specific to only one type of pharmacy. The code was deactivated after the respondent had initiated the survey (whether or not the survey was completed).

Respondents were given the option of taking the survey by telephone via the Survey Coordinating Center (SCC) or online via a secure website. The survey was estimated to take approximately 15 to 20 minutes to complete.

All respondents who completed the survey and provided their contact information were mailed a $50 gift card for participating. The mailing also included a copy of the Important Safety Information (ISI) and a copy of the correct answers to the key risk message questions.

3.2 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the pharmacists' understanding of the key risk messages (KRMs) of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that include statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I Don't Know" regarding statements about TIRF medicines.

For statements or questions that had "True" or "Yes" versus "False" or "No" response options, the desired response for key risk messages was generally "True" or "Yes" indicating knowledge of or behavior in accordance with the objectives of the REMS. However, some questions were formatted to have the respondent disagree with the statement as written by providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

The REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the survey protocol (Appendix A).

3.2.1 Key Risk Message 1

Key Risk Message 1 refers to the pharmacist's knowledge of the specific contraindications for TIRF medicines in opioid non-tolerant patients and under what conditions a patient is considered opioid tolerant.

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired Response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer	***True***
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	***False***
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	***False***

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired Response**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	***True***
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	***True***
7c	TIRF medicines may be used in opioid non-tolerant patients.	***False***
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	***True***
11	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:	
11a	8 mg oral hydromorphone/day	***True***
11b	60 mg oral morphine/day	***True***
11c	30 mg oral oxycodone/day	***True***
11d	25 mcg transdermal fentanyl/hour	***True***
11e	25 mg oral oxymorphone/day	***True***
11f	An equianalgesic dose of another oral opioid	***True***
12	TIRF medicines should only be taken by patients who are opioid tolerant.	***True***

3.2.2 Key Risk Message 2

Key Risk Message 2 refers to the pharmacist's knowledge of the indications for prescribing TIRF medicines for the management of breakthrough pain in opioid-tolerant adult cancer patients, and the timing of administration of the TIRF medicine in relation to the around-the-clock opioid therapy to ensure the patient is considered opioid tolerant.

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired Response**
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a	According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	***False***
6b	According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	***False***
6c	A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	***True***
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	***No***
9b	Headache or migraine pain	***No***
9c	Dental pain	***No***
9d	Breakthrough pain from cancer	***Yes***
9e	Chronic non-cancer pain	***No***

3.2.3 Key Risk Message 3

Key Risk Message 3 refers to the pharmacist's knowledge of the risk factors for opioid abuse and importance in monitoring for signs of abuse in patients who take TIRF medicines.

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer True, False, or I don't know for each statement about TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	***True***
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	***Yes***

8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	***Yes***
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	***True***
13	Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.	
13a	Misuse	***True***
13b	Abuse	***True***
13c	Addiction	***True***
13d	Overdose	***True***
13e	Hypothyroidism	***False***
13f	Infection	***False***

3.2.4 Key Risk Message 4

Key Risk Message 4 refers to the pharmacist's knowledge of the interchangeability of TIRF medicines based on route of administration, pharmacokinetic absorption, and dosage.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	***False***
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	***True***
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	***True***
16	Please answer True, False, or I don't know for each statement about TIRF medicines.	
16c	TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	***False***

3.3 Additional Questions

The survey also contained questions (Questions 14 and 15) about the requirements of the TIRF REMS Access program, receipt and understanding of the TIRF educational materials, and behaviors. The following questions about behaviors were asked after the key risk message questions:

Question No.	Question
14	How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
14a	Ask patients (or their caregivers) about the presence of children in the home
14b	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
14c	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
14d	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
14e	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
14f	Give patients (or their caregivers) the Medication Guide for their TIRF medicine
15	How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
15a	Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed.
15b	Instruct the patient on how to use the TIRF medicine that was most recently prescribed.
15c	Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed.

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 All Respondents

The All Respondents population consisted of respondents that accessed the survey using a unique code. These respondents were used as the denominator for percentages in survey administration statistics unless otherwise specified.

4.1.2 Completed Surveys (Primary Population)

The primary population for analysis was all eligible pharmacists who completed the survey. Eligible pharmacists were defined as those respondents who answered Yes to Question 1 (agree to take part in survey) and Yes to Question 3 (work at a pharmacy that is enrolled in the TIRF REMs Access program), and No to Question 2 (participated in past survey) and No to Question 4 (worked for a TRIG company, UBC, RelayHealth, McKesson Specialty Care Solutions, or FDA). A survey was considered "completed" when an eligible pharmacist answered all relevant questions.

4.1.3 General Population

The general population consists of pharmacists representing pharmacies that dispensed a TIRF medicine in the past 6 months. This population was used to compare the population represented in the survey to the general population to determine whether pharmacists completing the survey were representative of the general population. Characteristics of all pharmacies that dispensed a TIRF medicine in the last 6 months were extracted from the REMS switch provider data. Pharmacies represented in the survey were compared to the pharmacies enrolled in the TIRF REMS Access program who dispensed a TIRF medicine within the last 6 months, with the exception of inpatient pharmacies. Inpatient pharmacy REMS requirements differed from requirements of other pharmacy types and therefore data related to the timing of the last dispense were not available. Based on the difference in requirements for inpatient pharmacies, pharmacy comparisons only included data related to chain, independent, and closed-system pharmacies. Characteristics compared included geographic region, type of pharmacy, and (for outpatient pharmacies) number of orders for TIRF medicines by type of pharmacy. The analysis included calculation of p-values by a chi-square test.

4.2 Primary Analyses

Primary analyses were performed for all key risk messages. The primary analysis for a key risk message evaluated the number and percentage of correct responses for each individual question/item included in the key risk message. Confidence intervals (95% CI) were calculated using the exact binomial method around the percentage of correct responses.

Primary analyses were then stratified by questions/characteristics of interest:

1) Those who indicated they both received and read the Medication Guide or Full Prescribing Information versus those who did not receive/have access to or read the Full Prescribing Information or Medication Guide (Questions 21-24).
2) Whether the survey was completed via the internet or telephone
3) Time in pharmacy practice (Question 31).
4) The number of times per month they dispensed TIRF medicines within the last 6 months (Question 28).

Stratified analyses were conducted on all completed surveys.

4.3 Secondary Analyses

As an indicator of the overall level of comprehension of the entire key risk message, descriptive analyses of the number and percentage of responders who answered various proportions of the key risk message questions/items correctly are presented (e.g., the proportion who answered one question/item in the key risk message correctly, those who answered two questions/items correctly, those who answered 3 questions/items correctly, etc.).

A knowledge score was computed for each KRM and overall. The score was defined as the rate of the number of correct responses to all KRM questions to the total number of possible correct responses to all KRM questions. The average knowledge score was calculated as the mean of the score across all completed surveys. The 95% CIs were calculated based on the normal distribution function.

4.4 Pharmacist Report of a Potential Adverse Event, Product Complaint, or Medical Information Request during the Survey

A pharmacist may have reported a potential adverse event or other event experienced by a patient while taking a TIRF product either in free text fields while taking the online survey or while in conversation with the SCC Associate. If an event was mentioned to the SCC Associate, the Associate documented the event or complaint, the verbatim response, and the pharmacist's contact information, if provided. The pharmacist was also informed that a representative from the appropriate TIRF medicine sponsor may contact him/her to obtain additional information about the event. The Internet surveys were monitored for any comments recorded in the free text field. Information on all reports (Internet or telephone) that constituted an adverse event or other event was forwarded to the appropriate TIRF medicine sponsor for processing within 1 business day of awareness of the event as outlined in the Escalating Adverse Events, Product Complaints, and Medical Information Requests Identified During Execution of the Knowledge, Attitudes, and Behavior Survey Project Specific Procedure.

5. RESULTS

Results of the pharmacist's responses to questions in the KAB survey are summarized in this section; stratified analysis tables and overall listings are provided in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

A total of 11598 invitation letters were sent inviting pharmacists within the identified 3856 enrolled pharmacies to participate in the survey (Table 1). An additional 3772 reminder letters were sent to non-responders (See Section 3.1 for survey methodology details). Further outreach to assist in obtaining more CSPs as requested by the FDA included, outbound calling to the authorized representative identified as enrolling the pharmacy, outbound calling to additional resources, as identified by the authorized representative identified as enrolling

the pharmacy, where applicable, as well as sending the letters via Federal Express to boost participation.

As noted in Section 3.1 availability of the survey was expected through 13 December 2016. The survey launch date was delayed based on FDA-requested updates received on 29 July 2016. Successful recruitment resulted in the survey closing on schedule and exceeding the targeted number of 300 completed surveys.

From the total of 561 pharmacists who accessed the survey, 333 (59.4%) pharmacists met eligibility criteria, and of those who met eligibility criteria, 318 (95.5%) completed the survey. Of these 318 pharmacists, 314 (98.7%) completed the survey online, and 4 (1.3%) completed it by telephone (Table 3).

Table 1. Survey Administration Statistics

Parameter, n (%)	
Number of invitations distributed	11598
Number of invitations returned as undeliverable	139
Number of reminder letters distributed	3772
All Respondents[1]	561 (4.9)
Eligible Respondents[2]	333 (59.4)
Completed survey[3]	318 (95.5)
Did not complete the survey[3]	15 (4.5)
Respondents not eligible[2], [4]	228 (40.6)

Source: Appendix B: Survey Tables, Table 1.1
[1] Number of unique respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[2] Percentage is based on the number of all respondents.
[3] Percentage is based on the number of eligible respondents.
[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

As shown in Table 2, of the 561 pharmacists who accessed the survey, a total of 435 (77.5%) pharmacists agreed to participate in this survey. During the screening process it was determined 102 respondents were not eligible to participate in the survey because they either did not agree to participate in the survey (1 respondent), indicated they had participated in or did not know whether they participated in a survey about TIRF medicines before (54 respondents), worked in pharmacies that were not enrolled or did not know whether their pharmacy was enrolled in the TIRF REMS Access program (42 respondents), or indicated they, or an immediate family member, had worked for a TRIG company, UBC, or FDA in the past or the respondent did not know if they or an immediate family member had worked for a TRIG company, UBC, or FDA in the past (5 respondents). An additional 126 respondents discontinued the survey before completing all eligibility questions without being identified as ineligible. Thus, there were 333 eligible participants.

Table 2. Survey Participant Eligibility Results - All Respondents

Question	Pharmacists (N=561) n (%)
Question 1: Do you agree to participate in this survey?	
Yes	435 (77.5)
No[1]	1 (0.2)
Discontinued	125 (22.3)
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.	
Yes[1]	17 (3.0)
No	380 (67.7)
I don't know[1]	37 (6.6)
Question not asked [2]	1 (0.2)
Discontinued	126 (22.5)
Question 3: Do you work in a pharmacy that is enrolled in the TIRF REMS Access program?	
Yes	338 (60.2)
No[1]	10 (1.8)
I don't know[1]	32 (5.7)
Question not asked [2]	55 (9.8)
Discontinued	126 (22.5)
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[3]	
Actavis Laboratories FL, Inc.[1]	1 (0.2)
Anesta LLC[1]	0
BioDelivery Sciences International, Inc. (BDSI)[1]	0
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	1 (0.2)
Depomed, Inc.[1]	0
Galena Biopharma, Inc.[1]	0
Insys Therapeutics, Inc.[1]	0
Mallinckrodt Pharmaceuticals[1]	0
McKesson Specialty Care Solutions[1]	0
Mylan Inc.[1]	0
Par Pharmaceuticals, Inc.[1]	0
RelayHealth[1]	0
Sentynl Therapeutics, Inc.[1]	0
Teva Pharmaceuticals, Ltd.[1]	0

Question	Pharmacists (N=561) n (%)
United BioSource Corporation[1]	0
FDA[1]	2 (0.4)
None of these apply[4]	333 (59.4)
I don't know[1]	2 (0.4)
Prefer not to answer[1]	0
Question not asked [2]	97 (17.3)
Discontinued	126 (22.5)

Source: Appendix B: Survey Tables, Table 1.2
Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.
[1] Ineligible to participate in the survey.
[2] Question not asked due to termination response from a previous question.
[3] More than one response can be selected, so percentages may not sum to 100%.
[4] Ineligible if selected in addition to another response.

Pharmacists taking the survey online took a mean of 15.67 minutes to complete it, while those taking it by telephone took a mean of 21.63 minutes (Table 3).

Table 3. Time to Complete Survey - Completed Surveys

	Telephone	Internet	Total[1]
Summary Statistic (minutes)			
N	4	314	318
Mean (SD)	21.63 (4.391)	15.67 (8.557)	15.74 (8.540)
Minimum	18.1	3.6	3.6
Median	20.23	13.48	13.63
Maximum	28.0	55.8	55.8
Category, n			
0 to <5 Minutes	0	6	6
5 to <10 Minutes	0	85	85
10 to <15 Minutes	0	95	95
15 to <20 Minutes	2	49	51
20 to <25 Minutes	1	36	37
25 to <30 Minutes	1	16	17
30 Minutes or more	0	27	27

Source: Appendix B: Survey Tables, Table 1.3
[1] Total number of eligible respondents completing the survey.

5.1.2 Description of Eligible Pharmacists Who Completed the Survey

The characteristics of pharmacists who completed the survey are shown in Table 4.

Most pharmacists (238; 74.8%) were not the pharmacist-in-charge for the TIRF REMS Access program where they work. This indicates the success of efforts to ensure that a higher percentage of non-supervisory dispensing pharmacists were included for this reporting period per FDA request.

The majority of pharmacists had dispensed a TIRF medicine either not at all (60; 18.9%) or 1 to 2 times per month (149; 46.9%) within the past 6 months. The most frequently dispensed TIRF medicine within the 6 months prior to taking the survey was Actiq® or generic Actiq® (193; 74.8%).

About half of the pharmacists who completed the survey were male (155; 48.7%), and 167 (52.5%) had been a practicing pharmacist for 11 or more years. Most participants were from the South (101; 31.8%) or Northeast (83; 26.1%), followed by the West (75; 23.6%) and Midwest (58; 18.2%) regions of the United States (US).

As per FDA request (Section 1.1), information on "How many pharmacists were from the same pharmacies" is included as follows:

- Total number of unique chain/independent pharmacies:
  - Total number of unique chain/independent pharmacies with 1 completer 145
  - Total number of unique chain/independent pharmacies with 2 completers 40
  - Total number of unique chain/independent pharmacies with 3 completers 9
- Total number of unique inpatient pharmacies:
  - Total number of unique inpatient pharmacies with 1 completer 29
  - Total number of unique inpatient pharmacies with 2 completers 13
  - Total number of unique inpatient pharmacies with 3 completers 3

There was 1 completer who completed a survey from those invited from the listing of unique closed system pharmacies.

Table 4. Description of Eligible Pharmacists - Completed Surveys

Question	Pharmacists (N=318) n (%)
Question 27: Are you the Pharmacist in Charge for the TIRF REMS Access program where you work?	
Yes	77 (24.2)
No	238 (74.8)
I don't know	3 (0.9)
Question 28: On average, how many times per month have you dispensed TIRF medicine within the last 6 months?	
None	60 (18.9)
1 - 2 times per month	149 (46.9)
3 - 5 times per month	38 (11.9)
More than 5 times per month	47 (14.8)
I don't remember	24 (7.5)
Question 29: Please select the TIRF medicine(s) that you have dispensed within the last 6 months. Please select all that apply.[1], [2]	
Abstral®	26 (10.1)
Actiq® or generic Actiq®	193 (74.8)
Fentora®	105 (40.7)
Lazanda®	19 (7.4)
Subsys®	95 (36.8)
N/A (Answered "None" to Question 25)	60

Table 4. Description of Eligible Pharmacists - Completed Surveys

Question	Pharmacists (N=318) n (%)
Question 30: What is your gender?	
Male	155 (48.7)
Female	150 (47.2)
Prefer not to answer	13 (4.1)
Question 31: In total, how many years have you been a practicing pharmacist?	
Less than 3 years	37 (11.6)
3 - 5 years	51 (16.0)
6 - 10 years	56 (17.6)
11 - 15 years	35 (11.0)
More than 15 years	132 (41.5)
Prefer not to answer	7 (2.2)
Geographic Distribution (based on Question 32 - In which state do you practice?)[3]	
Northeast	83 (26.1)
Midwest	58 (18.2)
South	101 (31.8)
West	75 (23.6)
Other	0
Prefer not to answer	1 (0.3)

Source: Appendix B: Survey Tables, Table 2
[1] Percentages are calculated based on the number of respondents to whom the question was presented.
[2] More than one response can be selected, so percentages may not sum to 100%.
[3] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.

5.1.3 Comparison of Survey Respondents to the General Population of Pharmacists Dispensing TIRF Medicines

The respondents completing the survey represented a total of 240 pharmacies. The pharmacies were located in all US Census Bureau regions except Other. Comparison of pharmacies represented by the survey respondents to the general population of pharmacies that had dispensed TIRF medicines in the past 6 months (based on the REMS switch provider data) showed a similar distribution by geographic region (Table 5). The distribution of types of pharmacies was significantly different ($p<0.05$) for the 2 groups; most of the outpatient pharmacies represented by survey respondents were independent, while most of those in the

general population were chains. The distribution of outpatient pharmacy orders between independent and chain pharmacies was similar for the 2 groups; however, orders in the general population included a small percentage of orders from CSPs, which could not be represented for the survey respondents' pharmacies as the REMS Administrator can only provide aggregate data for these orders. This difference in orders from CSPs accounted for the significant p-value.

Table 5. Comparison of Pharmacies Represented by the Survey Respondents to the General Population of Pharmacies That Have Dispensed TIRF Medicines in the Past Six Months (REMS Database)

Parameter	Pharmacies Represented by Pharmacists Completing Survey (REMS Switch Provider Data) (N=240) n (%)	Pharmacies Dispensing TIRF Medicines in the Past Six Months (REMS Switch Provider Data) (N=3857) n (%)	p-value
Geographic region of pharmacy			
Northeast	59 (24.6)	783 (20.3)	0.4924
Midwest	44 (18.3)	660 (17.1)	
South	78 (32.5)	1396 (36.2)	
West	59 (24.6)	1017 (26.4)	
Other	0	1 (0.0)	
Prefer not to answer	0	*N/A*	
Type of pharmacy			
Inpatient Pharmacy[1]	45 (18.8)	763 (19.8)	<.0001
Independent Outpatient Pharmacy	165 (68.8)	1311 (34.0)	
Chain Outpatient Pharmacy	29 (12.1)	1769 (45.9)	
Closed System Pharmacy	1 (0.4)	14 (0.4)	
Number of orders by type of pharmacy[2]	**(N=8045)**	**(N=38702)**	
Inpatient Pharmacy	*N/A*	*N/A*	
Independent Outpatient Pharmacy	4830 (60.0)	23417 (60.5)	<.0001
Chain Outpatient Pharmacy	3215 (40.0)	15139 (39.1)	
Closed System Pharmacy	*N/A*	146 (0.4)	

Source: Appendix B: Survey Tables, Table 2b
Note: Switch provider data was provided by McKesson on September 6th, 2016. Each pharmacy is counted only once, regardless of how many pharmacists from that pharmacy completed the survey. Percentages for the number of orders by type of pharmacy were calculated based on the total number of dispensed TIRF medicines from the pharmacies represented by pharmacists completing the survey and from pharmacies dispensing TIRF medicines in the past 6 months, respectively. P-values are calculated by a chi-square test excluding prefer not to answer.
N/A = Not available.
[1] The TIRF REMS Access program database does not collect dispensing information for inpatient pharmacies. Therefore, the number of inpatient pharmacies is based on the number of all active pharmacies in the TIRF REMS.
[2] Number of orders are not available for inpatient pharmacies. Comparison is based on the number of orders from independent outpatient pharmacies, chain outpatient pharmacies and closed system pharmacies.

5.1.4 TIRF Medicines Educational Materials

Pharmacists were asked about their access to educational materials for TIRF medicines, specifically the Full Prescribing Information and the Medication Guide (Table 6). Almost all pharmacists reported they had received or had access to the Full Prescribing Information and the Medication Guide (305; 95.9% and 309; 97.2%, respectively). Of those with access to these materials, 80.7% and 88.0%, respectively, indicated that they had read the Full Prescribing Information and the Medication Guide.

Table 6. Responses to Questions about TIRF Medicine Educational Materials - Completed Surveys

Question	Pharmacists (N=318) n (%)
Question 21: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?	
Yes	305 (95.9)
No	3 (0.9)
I don't know	10 (3.1)
Question 22: Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?[1]	
Yes	246 (80.7)
No	51 (16.7)
I don't know	8 (2.6)
N/A (Answered "No" or "I don't know" to Question 21)	13
Question 23: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?	
Yes	309 (97.2)
No	0
I don't know	9 (2.8)
Question 24: Did you read the Medication Guide for the TIRF medicine(s) that you dispense?[1]	
Yes	272 (88.0)
No	34 (11.0)
I don't know	3 (1.0)
N/A (Answered "No" or "I don't know" to Question 23)	9

Table 6. Responses to Questions about TIRF Medicine Educational Materials - Completed Surveys

Question	Pharmacists (N=318) n (%)
Question 25: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?[2]	
Yes	6 (1.9)
No	293 (92.1)
I don't know	19 (6.0)

Source: Appendix B: Survey Tables, Table 4
[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[2] Verbatim text for questions about the Full Prescribing Information or Medication Guide is presented in Appendix B, Listing 1.

5.2 Key Risk Messages

5.2.1 Key Risk Message 1

Key Risk Message 1 states "TIRF medicines are contraindicated in opioid non-tolerant patients."

A high percentage of pharmacists knew that patients with cancer who are considered opioid tolerant are those who are taking around-the-clock opioid therapy for cancer pain for one week or longer (95.6%; 95% CI: 92.7 - 97.6) and that those who are not currently taking an opioid therapy are not opioid tolerant (87.4%, 95% CI: 83.3 - 90.9) (Table 7). In addition, most understood that cancer patients with no known contraindications to the drug fentanyl, but who are not taking around-the-clock opioid therapy, are not considered opioid tolerant (82.1%, 95% CI: 77.4 - 86.1).

The majority of pharmacists knew that TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur (88.4%, 95% CI: 84.3 - 91.7) and that death has occurred in opioid non-tolerant patients treated with some fentanyl products (95.3%, 95% CI: 92.3 - 97.3). The majority of pharmacists were aware that TIRF medicines may not be used to treat opioid non-tolerant patients (87.4%, 95% CI: 83.3 - 90.9) and, in response to a differently worded question on the same subject, that TIRF medicines should only be taken by patients who are opioid tolerant (95.6%, 95% CI: 92.7 - 97.6). Similarly, 84.0% (95% CI: 79.5 - 87.8) of pharmacists were aware that dose titration for patients starting a TIRF medicine must begin with the lowest available dose for that product.

The majority of pharmacists were aware of the regimens that defined an opioid-tolerant patient: 8 mg oral hydromorphone/day (74.5%, 95% CI: 69.4 - 79.2), 60 mg oral morphine/day (88.1%, 95% CI: 84.0 - 91.4), 30 mg oral oxycodone/day (77.7%, 95% CI: 72.7 - 82.1), 25 mcg transdermal fentanyl/hour (79.6%; 95% CI: 74.7 - 83.9), 25 mg oral

oxymorphone/day (72.0%, 95% CI: 66.7 - 76.9), and an equianalgesic dose of another oral opioid (65.1%, 95% CI: 59.6 - 70.3).

Table 7. Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Question	Pharmacists (N=318) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	
True[2]	304 (95.6) [92.7 - 97.6]
False	10 (3.1)
I don't know	4 (1.3)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before	
True	30 (9.4)
False[2]	278 (87.4) [83.3 - 90.9]
I don't know	10 (3.1)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	
True	46 (14.5)
False[2]	261 (82.1) [77.4 - 86.1]
I don't know	11 (3.5)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	
True[2]	281 (88.4) [84.3 - 91.7]
False	23 (7.2)
I don't know	14 (4.4)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	
True[2]	303 (95.3) [92.3 - 97.3]
False	3 (0.9)
I don't know	12 (3.8)
7c: TIRF medicines may be used in opioid non-tolerant patients.	
True	28 (8.8)
False[2]	278 (87.4) [83.3 - 90.9]
I don't know	12 (3.8)

Table 7. Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Question	Pharmacists (N=318) n (%) [95% CI][1]
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	
True[2]	267 (84.0) [79.5 - 87.8]
False	34 (10.7)
I don't know	17 (5.3)
Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:	
11a: 8 mg oral hydromorphone/day	
True[2]	237 (74.5) [69.4 - 79.2]
False	38 (11.9)
I don't know	43 (13.5)
11b: 60 mg oral morphine/day	
True[2]	280 (88.1) [84.0 - 91.4]
False	13 (4.1)
I don't know	25 (7.9)
11c: 30 mg oral oxycodone/day	
True[2]	247 (77.7) [72.7 - 82.1]
False	37 (11.6)
I don't know	34 (10.7)
11d: 25 mcg transdermal fentanyl/hour	
True[2]	253 (79.6) [74.7 - 83.9]
False	39 (12.3)
I don't know	26 (8.2)
11e: 25 mg oral oxymorphone/day	
True[2]	229 (72.0) [66.7 - 76.9]
False	30 (9.4)
I don't know	59 (18.6)
11f: An equianalgesic dose of another oral opioid	
True[2]	207 (65.1) [59.6 - 70.3]
False	51 (16.0)
I don't know	60 (18.9)

Table 7. Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Question	Pharmacists (N=318) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for the following statement about TIRF medicines:	
TIRF medicines should only be taken by patients who are opioid tolerant.	
True[2]	304 (95.6) [92.7 - 97.6]
False	12 (3.8)
I don't know	2 (0.6)

Source: Appendix B: Survey Tables, Table 6.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Overall, 30.8% of respondents answered all 14 questions/items of Key Risk Message 1 correctly, 50.6% missed no more than one item, and 62.6% missed no more than two (Table 8).

Table 8. Secondary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Correct Responses	Pharmacists (N=318) n (%)
0 correct responses	0
1 correct response	1 (0.3)
2 correct responses	1 (0.3)
3 correct responses	0
4 correct responses	2 (0.6)
5 correct responses	3 (0.9)
6 correct responses	4 (1.3)
7 correct responses	6 (1.9)
8 correct responses	25 (7.9)
9 correct responses	13 (4.1)
10 correct responses	31 (9.7)
11 correct responses	33 (10.4)
12 correct responses	38 (11.9)
13 correct responses	63 (19.8)
14 correct responses	98 (30.8)

Source: Appendix B: Survey Tables, Table 6.2

The analysis stratified by whether the Full Prescribing Information or Medication Guide were received and read (Received and read: N 279; Did not receive or read: N 39) showed significant differences favoring respondents who received and read the materials in Questions 11b, 11d and 11e (Table 9). A similar but non-significant trend was apparent for all other items within Question 11.

Table 9. Responses to Questions Linked to Key Risk Message #1 by Reading Full Prescribing Information or Medication Guide - Completed Surveys (Questions/Items with Apparent Trends)

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
11a: 8 mg oral hydromorphone/day		
True[2]	212 (76.0) [70.5 - 80.9]	25 (64.1) [47.2 - 78.8]
False	35 (12.5)	3 (7.7)
I don't know	32 (11.5)	11 (28.2)
11b: 60 mg oral morphine/day		
True[2]	252 (90.3) [86.2 - 93.5]	28 (71.8) [55.1 - 85.0]
False	13 (4.7)	0
I don't know	14 (5.0)	11 (28.2)
11c: 30 mg oral oxycodone/day		
True[2]	223 (79.9) [74.7 - 84.5]	24 (61.5) [44.6 - 76.6]
False	33 (11.8)	4 (10.3)
I don't know	23 (8.2)	11 (28.2)
11d: 25 mcg transdermal fentanyl/hour		
True[2]	230 (82.4) [77.5 - 86.7]	23 (59.0) [42.1 - 74.4]
False	34 (12.2)	5 (12.8)
I don't know	15 (5.4)	11 (28.2)
11e: 25 mg oral oxymorphone/day		
True[2]	208 (74.6) [69.0 - 79.6]	21 (53.8) [37.2 - 69.9]
False	25 (9.0)	5 (12.8)
I don't know	46 (16.5)	13 (33.3)

Table 9. Responses to Questions Linked to Key Risk Message #1 by Reading Full Prescribing Information or Medication Guide - Completed Surveys (Questions/Items with Apparent Trends)

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
11f: An equianalgesic dose of another oral opioid		
True[2]	189 (67.7) [61.9 - 73.2]	18 (46.2) [30.1 - 62.8]
False	43 (15.4)	8 (20.5)
I don't know	47 (16.8)	13 (33.3)

Source: Appendix B: Survey Tables, Table 6.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

No meaningful comparison was possible in the analysis stratified by survey modality (internet or telephone) as only 4 respondents completed the survey by telephone. Additionally, stratification by time in pharmacy practice (per categories in Question 31) or number of times TIRF medicines were dispensed in the last 6 months (per categories in Question 28) did not result in any uniform trends (Appendix B).

5.2.2 Key Risk Message 2

Key Risk Message 2 states "TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain."

A majority (61.9%, 95% CI: 56.4 - 67.3) of pharmacists correctly indicated that a cancer patient should not be started on a TIRF medicine and an around-the-clock opioid at the same time, and 80.5% (95% CI: 75.7 - 84.7) correctly indicated that a cancer patient who had been on an around-the-clock opioid for one day should not start taking a TIRF medicine for breakthrough pain (Table 10). Fewer than half (41.2%; 95% CI: 35.7 - 46.8) understood that a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.

A majority of pharmacists were aware that TIRF medicines are indicated for opioid-tolerant patients with breakthrough pain from cancer (91.8%, 95% CI: 88.2 - 94.6) and not for patients with acute or postoperative pain (85.8%, 95% CI: 81.5 - 89.5), headache or migraine pain (94.3%, 95% CI: 91.2 - 96.6), or dental pain (96.2%, 95% CI: 93.5 - 98.0). About half of respondents (50.9%, 95% CI: 45.3 - 56.6) correctly responded that TIRF medicines should not be prescribed for chronic non-cancer pain.

Table 10. Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Question	Pharmacists (N=318) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	
True	82 (25.8)
False[2]	197 (61.9) [56.4 - 67.3]
I don't know	39 (12.3)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	
True	34 (10.7)
False[2]	256 (80.5) [75.7 - 84.7]
I don't know	28 (8.8)
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	
True[2]	131 (41.2) [35.7 - 46.8]
False	151 (47.5)
I don't know	36 (11.3)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a: Acute or postoperative pain	
Yes	35 (11.0)
No[2]	273 (85.8) [81.5 - 89.5]
I don't know	10 (3.1)
9b: Headache or migraine pain	
Yes	7 (2.2)
No[2]	300 (94.3) [91.2 - 96.6]
I don't know	11 (3.5)
9c: Dental pain	
Yes	2 (0.6)
No[2]	306 (96.2) [93.5 - 98.0]
I don't know	10 (3.1)

Table 10. Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Question	Pharmacists (N=318) n (%) [95% CI][1]
9d: Breakthrough pain from cancer	
Yes[2]	292 (91.8) [88.2 - 94.6]
No	22 (6.9)
I don't know	4 (1.3)
9e: Chronic non-cancer pain	
Yes	138 (43.4)
No[2]	162 (50.9) [45.3 - 56.6]
I don't know	18 (5.7)

Source: Appendix B: Survey Tables, Table 7.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Overall, 22.3% of respondents correctly answered all 8 questions/items of the key risk message; 43.1% missed no more than one item, and 65.4% missed no more than two items (Table 11).

Table 11. Secondary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Correct Responses	Pharmacists (N=318) n (%)
0 correct responses	1 (0.3)
1 correct response	3 (0.9)
2 correct responses	6 (1.9)
3 correct responses	8 (2.5)
4 correct responses	38 (11.9)
5 correct responses	54 (17.0)
6 correct responses	71 (22.3)
7 correct responses	66 (20.8)
8 correct responses	71 (22.3)

Source: Appendix B: Survey Tables, Table 7.2

The analysis stratified by whether the Full Prescribing Information or Medication Guide were received and read (Received and read: N 279; Did not receive or read: N 39) showed a

significant difference favoring respondents who received and read the materials in Question 9e (Table 12). A similar but non-significant trend was apparent for all other questions/items linked to the key risk message.

Table 12. Responses to Questions Linked to Key Risk Message #2 by Reading Full Prescribing Information or Medication Guide - Completed Surveys (Questions/Items with Apparent Trends)

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.		
True	73 (26.2)	9 (23.1)
False[2]	175 (62.7) [56.8 - 68.4]	22 (56.4) [39.6 - 72.2]
I don't know	31 (11.1)	8 (20.5)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.		
True	31 (11.1)	3 (7.7)
False[2]	230 (82.4) [77.5 - 86.7]	26 (66.7) [49.8 - 80.9]
I don't know	18 (6.5)	10 (25.6)
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.		
True[2]	118 (42.3) [36.4 - 48.3]	13 (33.3) [19.1 - 50.2]
False	134 (48.0)	17 (43.6)
I don't know	27 (9.7)	9 (23.1)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
Yes	29 (10.4)	6 (15.4)
No[2]	244 (87.5) [83.0 - 91.1]	29 (74.4) [57.9 - 87.0]
I don't know	6 (2.2)	4 (10.3)
9b: Headache or migraine pain		
Yes	6 (2.2)	1 (2.6)
No[2]	267 (95.7) [92.6 - 97.8]	33 (84.6) [69.5 - 94.1]
I don't know	6 (2.2)	5 (12.8)

Table 12. Responses to Questions Linked to Key Risk Message #2 by Reading Full Prescribing Information or Medication Guide - Completed Surveys (Questions/Items with Apparent Trends)

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
9c: Dental pain		
Yes	2 (0.7)	0
No[2]	272 (97.5) [94.9 - 99.0]	34 (87.2) [72.6 - 95.7]
I don't know	5 (1.8)	5 (12.8)
9d: Breakthrough pain from cancer		
Yes[2]	258 (92.5) [88.7 - 95.3]	34 (87.2) [72.6 - 95.7]
No	19 (6.8)	3 (7.7)
I don't know	2 (0.7)	2 (5.1)
9e: Chronic non-cancer pain		
Yes	117 (41.9)	21 (53.8)
No[2]	150 (53.8) [47.7 - 59.7]	12 (30.8) [17.0 - 47.6]
I don't know	12 (4.3)	6 (15.4)

Source: Appendix B: Survey Tables, Table 7.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

No meaningful comparison was possible in the analysis stratified by survey modality (internet or telephone) as only 4 respondents completed the survey by telephone. Stratification by time in pharmacy practice (per categories in Question 31) or number of times TIRF medicines were dispensed in the last 6 months (per categories in Question 28) did not result in any uniform trends (Appendix B).

5.2.3 Key Risk Message 3

Key Risk Message 3 states "TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics."

Results in Table 13 show that 98.1% (95% CI: 95.9 - 99.3) of pharmacists were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines. In addition, most respondents correctly indicated that a personal history of psychiatric illness is a risk factor for opioid abuse (77.7%, 95% CI: 72.7 - 82.1), that a personal history of past or current alcohol or drug abuse or family history of drug or alcohol abuse is a risk factor for opioid abuse (98.7%, 95% CI: 96.8 - 99.7), and that TIRF medicines can be abused in a manner similar to other opioid agonists (93.7%, 95% CI: 90.5 - 96.1).

A majority of respondents correctly identified the following as risks associated with the use of TIRF medicines: misuse (98.7%, 95% CI: 96.8 - 99.7), abuse (99.1%, 95% CI: 97.3 - 99.8), addiction (98.7%, 95% CI: 96.8 - 99.7), and overdose (99.4%, 95% CI: 97.7 - 99.9). Most respondents correctly answered that the following are not associated with the use of TIRF medicines: hypothyroidism (84.0%, 95% CI: 79.5 - 87.8) and infection (89.3%, 95% CI: 85.4 - 92.5).

Table 13. Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Question	Pharmacists (N=318) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	
True[2]	312 (98.1) [95.9 - 99.3]
False	4 (1.3)
I don't know	2 (0.6)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a: A personal history of psychiatric illness	
Yes[2]	247 (77.7) [72.7 - 82.1]
No	42 (13.2)
I don't know	29 (9.1)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	
Yes[2]	314 (98.7) [96.8 - 99.7]
No	1 (0.3)
I don't know	3 (0.9)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.	
True[2]	298 (93.7) [90.5 - 96.1]
False	12 (3.8)
I don't know	8 (2.5)

Table 13. Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Question	Pharmacists (N=318) n (%) [95% CI][1]
Question 13: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.	
13a: Misuse	
True[2]	314 (98.7) [96.8 - 99.7]
False	3 (0.9)
I don't know	1 (0.3)
13b: Abuse	
True[2]	315 (99.1) [97.3 - 99.8]
False	2 (0.6)
I don't know	1 (0.3)
13c: Addiction	
True[2]	314 (98.7) [96.8 - 99.7]
False	3 (0.9)
I don't know	1 (0.3)
13d: Overdose	
True[2]	316 (99.4) [97.7 - 99.9]
False	1 (0.3)
I don't know	1 (0.3)
13e: Hypothyroidism	
True	10 (3.1)
False[2]	267 (84.0) [79.5 - 87.8]
I don't know	41 (12.9)
13f: Infection	
True	15 (4.7)
False[2]	284 (89.3) [85.4 - 92.5]
I don't know	19 (6.0)

Source: Appendix B: Survey Tables, Table 8.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Overall, 59.4% of pharmacists correctly answered all 10 questions/items of the key risk message, and 85.5% missed no more than one item (Table 14).

Table 14. Secondary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Correct Responses	Pharmacists (N=318) n (%)
0 correct responses	0
1 correct response	0
2 correct responses	0
3 correct responses	1 (0.3)
4 correct responses	0
5 correct responses	1 (0.3)
6 correct responses	4 (1.3)
7 correct responses	8 (2.5)
8 correct responses	32 (10.1)
9 correct responses	83 (26.1)
10 correct responses	189 (59.4)

Source: Appendix B: Survey Tables, Table 8.2

No meaningful comparison was possible in the analysis stratified by survey modality (internet or telephone) as only 4 respondents completed the survey by telephone. Stratification by receipt and reading of the Full Prescribing Information or Medication Guide (received and read versus did not receive or read), time in pharmacy practice (per categories in Question 31), or number of times TIRF medicines were dispensed in the last 6 months (per categories in Question 28) did not result in any uniform trends (Appendix B).

5.2.4 Key Risk Message 4

Key Risk Message 4 states "TIRF medicines are not interchangeable with each other, regardless of route of administration."

Almost all pharmacists (95.9%; 95% CI: 93.1 - 97.8) understood TIRF medicines are not interchangeable with each other regardless of the route of administration; 93.1% (95% CI: 89.7 - 95.6) understood the conversion of one TIRF medicine to another may result in a fatal overdose; and 89.0% (95% CI: 85.0 - 92.2) understood that dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (Table 15). Almost all pharmacists (95.6%, 95% CI: 92.7 - 97.6) correctly indicated that TIRF medicines with the same route of administration cannot be substituted with each other if the pharmacy is out of stock.

Table 15. Primary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Question	Pharmacists (N=318) n (%) [95% CI][1]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b: TIRF medicines are interchangeable with each other regardless of route of administration.	
True	6 (1.9)
False[2]	305 (95.9) [93.1 - 97.8]
I don't know	7 (2.2)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	
True[2]	296 (93.1) [89.7 - 95.6]
False	10 (3.1)
I don't know	12 (3.8)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	
True[2]	283 (89.0) [85.0 - 92.2]
False	16 (5.0)
I don't know	19 (6.0)
Question 16: Please answer True, False, or I don't know for each statement about TIRF medicines.	
16c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	
True	10 (3.1)
False[2]	304 (95.6) [92.7 - 97.6]
I don't know	4 (1.3)

Source: Appendix B: Survey Tables, Table 9.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Overall, 79.9% of pharmacists correctly answered all 4 questions/items of the key risk message, and 95.6% missed no more than one item (Table 16).

Table 16. Secondary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Correct Responses	Pharmacists (N=318) n (%)
0 correct responses	0
1 correct response	6 (1.9)
2 correct responses	8 (2.5)
3 correct responses	50 (15.7)
4 correct responses	254 (79.9)

Source: Appendix B: Survey Tables, Table 9.2

The analysis stratified by whether the Full Prescribing Information or Medication Guide were received and read (Received and read: N 279; Did not receive or read: N 39) showed a trend favoring respondents who received and read the materials in Question 10d (Table 17).

Table 17. Responses to Questions Linked to Key Risk Message #4 by Reading Full Prescribing Information or Medication Guide - Completed Surveys (Questions/Items with Apparent Trends)

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2]	253 (90.7) [86.6 - 93.8]	30 (76.9) [60.7 - 88.9]
False	15 (5.4)	1 (2.6)
I don't know	11 (3.9)	8 (20.5)

Source: Appendix B: Survey Tables, Table 9.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

No meaningful comparison was possible in the analysis stratified by survey modality (internet or telephone) as only 4 respondents completed the survey by telephone. Stratification by time in pharmacy practice (per categories in Question 31) or number of times TIRF medicines were dispensed in the last 6 months (per categories in Question 28) did not result in any uniform trends (Appendix B).

5.2.5 Key Risk Message Average Knowledge Scores

Table 18 presents the average knowledge score for each key risk message and an overall knowledge score for all key risk messages combined. The overall knowledge score of 85.7 (95% CI: 84.4 87.0) indicates most respondents demonstrated understanding of the key risk messages. The average knowledge score for each of the key risk messages was ≥83.8 for 3 of the 4 key risk messages and was 75.4 for Key Risk Message 2 (TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older [16 years of age and older for Actiq® brand and generic equivalents] who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain).

Table 18. Average Knowledge Scores - Completed Surveys

	Score [95% CI][1]
KRM #1	83.8 [81.8, 85.7]
KRM #2	75.4 [73.1, 77.6]
KRM #3	93.7 [92.7, 94.8]
KRM #4	93.4 [91.7, 95.0]
Overall Knowledge Score	85.7 [84.4, 87.0]

Source: Appendix B: Survey Tables, Table 10
[1] 95% CIs are constructed based on normal distribution function.

5.2.6 Other Survey Questions

5.2.6.1 Additional Questions about TIRF Medicines Safety

Table 19 summarizes the responses of pharmacists to additional questions about the safe use of TIRF medicines beyond those associated with the key risk messages. Most pharmacists (92.1%) correctly indicated that use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment and monitoring of the patient as potentially fatal respiratory depression could occur.

The majority of pharmacists correctly indicated that a family history of asthma is not a risk factor for opioid abuse (85.2%). In addition, majorities of pharmacists correctly indicated that TIRF medicines may not be sold, loaned, or transferred to another pharmacy (90.6%) and that pharmacy staff who dispense TIRF medicines must be educated on the requirements of the TIRF REMS Access program (89.9%).

A majority of inpatient pharmacists (54/65; 83.1%) correctly indicated that it is not permissible to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for home use (Table 20).

Table 19. Responses to Additional Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Pharmacists (N=318) n (%)
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6d: Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment and monitoring of the patient for opioid toxicity as potentially fatal respiratory depression could occur.	
True[1]	293 (92.1)
False	3 (0.9)
I don't know	22 (6.9)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8c: A family history of asthma	
Yes	28 (8.8)
No[1]	271 (85.2)
I don't know	19 (6.0)
Question 16: Please answer True, False, or I don't know for each statement about TIRF medicines.	
16a: TIRF medicines may be sold, loaned, or transferred to another pharmacy.	
True	16 (5.0)
False[1]	288 (90.6)
I don't know	14 (4.4)
16b: All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access program.	
True[1]	286 (89.9)
False	18 (5.7)
I don't know	14 (4.4)

Source: Appendix B: Survey Tables, Table 3
[1] Correct response.

Table 20. Responses to Additional Questions about the Safe Use of TIRF Medicines: Question Asked of Inpatient Pharmacists Only - Completed Surveys

Question	Inpatient Pharmacists (N=65) n (%)
Question 20: Please answer True, False, or I don't know for the following statement about TIRF medicines. (Inpatient Pharmacists, only)[1]	
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.	
True	3 (4.6)
False[2]	54 (83.1)
I don't know	8 (12.3)

Source: Appendix B: Survey Tables, Table 5
[1] Percentages are calculated based on the sample presented with this question.
[2] Correct response.

5.2.6.2 Pharmacist Activities When Dispensing TIRF Medicines

Pharmacists were asked about specific activities performed when dispensing TIRF medicines (Table 21).

Of the 318 eligible pharmacists who completed the survey, 54.7% responded they always ask their patients (or a patient's caregiver) about the presence of children in the home; 26.7% responded that they ask only with the first prescription. Additionally, 70.1% responded they always instruct patients (or their caregivers) not to share TIRF medicines; 65.1% responded they always counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal, 67.3% responded they always instruct patients (or their caregivers) to keep TIRF medicines out of reach of children, 61.6% responded they always instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines, and 87.1% responded they always give patients (or their caregivers) the Medication Guide for TIRF medicine. Most respondents reported performing the following activities always or only with the first prescription: talking to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed (always 53.8%; only with first prescription 36.8%), instructing the patient on how to use the TIRF medicine that was most recently prescribed (always 57.9%; only with first prescription 34.9%), and instructing the patient on how to store or keep the TIRF medicine that was most recently prescribed (always 48.4%; only with first prescription 39.3%).

Table 21. Responses to Questions about the Activities When Dispensing TIRF Medicines - Completed Surveys

Question	Pharmacists (N=318) n (%)
Question 14: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.	
14a: Ask patients (or their caregivers) about the presence of children in the home	
Always	174 (54.7)
Only with the first prescription	85 (26.7)
Sometimes	33 (10.4)
Never	19 (6.0)
I don't know	7 (2.2)
14b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	
Always	223 (70.1)
Only with the first prescription	62 (19.5)
Sometimes	17 (5.3)
Never	13 (4.1)
I don't know	3 (0.9)
14c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	
Always	207 (65.1)
Only with the first prescription	69 (21.7)
Sometimes	24 (7.5)
Never	15 (4.7)
I don't know	3 (0.9)
14d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	
Always	214 (67.3)
Only with the first prescription	67 (21.1)
Sometimes	22 (6.9)
Never	11 (3.5)
I don't know	4 (1.3)

Table 21. Responses to Questions about the Activities When Dispensing TIRF Medicines - Completed Surveys

Question	Pharmacists (N=318) n (%)
14e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	
Always	196 (61.6)
Only with the first prescription	86 (27.0)
Sometimes	21 (6.6)
Never	11 (3.5)
I don't know	4 (1.3)
14f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine	
Always	277 (87.1)
Only with the first prescription	24 (7.5)
Sometimes	6 (1.9)
Never	8 (2.5)
I don't know	3 (0.9)
Question 15: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.	
15a: Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed.	
Always	171 (53.8)
Only with the first prescription	117 (36.8)
Sometimes	21 (6.6)
Never	8 (2.5)
I don't know	1 (0.3)
15b: Instruct the patient on how to use the TIRF medicine that was most recently prescribed.	
Always	184 (57.9)
Only with the first prescription	111 (34.9)
Sometimes	14 (4.4)
Never	8 (2.5)
I don't know	1 (0.3)

Table 21. Responses to Questions about the Activities When Dispensing TIRF Medicines - Completed Surveys

Question	Pharmacists (N=318) n (%)
15c: Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed.	
Always	154 (48.4)
Only with the first prescription	125 (39.3)
Sometimes	24 (7.5)
Never	13 (4.1)
I don't know	2 (0.6)

Source: Appendix B: Survey Tables, Table 5
[1] Percentages are calculated based on the sample presented with this question.
[2] Correct response.

Specific pharmacy types (inpatient, outpatient, and CSP pharmacies) were each asked a single, different question regarding pharmacy systems and processes. Question 17 was presented only to respondents from inpatient pharmacies as identified through the unique survey access code provided by the respondent to enter the survey (Table 22). Of the 65 inpatient pharmacy respondents, 61.5% reported their pharmacy has processes to ensure compliance with the TIRF REMS Access program requirements.

Table 22. Responses to All Questions about Activities When Dispensing TIRF Medicines: Asked of Inpatient Pharmacies Only - Completed Surveys

Question	Inpatient Pharmacists (N=65) n (%)
Question 17: Does the inpatient pharmacy where you work have an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program? (Inpatient Pharmacists, only)[1]	
Yes	40 (61.5)
No	11 (16.9)
I don't know	14 (21.5)

Source: Appendix B: Survey Tables, Table 5
[1] Percentages are calculated based on the sample presented with this question.

Question 18 was presented only to pharmacy respondents from outpatient pharmacies as identified through the unique survey access code provided by the respondent to enter the survey. This sub-population did not include respondents from CSPs (Table 23). Of the 252 outpatient pharmacy respondents, 81.7% reported their pharmacy processes prescriptions for TIRF medicines through their pharmacy management system regardless of the method of payment.

Table 23. Responses to All Questions about Activities When Dispensing TIRF Medicines: Outpatient Pharmacists Only - Completed Surveys

Question	Outpatient Pharmacists (N=252) n (%)
Question 18: Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system? (Outpatient Pharmacists, only)[1]	
Yes	206 (81.7)
No	11 (4.4)
I don't know	35 (13.9)

Source: Appendix B: Survey Tables, Table 5
[1] Percentages are calculated based on the sample presented with this question.

Question 19 (*Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center?*) was presented only to pharmacy respondents from CSPs. The single CSP outpatient pharmacist who participated in the survey responded that his/her pharmacy does process all TIRF medicine prescriptions through the TIRF REMS Call Center regardless of method of payment (Appendix B: Survey Tables, Table 5).

5.3 Spontaneous Reporting of Potential Adverse Events, Product Complaints, or Medical Information Requests

Among all survey respondents (N 561, Table 1), there were 4 reports of a potential adverse event or product complaint associated with the use of TIRF medicines made within the survey free text field during the online survey and 1 report recorded during the telephone survey. Verbatim statements are provided in Appendix B, Listing 2.

6. DISCUSSION AND CONCLUSIONS

Discussion

Survey invitations (and reminders) were sent to a random sample of pharmacies enrolled in the TIRF REMS Access program that had dispensed a TIRF medicine in the last 6 months, a revision to the survey recruitment strategy per FDA request. From among those who responded to the invitation, 318 pharmacists completed the survey. Thus, the required sample size of 300 was achieved within the planned survey period.

The respondents completing the survey represented a total of 240 pharmacies; 175 pharmacies (145 outpatient, 29 inpatient, 1 CSP) had 1 respondent each, 53 (40 outpatient, 13 inpatient) had 2 respondents each, and 12 (9 outpatient, 3 inpatient) had 3 respondents each. The pharmacies were located in all US Census Bureau regions except Other. Comparison of pharmacies represented by the survey respondents to the general population of pharmacies that had dispensed TIRF medicines in the past 6 months based on REMS switch provider

data (N 3,857) showed a similar distribution by geographic region (Table 5). The pharmacy groups differed with respect to distribution of types of pharmacies due to differing percentages of independent versus chain outpatient pharmacies. The distribution of outpatient pharmacy orders between independent and chain pharmacies was similar for the 2 groups; however, a chi-square test showed a significant difference because orders in the general population included a small percentage of orders from CSPs, which could not be represented in orders from the survey respondents' pharmacies.

The overall knowledge score of 85.7 (95% CI: 84.4 87.0) for the survey indicates most respondents demonstrated understanding of the key risk messages (Table 18). The average knowledge score for each of the key risk messages was ≥83.8 for 3 of the 4 key risk messages and was 75.4 for Key Risk Message 2 (TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older [16 years of age and older for Actiq® brand and generic equivalents] who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain). The lower average knowledge score for Key Risk Message 2 reflected 3 linked questions/items (described below) with correct response rates <65%.

Of the 36 questions/items included as part of key risk messages, 27 items of the key risk messages had a correct response rate >80%, and 6 items had correct response rates from 65.1% to 79.6%. Three questions/items of Key Risk Message 2 had a correct response rate below the desired threshold of 65% (Items 6a, 6c, and 9e).

- The correct response rate for Item 6a (*According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time*) was 61.9%. This is slightly lower than the correct response rates of 63.3%-69.1% observed for the previous 3 pharmacist KAB surveys conducted (24-month, 36-month, and 48-month surveys) (Table 24).
- The correct response rate for Item 6c (*A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine*) was 41.2%. This item was added to the 48-month survey based on feedback provided by FDA in the 24-month and the 36-month FDA REMS Acknowledgement Letter (See Section 1.1). The item had a similar correct response rate of 41.9% in the 48-month survey.
- The correct response rate for Item 9e (*Chronic non-cancer pain* is not an indication for which TIRF medicines can be prescribed) was 43.4%. Item 9e has also had a low correct response rate across all previous pharmacist KAB surveys conducted (annual waves from the 12-month through the 48-month surveys) (Table 24). The survey score for Item 9e may indicate that some respondents are dispensing TIRF medicines for non-cancer associated indications.

As previously discussed, the survey was updated prior to launch based on FDA feedback received on 21 July 2016. Changes to the 60-month KAB survey for pharmacists based on FDA feedback included the addition of 3 survey questions and a change to the recruitment strategy to limit the survey to pharmacists who had dispensed TIRF medicines in the past 6 months and attempt to recruit more closed system pharmacists and non-supervisory

pharmacists. Added questions relating to key risk messages included Question 12 (*TIRF medicines should only be taken by patients who are opioid tolerant [True/False]*) and Question 13 (*Which of the following risks are associated with the use of TIRF medicines? [True/False for each of the following: misuse, abuse, addiction, overdose, hypothyroidism, and infection]*). Correct response rates for these new questions/items were ≥95.6% for Question 12 and 4 items of Question 13 and 84.0%-89.3% for the 2 false items of Question 13 (hypothyroidism and infection). Question 15 (*How frequently do you perform the following activities when dispensing TIRF medicines?*) included 3 response items about pharmacist-reported activity. For each item, most respondents selected *always* or *only with the first prescription*; and few respondents selected *sometimes*, *never*, or *I don't know*. Changes to recruitment efforts included a revised invitation letter addressed to the "pharmacist-in-charge" including 3 letters with unique codes; the pharmacist-in-charge was asked to distribute these letters to non-supervisory staff involved in the dispensing of TIRF medicines. This strategy was successful, with 74.8% of respondents indicating they were not the pharmacist-in-charge.

As shown in Table 24, no trend was evident for this 60-month survey in knowledge and understanding of the key risk messages. Table 24 includes key risk messages and questions/items within each key risk message as presented in the 60-month survey. It is important to note the question/item numbering, wording, and association with a specific key risk message may have changed across survey waves based on FDA feedback or other decisions made by the TRIG. A limitation to looking at correct response rates over time is that survey questions may have been modified. The primary focus of this table is to show general trends over time with a specific focus on changes from the 48-month survey to the 60-month survey.

Table 24. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients						
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those: [1]					
5a	Who are taking around-the-clock opioid therapy for underlying persistent cancer pain for one week or longer (*Correct Response True*) [1]	12.6[2]	90.3 (86.4, 93.4)	93.7 (90.3, 96.1)	92.7 (89.1 - 95.4)	95.6 (92.7 - 97.6)
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before (*Correct Response "False"*)	80.1[2]	80.7 (75.7, 85.0)	87.0 (82.7, 90.6)	87.4 (83.1 - 90.9)	87.4 (83.3 - 90.9)
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy (*Correct Response False*) [1]	15.6[2]	76.0 (70.8, 80.7)	78.7 (73.6, 83.2)	82.4 (77.6 - 86.5)	82.1 (77.4 - 86.1)
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines. [1]					
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose (*Correct Response True*)	86.1 (81.7, 89.8)	86.0 (81.6, 89.7)	90.7 (86.8, 93.7)	91.0 (87.2 - 94.0)	88.4 (84.3 - 91.7)

Table 24. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products (*Correct Response True*)	92.1 (88.4, 94.8)	93.7 (90.3, 96.1)	93.7 (90.3, 96.1)	95.3 (92.3 - 97.4)	95.3 (92.3 - 97.3)
7c	TIRF medicines may be used to treat opioid non-tolerant patients (*Correct Response False*) [1]	78.5 (73.4, 83.0)	82.0 (77.2, 86.2)	83.7 (79.0, 87.7)	85.4 (80.9 - 89.2)	87.4 (83.3 - 90.9)
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine (*Correct Response True*)	78.5 (73.4, 83.0)	82.7 (77.9, 86.8)	79.0 (73.9, 83.5)	80.7 (75.8 - 85.0)	84.0 (79.5 - 87.8)
11	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:					
11a	8 mg oral hydromorphone/day (*Correct Response True*)	N/A [3]	79.0 [2]	76.3 [2]	78.7 (73.7 - 83.2)	74.5 (69.4 - 79.2)
11b	60 mg oral morphine/day (*Correct Response True*)	N/A [3]	85.0 [2]	84.7 [2]	89.7 (85.7 - 92.9)	88.1 (84.0 - 91.4)
11c	30 mg oral oxycodone/day (*Correct Response True*)	N/A [3]	71.3 [2]	73.3 [2]	77.1 (71.9 - 81.7)	77.7 (72.7 - 82.1)

Table 24. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
11d	25 mcg transdermal fentanyl/hour (*Correct Response True*)	N/A[3]	72.0[2]	74.3[2]	77.1 (71.9 - 81.7)	79.6 (74.7 - 83.9)
11e	25 mg oral oxymorphone/day (*Correct Response True*)	N/A[3]	71.0[2]	71.0[2]	73.4 (68.1 - 78.3)	72.0 (66.7 - 76.9)
11f	An equianalgesic dose of another oral opioid (*Correct Response True*)	N/A[3]	59.0[2]	59.0[2]	65.1 (59.4 - 70.5)	65.1 (59.6 - 70.3)
12	Please answer True, False, or I don't know for the following statement about TIRF medicines:					
	TIRF medicines should only be taken by patients who are opioid tolerant. (*Correct Response True*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	95.6 (92.7 - 97.6)
Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-the-Clock Opioid Therapy for Their Underlying Persistent Cancer Pain						
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicine.					
6a	According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time (*Correct Response False*) [1]	N/A[3]	65.3[2]	63.3[2]	69.1 (63.5 - 74.3)	61.9 (56.4 - 67.3)

Table 24. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
6b	According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain (*Correct Response False*) [1]	N/A[3]	74.7[2]	74.0[2]	82.1 (77.2 - 86.2)	80.5 (75.7 - 84.7)
6c	A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine (*Correct Response True*)	N/A[3]	N/A[3]	N/A[3]	41.9 (36.2 - 47.7)	41.2 (35.7 - 46.8)
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.					
9a	Acute or postoperative pain (*Correct Response No*)	78.1 (73.1, 82.7)	84.7 (80.1, 88.6)	86.7 (82.3, 90.3)	90.0 (86.1 - 93.2)	85.8 (81.5 - 89.5)
9b	Headache or migraine pain (*Correct Response No*)	89.1 (85.0, 92.4)	92.3 (88.7, 95.1)	90.7 (86.8, 93.7)	93.0 (89.5 - 95.6)	94.3 (91.2 - 96.6)
9c	Dental pain (*Correct Response No*)	94.7 (91.5, 96.9)	96.7 (94.0, 98.4)	97.0 (94.4, 98.6)	98.3 (96.2 - 99.5)	96.2 (93.5 - 98.0)
9d	Breakthrough pain from cancer (*Correct Response Yes*)	83.4 (78.8, 87.5)	89.3 (85.3, 92.6)	91.7 (87.9, 94.5)	92.0 (88.4 - 94.8)	91.8 (88.2 - 94.6)
9e	Chronic non-cancer pain (*Correct Response No*)	29.8[2]	47.0 (41.2, 52.8)	43.7 (38.0, 49.5)	50.8 (45.0 - 56.6)	50.9 (45.3 - 56.6)

Table 24. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, with Abuse Liability Similar to other Opioid Analgesics						
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines *(Correct Response True)*	97.7 (95.3, 99.1)	96.7 (94.0, 98.4)	96.0 (93.1, 97.9)	97.3 (94.8 - 98.8)	98.1 (95.9 - 99.3)
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.					
8a	A personal history of psychiatric illness (*Correct Response Yes*)	66.6 (60.9, 71.9)	72.0 (66.6, 77.0)	71.0 (65.5, 76.1)	75.4 (70.1 - 80.2)	77.7 (72.7 - 82.1)
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse (*Correct Response Yes*)	99.7 (98.2, 100.0)	99.0 (97.1, 99.8)	99.3 (97.6, 99.9)	98.7 (96.6 - 99.6)	98.7 (96.8 - 99.7)
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines. [1]					
10a	TIRF medicines can be abused in a manner similar to other opioid agonists (*Correct Response True*)	90.4 (86.5, 93.5)	94.0 (90.7, 96.4)	94.3 (91.1, 96.7)	95.7 (92.7 - 97.7)	93.7 (90.5 - 96.1)
13	Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.					
13a	Misuse (*Correct Response True*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	98.7 (96.8 - 99.7)

Table 24. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
13b	Abuse (*Correct Response True*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	99.1 (97.3 - 99.8)
13c	Addiction (*Correct Response True*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	98.7 (96.8 - 99.7)
13d	Overdose (*Correct Response True*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	99.4 (97.7 - 99.9)
13e	Hypothyroidism (*Correct Response False*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	84.0 (79.5 - 87.8)
13f	Infection (*Correct Response False*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	89.3 (85.4 - 92.5)
Key Risk Message 4: TIRF Medicines Are Not Interchangeable with Each Other, Regardless of Route of Administration						
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines. [1]					
10b	TIRF medicines are interchangeable with each other regardless of route of administration (*Correct Response False*)	95.0 (91.9, 97.2)	94.7 (91.5, 96.9)	93.3 (89.9, 95.9)	93.4 (89.9 - 95.9)	95.9 (93.1 - 97.8)
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption (*Correct Response True*)	92.7 (89.2, 95.4)	92.0 (88.3, 94.8)	93.0 (89.5, 95.6)	92.7 (89.1 - 95.4)	93.1 (89.7 - 95.6)

Table 24. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
10d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (*Correct Response True*)	92.4 (88.8, 95.1)	91.3 (87.6, 94.3)	90.0 (86.0, 93.2)	92.7 (89.1 - 95.4)	89.0 (85.0 - 92.2)
16	Please answer True, False, or I don't know for each statement about TIRF medicines.					
16c	TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product (*Correct Response False*)	95.7[2]	96.3[2]	97.7[2]	98.3 (96.2 - 99.5)	95.6 (92.7 - 97.6)

[1] Question was revised for the 60-month survey.
[2] 95% confidence interval is not provided since the question/item was not part of a key risk message during the reporting period.
[3] Question was not asked during the reporting period.

The analysis stratified by whether the Full Prescribing Information or Medication Guide were received and read (received and read versus did not receive or read) showed a trend of higher correct-response rates for respondents who received and read the materials in some or all questions/items linked to Key Risk Messages 1, 2, and 4. No meaningful comparison was possible in the analysis stratified by survey modality (internet or telephone) as only 4 respondents completed the survey by telephone. Stratification by time in pharmacy practice or number of times TIRF medicines were dispensed in the last 6 months did not result in any uniform trends.

Conclusions

In general, there is an overall trend over time toward maintaining, or increasing, pharmacist knowledge and understanding of the key risk messages. Three exceptions where pharmacists scored low included understanding that a cancer patient may not start a TIRF medicine and an around-the-clock opioid at the same time, that a patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine, and that TIRF medicines are not indicated for chronic non-cancer pain, which may indicate that some respondents are dispensing TIRF medicines for non-cancer associated indications.

Overall, this 60-month survey shows a high level (greater than or equal to 65% for all but three items) of pharmacist understanding of key risk messages based on the REMS goals. TRIG acknowledges that there is room for improvement around pharmacist knowledge related to indications for TIRF medicines and safe use of TIRF medicines by patients also using around-the-clock opioid pain medicines.

Appendix A Pharmacy Survey Protocol Track Change Document: Comparison of 48-month Survey to 60-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Pharmacist Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Actavis Laboratories FL, Inc.** **BioDelivery Sciences International, Inc. ~~(BDSI) *(replaced Meda Pharmaceuticals on March 11, 2015)*~~(BDSI)** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Depomed, Inc.** **~~Galena Biopharma, Inc.~~** **Insys Therapeutics, Inc.** **Mallinckrodt Pharmaceuticals** **Mylan~~,~~ Inc.** **Par ~~Pharmaceutical~~Pharmaceuticals, Inc.** **Sentynl Therapeutics, Inc.**
VERSION:	**~~9~~11.0**
DATE:	**~~12AUG2015~~04AUG2016**
APPROVED:	**~~FINAL~~Final**

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1. LIST OF ABBREVIATIONS

BDSI	BioDelivery Sciences International, Inc.
CATI	Computer-Assisted Telephone Interviewing
CSP	Closed System Pharmacy
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes, and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access ~~Program~~program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI) (replaced Meda Pharmaceuticals on March 11, 2015(BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan Inc.; Par Pharmaceuticals, Inc.; and Par PharmaceuticalSentynl Therapeutics, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the riskrisks of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access Programprogram (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the riskrisks of misuse, abuse, addiction, overdose, and serious complications due to medication errors by:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients

2. Preventing inappropriate conversion between TIRF medicines

3. Preventing accidental exposure to children and others for whom it was not prescribed

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines

An important component of the TIRF REMS is the conduct of quantitative evaluation surveys to assess pharmacists' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, enrollment formPharmacy Enrollment Form, and Prescribing Information (PI). This protocol will describe the administration of the surveys that will be conducted among pharmacists who are enrolled in the TIRF REMS Access Programprogram.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE PHARMACIST EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of pharmacists around the following key information and risk messages communicated through REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.

2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.

3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.

4. TIRF medicines are not interchangeable with each other, regardless of route of administration.

5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC), and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among ~~a sample of~~ pharmacists who are affiliated with pharmacies enrolled in the TIRF REMS Access ~~Program~~program that have dispensed a TIRF medicine within the last 6 months. Respondents who have participated in a previous wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered via the Internet through a secure website

- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take up to 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA ~~provided feedback to the TRIG on the Knowledge, Attitudes, and Behavior (KAB) survey results for pharmacists included in the 12-month REMS Assessment results. The FDA~~ requested ~~that~~ the TRIG to investigate the causes ~~for~~of low correct response rates ~~to specific questions in the survey by conducting~~reported in the 12-month REMS Assessment Report. Qualitative research was conducted in 2013 to determine the reasons for the poor performance on these questions and to assess proposed revised wording to select questions. ~~Qualitative research was performed in 2013 prior to Wave 2 of the survey.~~ Findings were incorporated into the survey and results from the revised survey were included in the 24-month REMS Assessment Report~~,~~.

4.1.2 Questions and Statements on REMS Goals

The KAB questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These questions will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Questions ~~will be~~are presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use “yes” or “no” as potential response options);

- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and

- One question allowing for the respondent to list questions or comments.

Questionnaires will be analyzed to determine pharmacist understanding of each key risk message.

For statements or questions that use “true” or “yes” vs. “false” or “no” response options, the desired response for the key risk messages is generally “true” or “yes” indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response

options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired Response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
7c	TIRF medicines may be used in opioid non-tolerant patients.	**FALSE**
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**
11	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:	
11a	8 mg oral hydromorphone/day	**TRUE**
11b	60 mg oral morphine/day	**TRUE**
11c	30 mg oral oxycodone/day	**TRUE**
11d	25 mcg transdermal fentanyl/hour	**TRUE**
11e	25 mg oral oxymorphone/day	**TRUE**
11f	An equianalgesic dose of another oral opioid	**TRUE**
12	TIRF medicines should only be taken by patients who are opioid tolerant.	**TRUE**

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired Response**
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a	According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	**FALSE**
6b	According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	**FALSE**
6c	A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	**TRUE**
9	Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	**NO**
9b	Headache or migraine pain	**NO**
9c	Dental pain	**NO**
9d	Breakthrough pain from cancer	**YES**
9e	Chronic non-cancer pain	**NO**

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired Response**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**
13	Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.	
13a	Misuse	**TRUE**
13b	Abuse	**TRUE**
13c	Addiction	**TRUE**
13d	Overdose	**TRUE**
13e	Hypothyroidism	**FALSE**
13f	Infection	**FALSE**

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired Response**
10	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
10c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**
10d	Dosing of TIRF medicines is not equivalent	**TRUE**

	on a microgram-to-microgram basis.	
~~13~~16	Please answer True, False, or I don't know for each statement about TIRF medicines.	
~~13e~~16c	TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	**FALSE**

4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access ~~Program~~program, receipt and understanding of the TIRF educational materials, and pharmacist behaviors~~.~~ in counseling patients and caregivers regarding TIRF medicines. The following question about behaviors will be asked ~~after the key risk message questions.~~:

Question 12: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

Demographic information will be collected at the end of the survey.

4.2 Participant Recruitment

A random sample of pharmacists identified from pharmacies that are enrolled in the TIRF REMS Access ~~Program~~program and that have dispensed a TIRF medicine in the last 6 months will be invited to participate via an invitation letter to their pharmacy's "pharmacist in charge". The text of the ~~sample~~ written invitation to pharmacists can be found in Appendix B.

If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to ~~non-responders~~the pharmacy's "pharmacist in charge" from ~~the original sample~~which no responses were received with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. ~~The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample.~~ If these efforts do not result in the required number of surveys within two to three weeks, then a new sample of

~~pharmacists~~pharmacies will be randomly selected. The distribution within the mailing to the second sample will be adjusted by completion rate for each pharmacy type. The unique code provided in the invitation letter will be linked to the type of pharmacy (inpatient, outpatient, or Closed System Pharmacy [CSP]) in which the pharmacist works, based on the information provided as part of the TIRF REMS Access ~~Program~~program enrollment.

All respondents who complete the survey and who provide their contact information will be mailed a $50 honorarium to thank them for their participation. The mailing will include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of participating pharmacistspharmacies will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of pharmacies (e.g., inpatient, outpatient [chain and independent store] and CSP) for participation.

Pharmacists will be offered Internet-based or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the Internet-based survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

5. STUDY POPULATION

5.1.1 Sample Size

A sample of 300 pharmacists whofrom pharmacies that are enrolled in the TIRF REMS Access Programprogram is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. There is no target comprehension rate specified *a priori*.. A sample of 300 completed surveys will allow estimation of the comprehension rate for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.2 Inclusion Criteria

Pharmacists who work at pharmacies that are enrolled in the TIRF REMS Access ~~Program~~program and that have dispensed a TIRF medicine in the last 6 months are eligible to participate in this survey, with the exceptions noted below.

5.1.3 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Pharmacists who have previously participated in the TIRF REMS KAB survey.
- Pharmacists or their immediate family members who have ever worked for Actavis Laboratories FL, Inc.; Anesta LLC; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan~~,~~ Inc.; Par ~~Pharmaceutical~~Pharmaceuticals, Inc.; Teva Pharmaceuticals, Ltd.; Sentynl Therapeutics, Inc.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

6. SURVEY PROCESS

~~The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.~~

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm pharmacist eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. An Internet-based data repository will be used to store survey data and other relevant program information. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Pharmacist-identifying information will be stored separately from survey data.

Completion of the entire survey is expected to take approximately 20 minutes.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of pharmacists who do not have Internet access or prefer taking the survey over the telephone. It will also be convenient for pharmacists to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the pharmacist selects to participate in the survey via the Internet, he/she will be directed to a secured website where he/she will be instructed to complete screening questions. An Internet-based survey will be convenient for respondents to participate since they can complete the questionnaire at any convenient time and location during the specified survey time period ~~when the Survey Coordinating Center is available~~.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to pharmacists
- The number of invitations returned as undeliverable
- The number of reminder letters issued to pharmacists
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who answered all questions presented to them
- Representativeness of pharmacists based on geography
- Description of survey participants, including:
    - Gender
    - Years of professional experience
    - How many times per month TIRF medicines were dispensed by the pharmacist in the last 6 months

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible pharmacists who completed all questions presented to them in the survey ("completers").

7.1.1.1 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response torate for each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

7.1.1.2 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. The secondary analysis entails a frequency distribution of the number of completers who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

Mean knowledge scores will be computed for each key risk message; an overall knowledge score will be computed for each respondent as well.

Additional analyses may be performed as needed.

8. SAFETY EVENT REPORTING

The term '~~Safety Event~~'safety event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a ~~Safety Event~~safety event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if they have questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $50 honorarium, a Thank You Letter, correct survey responses to key risk message questions, and the ISI after the survey is completed. Respondent contact information is also needed in the event that a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to dispense TIRF medicines.

Appendix A Pharmacist Questionnaire

Survey Legend

[PROGRAMMER] is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

(INTERVIEWER) is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

[ONLINE] indicates a question is worded specifically for administering the survey online. **[PHONE]** indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

[BEGIN SURVEY CONTENT] and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

[TERMINATE] is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

> *Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.*

[RANDOMIZE LIST] is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.

Response options for questions that allow multiple responses must be indicated with check boxes (□). At least one option must be selected for the question to be considered answered.

> If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option, if applicable.

Response options for questions that allow only one response must be indicated with radio buttons (○).

> If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option, if applicable.

[GO TO Qx] (skip logic) is inserted after a response to indicate to the programmer that the survey should skip to the indicated question (for example, **[GO TO Q17]** skips to question 17). If no skip logic is indicated the survey continues to the next question in the sequence.

Survey Legend

[FREE TEXT] indicates to the programmer that one line should be provided for data entry.

[MULTILINE INPUT] indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines).

[DROP-DOWN LIST INPUT WITH STATES TABLE] indicates to the programmer that the response should be a drop-down list containing the states in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS
  West South Central Division - AR, LA, OK, TX

Survey Legend

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

The following US territories are categorized as Other: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[BEGIN ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; ~~Galena Biopharma, Inc.;~~ Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan Inc.; Par Pharmaceuticals, Inc.; and ~~Par Pharmaceutical~~Sentynl Therapeutics, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send ~~you~~ the honorarium to you after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[BEGIN PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess pharmacists' understanding of the safe use and dispensing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; ~~Galena Biopharma, Inc.;~~ Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan Inc.; Par Pharmaceuticals, Inc.; and ~~Par Pharmaceutical~~Sentynl Therapeutics, Inc. The survey will take 15-20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to dispense TIRF medicines.

Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other pharmacists taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $50 honorarium for your time and participation.

Your name and address will be used to send ~~you~~ the honorarium to you after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call should you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have questions at a later time, please contact the Survey Coordinating Center at 1-877-379-3297.

Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, you cannot go back and change your answers. Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - ○ Yes
   - ○ No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.

   - ○ Yes **[TERMINATE]**
   - ○ No
   - ○ I don't know **[TERMINATE]**

3. Do you work in a pharmacy that is enrolled in the TIRF REMS Access ~~Program~~program?

   - ○ Yes
   - ○ No **[TERMINATE]**
   - ○ I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

   - □ Actavis Laboratories FL, Inc. **[TERMINATE]**
   - □ Anesta LLC **[TERMINATE]**
   - □ BioDelivery Sciences International, Inc. (BDSI) **[TERMINATE]**
   - □ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
   - □ Depomed, Inc. **[TERMINATE]**

- ☐ Galena Biopharma, Inc. **[TERMINATE]**
- ☐ Insys Therapeutics, Inc. **[TERMINATE]**
- ☐ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Mylan~~,~~ Inc. ~~-~~**[TERMINATE]**
- ☐ Par ~~Pharmaceutical~~Pharmaceuticals, Inc. **[TERMINATE]**
- ☐ RelayHealth **[TERMINATE]**
- ☐ Sentynl Therapeutics, Inc. **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA **[TERMINATE]**
- ☐ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**
- ☐ Prefer not to answer **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

5. Please select True, False, or I don't know for each of the following.

   According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
5a.	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	○	○	○
5b.	Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c.	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

6. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
6a. According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b. According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	○	○	○
6c. A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	○	○	○
6d. Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment and monitoring of the patient for opioid toxicity as potentially fatal respiratory depression could occur.	○	○	○

7. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
7a. TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b. Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c. TIRF medicines may be used in opioid non-tolerant patients.	○	○	○
7d. Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e. It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

8. Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

9. Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
9a.	Acute or postoperative pain	○	○	○
9b.	Headache or migraine pain	○	○	○
9c.	Dental pain	○	○	○
9d.	Breakthrough pain from cancer	○	○	○
9e.	Chronic non-cancer pain	○	○	○

10. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
10a.	TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
10b.	TIRF medicines are interchangeable with each other regardless of route of administration.	○	○	○
10c.	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○
10d.	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

11. Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

		True	False	I don't know
11a.	8 mg oral hydromorphone/day	○	○	○
11b.	60 mg oral morphine/day	○	○	○
11c.	30 mg oral oxycodone/day	○	○	○
11d.	25 mcg transdermal fentanyl/hour	○	○	○
11e.	25 mg oral oxymorphone/day	○	○	○
11f.	An equianalgesic dose of another oral opioid	○	○	○

12. Please answer True, False, or I don't know for the following statement about TIRF medicines:

TIRF medicines should only be taken by patients who are opioid tolerant.

- ○ True
- ○ False
- ○ I don't know

13. Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.

		True	False	I don't know
13a.	Misuse	○	○	○
13b.	Abuse	○	○	○
13c.	Addiction	○	○	○
13d.	Overdose	○	○	○
13e.	Hypothyroidism	○	○	○
13f.	Infection	○	○	○

~~12.~~14. How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.

	[RANDOMIZE LIST]	Always	Only with the first prescription	Sometimes	Never	I don't know
~~12a.~~14a.	Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
~~12b.~~14b.	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
~~12c.~~14c.	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
~~12d.~~14d.	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
~~12e.~~14e.	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○
~~12f.~~14f.	Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

~~13.~~15 How frequently do you perform the following activities when dispensing TIRF medicines? Please answer ~~True, False~~Always, Only with the first prescription, Sometimes, Never, or I don't know ~~for each statement about TIRF medicines~~.

	[RANDOMIZE LIST]	~~True~~Always	~~False~~Only with the first prescription	Sometimes	Never	I don't know
15a	Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed.	○	○	○	○	○
15b	Instruct the patient on how to use the TIRF medicine that was most recently prescribed.	○	○	○	○	○

15c Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed.	○	○	○	○	○

16. Please answer True, False, or I don't know for each statement about TIRF medicines.

[RANDOMIZE LIST]	True	False	I don't know
~~13a.~~1(TIRF medicines may be sold, loaned, or transferred to another pharmacy.	○	○	○
~~13b.~~1(All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access ~~Program~~program.	○	○	○
~~13c.~~1(TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	○	○	○

~~14.~~17 **[INPATIENT PHARMACIST]** Does the inpatient pharmacy where you work have an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access ~~Program~~program?

- ○ Yes
- ○ No
- ○ I don't know

~~15.~~18 **[OUTPATIENT PHARMACIST]** Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system?

- ○ Yes
- ○ No
- ○ I don't know

~~16.~~19. **[CSP OUTPATIENT PHARMACIST]** Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center?

- ○ Yes
- ○ No
- ○ I don't know

~~17.~~20 **[INPATIENT PHARMACIST]** Please answer True, False, or I don't know for the following statement about TIRF medicines.

	True	False	I don't know
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.	○	○	○

[BEGIN PREAMBLE ~~3~~2]

The next set of questions is about the educational materials for TIRF medicines. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.

[END PREAMBLE ~~3~~2]

~~18.~~21 Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- ○ Yes
- ○ No **[GO TO Q23~~20~~23]**
- ○ I don't know **[GO TO Q23~~20~~23]**

~~19.~~22 Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?

- Yes
- No
- I don't know

~~20.~~23 Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?

- Yes
- No -**[GO TO Q25~~2225~~]**
- I don't know **[GO TO Q25~~2225~~]**

~~21.~~24 Did you read the Medication Guide for the TIRF medicine(s) that you dispense?

- Yes
- No
- I don't know

~~22.~~25 Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- Yes
- No **[GO TO DEMOGRAPHICS PREAMBLE 1]**
- I don't know **[GO TO DEMOGRAPHICS PREAMBLE 1]**

[IF QUESTION ~~22~~25 YES, DISPLAY QUESTION 26 ON SAME PAGE]

~~23.~~26 What are your questions? **[MULTILINE INPUT]**

[BEGIN DEMOGRAPHICS PREAMBLE 1 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

There are just a few more questions to help us combine your answers with other answers we have received.

[END DEMOGRAPHICS PREAMBLE 1]

~~24.~~27 Are you the Pharmacist in Charge for the TIRF REMS Access ~~Program~~program where you work?

- ○ Yes
- ○ No
- ○ I don't know

~~25.~~28 On average, how many times per month have you dispensed TIRF medicine within the last 6 months?

- ○ None **[Go to DEMOGRAPHICS PREAMBLE 2]**
- ○ 1 2 times per month
- ○ 3 5 times per month
- ○ More than 5 times per month
- ○ I don't remember

~~26.~~29 Please select the TIRF medicine(s) that you have dispensed within the last 6 months. Please select all that apply.

- ☐ Abstral®
- ☐ Actiq® or generic Actiq®
- ☐ Fentora®
- ☐ Lazanda®
- ☐ Subsys®

[BEGIN DEMOGRAPHICS PREAMBLE 2 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

These last few questions are for demographic purposes.

[END DEMOGRAPHICS PREAMBLE 2]

~~27.~~30 What is your gender?

- ○ Male
- ○ Female
- ○ Prefer not to answer

~~28.~~31 In total, how many years have you been a practicing pharmacist?

- ○ Less than 3 years
- ○ 3 5 years
- ○ 6 10 years
- ○ 11 15 years
- ○ More than 15 years
- ○ Prefer not to answer

~~29.~~32 In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" AT END]

[PHONE - BEGIN ADVERSE EVENT/PRODUCT COMPLAINT – KEEP ON ONE PAGE]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- ○ Yes
- ○ No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[BEGIN CLOSING 1 – KEEP ON ONE PAGE]

We would like to send you a $50 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the honorarium for your time and participation in the survey.

Do you agree to give us your name and mailing address so we can send you the

honorarium?

- ○ Yes
- ○ No **[GO TO CLOSING 2]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: **[MUST BE 5 NUMERIC-ONLY CHARACTERS]**

[END CLOSING 1]

[BEGIN CLOSING 2 – KEEP ON ONE PAGE]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

- ○ Yes
- ○ No **[GO TO CLOSING 3]**

Telephone: **[MUST BE 10-DIGIT NUMERIC-ONLY CHARACTERS]**
[END CLOSING 2]

[BEGIN CLOSING 3]

That ends the survey. Thank you again for your help.

[END CLOSING 3]

[END SURVEY CONTENT]

Appendix B SAMPLE Pharmacist Recruitment Materials

INVITATION LETTER

[
CURR_DATE]

[PHARMACY_NAME]

[PHARMACY _STREET_ADDR]
[PHARMACY_CITY], [PHARMACY _STATE] [PHARMACY _ZIP]

[PHARMACY_FAX_NUMBER]

Dear [PHARMACIST– IN CHARGE]

Your Pharmacypharmacy was selected to receive this letter, because of enrollment in the TIRF Transmucosal Immediate Release Fentanyl (TIRF) Risk Evaluation and Mitigation Strategy (REMS) Access Program.program and dispensing of TIRF medicines in the last 6 months. We are contacting you to inform you about a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicinesTIRF Medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess pharmacists' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.

The FDA has requested that non-supervisory pharmacists participate in this survey; therefore, as part of this FDA request, we are asking for your help in distributing these surveys to non-supervisory pharmacists in your pharmacy. The survey will be open through [ENTER DATE] but could be extended if the desired number of completed surveys has not been collected. The survey should take about 20 minutes to complete.

You will find enclosed, [ENTER NUMBER] invitation letters to provide to [ENTER NUMBER] non-supervisory pharmacists.

The manufacturers of TIRF medicines include Actavis Laboratories FL, Inc.;, BioDelivery Sciences International, Inc. (BDSI);, Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.);), Depomed, Inc.; Galena Biopharma, Inc.;, Insys Therapeutics, Inc.;, Mallinckrodt Pharmaceuticals;, Mylan Inc., Par Pharmaceuticals, Inc.;, and Par PharmaceuticalSentynl Therapeutics, Inc. (collectively referred to as the "TIRF REMS Industry Group"). These manufacturers are looking for 300 non-supervisory pharmacists to complete the survey. Eligible pharmacists who complete the survey will be sent a $50 honorarium to thank them for their time. The survey will take 15-20 minutes.

Your answers will be kept strictly confidential and will be combined with the answers from other pharmacists who take this survey. Your name will not be used in the report of this survey and your contact information, if provided, will only be used to send you a $50 honorarium for your time to complete the survey.

~~You are under no obligation to participate in this survey.~~ ~~Only one pharmacist from each enrolled~~Your answers will be kept strictly confidential and will be combined with the answers from other pharmacists who take this survey. Your name will not be used in the report of this survey and your contact information, if provided, will only be used to send you a $50 honorarium for your time to complete the survey.

Your pharmacy ~~can~~is under no obligation to participate in this survey. If you ~~are~~or a staff pharmacist at your pharmacy is interested in participating and to find out if you are eligible:

- Go online* to www.TIRFREMSsurvey.com any time or
- Call 1-877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**. ~~***We recommend***~~

****Please note** that you **should** take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.*

Neither taking the survey nor your answers to the questions will affect your ability to dispense any of the TIRF medicines identified above.

Sincerely,

The TIRF REMS Survey Team

1-877-379-3297

www.TIRFREMSsurvey.com

Dear Pharmacist,

The Food and Drug Administration (FDA) has requested that the sponsors of TIRF medicines conduct a survey to assess pharmacists' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands. The FDA has requested that non-supervisory pharmacists, like yourself, participate in this survey.

The manufacturers of TIRF medicines include Actavis Laboratories FL Inc., BioDelivery Sciences International, Inc., Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.), Depomed, Inc., Insys Therapeutics, Inc., Mallinckrodt Pharmaceuticals, Mylan Inc., Par Pharmaceuticals, Inc., and Sentynl Therapeutics, Inc. (collectively referred to as the "TIRF REMS Industry Group"). These manufacturers are looking for 300 non-supervisory pharmacists to complete the survey. Eligible pharmacists who complete the survey will be sent a $50 honorarium to thank them for their time. The survey will take 20 minutes to complete.

Your answers will be kept strictly confidential and will be combined with the answers from other pharmacists who take this survey. Your name will not be used in the report of this survey and your contact information, if provided, will only be used to send you a $50 honorarium for your time to complete the survey.

You are under no obligation to participate in this survey. If you are interested in participating and to find out if you are eligible:

- Go online* to www.TIRFREMSsurvey.com any time or
- Call 1-877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.

Please note that you should take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

Neither taking the survey nor your answers to the questions will affect your ability to dispense any of the TIRF medicines identified above.

Sincerely,

The TIRF REMS Survey Team

1-877-379-3297

www.TIRFREMSsurvey.com

THANK YOU LETTER

[CURR_DATE]

[PHARMACIST_FIRST_NAME] [[PHARMACIST_LAST NAME], [TITLE]
[PHARMACIST_STREET_ADDR]
[PHARMACIST_CITY], [PHARMACIST_STATE] [PHARMACIST_ZIP]

Dear [PHARMACIST_FULL_NAME],

On behalf of TIRF REMS Industry Group, we want to thank you for taking part in the TIRF REMS Survey. To express our appreciation for your valuable time, enclosed is a gift card for $50.

Card Activation Instructions:

To prevent loss, the enclosed card is not activated. Prior to using your card, please call the TIRF REMS Coordinating Center at 1-877-379-3297 between 8:00 a.m. and 8:00 p.m. Eastern Time, Monday through Friday, to activate your card. Please have your card available when you make the call. Also, please read the enclosed Terms and Conditions document before using your gift card as well as the privacy policy that can be found at: http://www.ctpayer.com/downloads/privacy_policy.pdf

Please note the enclosed card needs to be activated on or before: **xx xxx xxxx**

Additionally, for your information and to reinforce important safety messages about TIRF Medications, we have enclosed the following two documents:

1. A copy of the correct answers to the important survey questions about the TIRF REMS key risk message questions.
2. A copy of the Important Safety Information.

Additional information regarding TIRF REMS Access program can be found at www.TIRFREMSaccess.com.

Thank you for your time and consideration regarding this important safety information.

Sincerely,
The TIRF REMS Survey Team
1-877-379-3297
www.TIRFREMSsurvey.com

Enclosures: Gift Card and Terms and Conditions
Correct Answers to Important Survey Questions
TIRF Important Safety Information

Appendix C Correct Answer Document

Correct Responses to Select PHARMACIST Survey Questions about Important Safety Messages for Transmucosal Immediate Release Fentanyl (TIRF) medicines (TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands)

Q: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

STATEMENT	DESIRED RESPONSE
Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	**TRUE**
Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**

Q: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

STATEMENT	DESIRED RESPONSE
TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
TIRF medicines may be used in opioid non-tolerant patients.	**FALSE**
Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**
According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	**FALSE**
According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	**FALSE**
A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	**TRUE**

Q: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

STATEMENT	DESIRED RESPONSE
8 mg oral hydromorphone/day	**TRUE**
60 mg oral morphine/day	**TRUE**
30 mg oral oxycodone/day	**TRUE**
25 mcg transdermal fentanyl/hour	**TRUE**
25 mg oral oxymorphone/day	**TRUE**
An equianalgesic dose of another oral opioid	**TRUE**

Q: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.

STATEMENT	DESIRED RESPONSE
Acute or postoperative pain	**NO**
Headache or migraine pain	**NO**
Dental pain	**NO**
Breakthrough pain from cancer	**YES**
Chronic non-cancer pain	**NO**

Q: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

STATEMENT	DESIRED RESPONSE
It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**
TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**
Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**

Q: Please answer True, False, or I don't know for each statement about TIRF medicines.

STATEMENT	DESIRED RESPONSE
TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	**FALSE**
TIRF medicines should only be taken by patients who are opioid tolerant.	**TRUE**

Q: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

STATEMENT	DESIRED RESPONSE
A personal history of psychiatric illness	**YES**
A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**

Q: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.

STATEMENT	DESIRED RESPONSE
Misuse	**TRUE**
Abuse	**TRUE**
Addiction	**TRUE**

Overdose	**TRUE**
Hypothyroidism	**FALSE**
Infection	**FALSE**

If you have questions or are unclear about any of these responses, please refer to the Full Prescribing Information, the Important Safety Information, and the Medication Guide for TIRF medicines.

Appendix B Survey Tables

Table 1.1: Survey Administration Statistics	
Parameter, n (%)	
Number of invitations distributed	11598
Number of invitations returned as undeliverable	139
Number of reminder letters distributed	3772
All Respondents[1]	561 (4.9)
Eligible Respondents[2]	333 (59.4)
Completed survey[3]	318 (95.5)
Did not complete the survey[3]	15 (4.5)
Respondents not eligible[2], [4]	228 (40.6)

Source: Appendix B: Survey Tables, Table 1.1
[1] Number of unique respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[2] Percentage is based on the number of all respondents.
[3] Percentage is based on the number of eligible respondents.
[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

Table 1.2: Survey Participant Eligibility Results - All Respondents	
Question	**Pharmacists (N=561) n (%)**
Question 1: Do you agree to participate in this survey?	
Yes	435 (77.5)
No[1]	1 (0.2)
Discontinued	125 (22.3)
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.	
Yes[1]	17 (3.0)
No	380 (67.7)
I don't know[1]	37 (6.6)
Question not asked [2]	1 (0.2)
Discontinued	126 (22.5)
Question 3: Do you work in a pharmacy that is enrolled in the TIRF REMS Access program?	
Yes	338 (60.2)
No[1]	10 (1.8)
I don't know[1]	32 (5.7)
Question not asked [2]	55 (9.8)
Discontinued	126 (22.5)
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[3]	
Actavis Laboratories FL, Inc.[1]	1 (0.2)
Anesta LLC[1]	0
BioDelivery Sciences International, Inc. (BDSI)[1]	0
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	1 (0.2)
Depomed, Inc.[1]	0
Galena Biopharma, Inc.[1]	0
Insys Therapeutics, Inc.[1]	0
Mallinckrodt Pharmaceuticals[1]	0
McKesson Specialty Care Solutions[1]	0
Mylan Inc.[1]	0

Table 1.2: Survey Participant Eligibility Results - All Respondents	
Question	**Pharmacists (N=561) n (%)**
Par Pharmaceuticals, Inc.[1]	0
RelayHealth[1]	0
Sentynl Therapeutics, Inc.[1]	0
Teva Pharmaceuticals, Ltd.[1]	0
United BioSource Corporation[1]	0
FDA[1]	2 (0.4)
None of these apply[4]	333 (59.4)
I don't know[1]	2 (0.4)
Prefer not to answer[1]	0
Question not asked [2]	97 (17.3)
Discontinued	126 (22.5)

Source: Appendix B: Survey Tables, Table 1.2
Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.
[1] Ineligible to participate in the survey.
[2] Question not asked due to termination response from a previous question.
[3] More than one response can be selected, so percentages may not sum to 100%.
[4] Ineligible if selected in addition to another response.

Table 1.3: Time to Complete Survey - Completed Surveys			
	Telephone	**Internet**	**Total[1]**
Summary Statistic (minutes)			
N	4	314	318
Mean (SD)	21.63 (4.391)	15.67 (8.557)	15.74 (8.540)
Minimum	18.1	3.6	3.6
Median	20.23	13.48	13.63
Maximum	28.0	55.8	55.8
Category, n			
0 to <5 Minutes	0	6	6
5 to <10 Minutes	0	85	85
10 to <15 Minutes	0	95	95
15 to <20 Minutes	2	49	51
20 to <25 Minutes	1	36	37
25 to <30 Minutes	1	16	17
30 Minutes or more	0	27	27

Source: Appendix B: Survey Tables, Table 1.3
[1] Total number of eligible respondents completing the survey.

Table 2: Description of Eligible Pharmacists - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
Question 27: Are you the Pharmacist in Charge for the TIRF REMS Access program where you work?	
Yes	77 (24.2)
No	238 (74.8)
I don't know	3 (0.9)
Question 28: On average, how many times per month have you dispensed TIRF medicine within the last 6 months?	
None	60 (18.9)
1 - 2 times per month	149 (46.9)
3 - 5 times per month	38 (11.9)
More than 5 times per month	47 (14.8)
I don't remember	24 (7.5)
Question 29: Please select the TIRF medicine(s) that you have dispensed within the last 6 months. Please select all that apply.[1], [2]	
Abstral®	26 (10.1)
Actiq® or generic Actiq®	193 (74.8)
Fentora®	105 (40.7)
Lazanda®	19 (7.4)
Subsys®	95 (36.8)
N/A (Answered "None" to Question 25)	60
Question 30: What is your gender?	
Male	155 (48.7)
Female	150 (47.2)
Prefer not to answer	13 (4.1)
Question 31: In total, how many years have you been a practicing pharmacist?	
Less than 3 years	37 (11.6)
3 - 5 years	51 (16.0)
6 - 10 years	56 (17.6)
11 - 15 years	35 (11.0)
More than 15 years	132 (41.5)

Table 2: Description of Eligible Pharmacists - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
Prefer not to answer	7 (2.2)
Geographic Distribution (based on Question 32 - In which state do you practice?)[3]	
Northeast	83 (26.1)
Midwest	58 (18.2)
South	101 (31.8)
West	75 (23.6)
Other	0
Prefer not to answer	1 (0.3)

Source: Appendix B: Survey Tables, Table 2
[1] Percentages are calculated based on the number of respondents to whom the question was presented.
[2] More than one response can be selected, so percentages may not sum to 100%.
[3] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.

Table 2b: Comparison of Pharmacies Represented by the Survey Respondents to the General Population of Pharmacies that Have Dispensed TIRF Medicines in the Past Six Months (REMS database)

Parameter	Pharmacies Represented by Pharmacists Completing Survey (REMS Switch Provider Data) (N=240) n (%)	Pharmacies Dispensing TIRF Medicines in the Past Six Months (REMS Switch Provider Data) (N=3857) n (%)	p-value
Geographic region of pharmacy			
Northeast	59 (24.6)	783 (20.3)	
Midwest	44 (18.3)	660 (17.1)	
South	78 (32.5)	1396 (36.2)	
West	59 (24.6)	1017 (26.4)	
Other	0	1 (0.0)	0.4924
Prefer not to answer	0	*N/A*	
Type of pharmacy			
Inpatient Pharmacy[1]	45 (18.8)	763 (19.8)	
Independent Outpatient Pharmacy	165 (68.8)	1311 (34.0)	
Chain Outpatient Pharmacy	29 (12.1)	1769 (45.9)	
Closed System Pharmacy	1 (0.4)	14 (0.4)	<.0001
Number of orders by type of pharmacy[2]	**(N=8045)**	**(N=38702)**	
Inpatient Pharmacy	*N/A*	*N/A*	
Independent Outpatient Pharmacy	4830 (60.0)	23417 (60.5)	
Chain Outpatient Pharmacy	3215 (40.0)	15139 (39.1)	

Table 2b: Comparison of Pharmacies Represented by the Survey Respondents to the General Population of Pharmacies that Have Dispensed TIRF Medicines in the Past Six Months (REMS database)

Parameter	Pharmacies Represented by Pharmacists Completing Survey (REMS Switch Provider Data) (N=240) n (%)	Pharmacies Dispensing TIRF Medicines in the Past Six Months (REMS Switch Provider Data) (N=3857) n (%)	p-value
Closed System Pharmacy	*N/A*	146 (0.4)	<.0001

Note: Switch provider data was provided by McKesson on September 6th, 2016. Each pharmacy is counted only once, regardless of how many pharmacists from that pharmacy complete the survey. Percentages for the number of orders by type of pharmacy were calculated based on the total number of dispensed TIRF medicines from the pharmacies represented by pharmacists completing the survey and from pharmacies dispensing TIRF medicines in the past 6 months, respectively. P-values are calculated by a chi-square test excluding prefer not to answer.

N/A = Not available.

[1] The REMS database does not collect dispensing information for inpatient pharmacies. Therefore, the number of inpatient pharmacies is based on the number of all active pharmacies in the REMS.

[2] Number of orders are not available for inpatient pharmacies. Comparison is based on the number of orders from independent outpatient pharmacies, chain outpatient pharmacies and closed system pharmacies.

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	
True[1]	304 (95.6)
False	10 (3.1)
I don't know	4 (1.3)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before	
True	30 (9.4)
False[1]	278 (87.4)
I don't know	10 (3.1)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	
True	46 (14.5)
False[1]	261 (82.1)
I don't know	11 (3.5)
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	
True	82 (25.8)
False[1]	197 (61.9)
I don't know	39 (12.3)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	
True	34 (10.7)
False[1]	256 (80.5)
I don't know	28 (8.8)
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	
True[1]	131 (41.2)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
False	151 (47.5)
I don't know	36 (11.3)
6d: Use of a TIRF medicine with a CYP3A4 inhibitor may require dosage adjustment and monitoring of the patient for opioid toxicity as potentially fatal respiratory depression could occur.	
True[1]	293 (92.1)
False	3 (0.9)
I don't know	22 (6.9)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	
True[1]	281 (88.4)
False	23 (7.2)
I don't know	14 (4.4)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	
True[1]	303 (95.3)
False	3 (0.9)
I don't know	12 (3.8)
7c: TIRF medicines may be used in opioid non-tolerant patients.	
True	28 (8.8)
False[1]	278 (87.4)
I don't know	12 (3.8)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	
True[1]	267 (84.0)
False	34 (10.7)
I don't know	17 (5.3)
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	
True[1]	312 (98.1)
False	4 (1.3)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
I don't know	2 (0.6)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a: A personal history of psychiatric illness	
Yes[1]	247 (77.7)
No	42 (13.2)
I don't know	29 (9.1)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	
Yes[1]	314 (98.7)
No	1 (0.3)
I don't know	3 (0.9)
8c: A family history of asthma	
Yes	28 (8.8)
No[1]	271 (85.2)
I don't know	19 (6.0)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a: Acute or postoperative pain	
Yes	35 (11.0)
No[1]	273 (85.8)
I don't know	10 (3.1)
9b: Headache or migraine pain	
Yes	7 (2.2)
No[1]	300 (94.3)
I don't know	11 (3.5)
9c: Dental pain	
Yes	2 (0.6)
No[1]	306 (96.2)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
I don't know	10 (3.1)
9d: Breakthrough pain from cancer	
Yes[1]	292 (91.8)
No	22 (6.9)
I don't know	4 (1.3)
9e: Chronic non-cancer pain	
Yes	138 (43.4)
No[1]	162 (50.9)
I don't know	18 (5.7)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.	
True[1]	298 (93.7)
False	12 (3.8)
I don't know	8 (2.5)
10b: TIRF medicines are interchangeable with each other regardless of route of administration.	
True	6 (1.9)
False[1]	305 (95.9)
I don't know	7 (2.2)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	
True[1]	296 (93.1)
False	10 (3.1)
I don't know	12 (3.8)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	
True[1]	283 (89.0)
False	16 (5.0)
I don't know	19 (6.0)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:	
11a: 8 mg oral hydromorphone/day	
True[1]	237 (74.5)
False	38 (11.9)
I don't know	43 (13.5)
11b: 60 mg oral morphine/day	
True[1]	280 (88.1)
False	13 (4.1)
I don't know	25 (7.9)
11c: 30 mg oral oxycodone/day	
True[1]	247 (77.7)
False	37 (11.6)
I don't know	34 (10.7)
11d: 25 mcg transdermal fentanyl/hour	
True[1]	253 (79.6)
False	39 (12.3)
I don't know	26 (8.2)
11e: 25 mg oral oxymorphone/day	
True[1]	229 (72.0)
False	30 (9.4)
I don't know	59 (18.6)
11f: An equianalgesic dose of another oral opioid	
True[1]	207 (65.1)
False	51 (16.0)
I don't know	60 (18.9)
Question 12: Please answer True, False, or I don't know for the following statement about TIRF medicines:	
TIRF medicines should only be taken by patients who are opioid tolerant.	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
True[1]	304 (95.6)
False	12 (3.8)
I don't know	2 (0.6)
Question 13: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.	
13a: Misuse	
True[1]	314 (98.7)
False	3 (0.9)
I don't know	1 (0.3)
13b: Abuse	
True[1]	315 (99.1)
False	2 (0.6)
I don't know	1 (0.3)
13c: Addiction	
True[1]	314 (98.7)
False	3 (0.9)
I don't know	1 (0.3)
13d: Overdose	
True[1]	316 (99.4)
False	1 (0.3)
I don't know	1 (0.3)
13e: Hypothyroidism	
True	10 (3.1)
False[1]	267 (84.0)
I don't know	41 (12.9)
13f: Infection	
True	15 (4.7)
False[1]	284 (89.3)
I don't know	19 (6.0)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
Question 16: Please answer True, False, or I don't know for each statement about TIRF medicines.	
16a: TIRF medicines may be sold, loaned, or transferred to another pharmacy.	
True	16 (5.0)
False[1]	288 (90.6)
I don't know	14 (4.4)
16b: All pharmacy staff that dispenses TIRF medicines must be educated on the requirements of the TIRF REMS Access program.	
True[1]	286 (89.9)
False	18 (5.7)
I don't know	14 (4.4)
16c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	
True	10 (3.1)
False[1]	304 (95.6)
I don't know	4 (1.3)

Source: Appendix B: Survey Tables, Table 3
[1] Correct response.

Table 4: Responses to Questions about TIRF Medicine Educational Materials - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
Question 21: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you dispense?	
Yes	305 (95.9)
No	3 (0.9)
I don't know	10 (3.1)
Question 22: Did you read the Full Prescribing Information for the TIRF medicine(s) that you dispense?[1]	
Yes	246 (80.7)
No	51 (16.7)
I don't know	8 (2.6)
N/A (Answered "No" or "I don't know" to Question 21)	13
Question 23: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you dispense?	
Yes	309 (97.2)
No	0
I don't know	9 (2.8)
Question 24: Did you read the Medication Guide for the TIRF medicine(s) that you dispense?[1]	
Yes	272 (88.0)
No	34 (11.0)
I don't know	3 (1.0)
N/A (Answered "No" or "I don't know" to Question 23)	9
Question 25: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?[2]	
Yes	6 (1.9)
No	293 (92.1)
I don't know	19 (6.0)

Source: Appendix B: Survey Tables, Table 4
[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[2] Verbatim text for questions about the Full Prescribing Information or Medication Guide is presented in Listing 1.

Table 5: Responses to Questions about the Activities when Dispensing TIRF Medicines - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
Question 14: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.	
14a: Ask patients (or their caregivers) about the presence of children in the home	
Always	174 (54.7)
Only with the first prescription	85 (26.7)
Sometimes	33 (10.4)
Never	19 (6.0)
I don't know	7 (2.2)
14b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	
Always	223 (70.1)
Only with the first prescription	62 (19.5)
Sometimes	17 (5.3)
Never	13 (4.1)
I don't know	3 (0.9)
14c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	
Always	207 (65.1)
Only with the first prescription	69 (21.7)
Sometimes	24 (7.5)
Never	15 (4.7)
I don't know	3 (0.9)
14d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	
Always	214 (67.3)
Only with the first prescription	67 (21.1)
Sometimes	22 (6.9)
Never	11 (3.5)
I don't know	4 (1.3)
14e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	

Table 5: Responses to Questions about the Activities when Dispensing TIRF Medicines - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
Always	196 (61.6)
Only with the first prescription	86 (27.0)
Sometimes	21 (6.6)
Never	11 (3.5)
I don't know	4 (1.3)
14f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine	
Always	277 (87.1)
Only with the first prescription	24 (7.5)
Sometimes	6 (1.9)
Never	8 (2.5)
I don't know	3 (0.9)
Question 15: How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.	
15a: Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed.	
Always	171 (53.8)
Only with the first prescription	117 (36.8)
Sometimes	21 (6.6)
Never	8 (2.5)
I don't know	1 (0.3)
15b: Instruct the patient on how to use the TIRF medicine that was most recently prescribed.	
Always	184 (57.9)
Only with the first prescription	111 (34.9)
Sometimes	14 (4.4)
Never	8 (2.5)
I don't know	1 (0.3)
15c: Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed.	
Always	154 (48.4)
Only with the first prescription	125 (39.3)

Table 5: Responses to Questions about the Activities when Dispensing TIRF Medicines - Completed Surveys	
Question	**Pharmacists (N=318) n (%)**
Sometimes	24 (7.5)
Never	13 (4.1)
I don't know	2 (0.6)
Question 17: Does the inpatient pharmacy where you work have an established system, order sets, protocols and/or other measures to help ensure appropriate patient selection and compliance with the requirements of the TIRF REMS Access program? (Inpatient Pharmacists, only)[1]	
Yes	40 (61.5)
No	11 (16.9)
I don't know	14 (21.5)
Question 18: Does the outpatient or retail pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the pharmacy management system? (Outpatient Pharmacists, only)[1]	
Yes	206 (81.7)
No	11 (4.4)
I don't know	35 (13.9)
Question 19: Does the pharmacy where you work process all TIRF medicine prescriptions, regardless of method of payment, through the TIRF REMS Access Call Center? (CSP Outpatient Pharmacists, only)[1]	
Yes	1 (100.0)
No	0
I don't know	0
Question 20: Please answer True, False, or I don't know for the following statement about TIRF medicines. (Inpatient Pharmacists, only)[1]	
It is OK to dispense TIRF medicines from the inpatient pharmacy inventory to an outpatient for use at home.	
True	3 (4.6)
False[2]	54 (83.1)
I don't know	8 (12.3)

Source: Appendix B: Survey Tables, Table 5
[1] Percentages are calculated based on the sample presented with this question.
[2] Correct response.

Table 6.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys	
Question	**Pharmacists (N=318) n (%) [95% CI][1]**
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	
True[2]	304 (95.6) [92.7 - 97.6]
False	10 (3.1)
I don't know	4 (1.3)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before	
True	30 (9.4)
False[2]	278 (87.4) [83.3 - 90.9]
I don't know	10 (3.1)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	
True	46 (14.5)
False[2]	261 (82.1) [77.4 - 86.1]
I don't know	11 (3.5)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	
True[2]	281 (88.4) [84.3 - 91.7]
False	23 (7.2)
I don't know	14 (4.4)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	
True[2]	303 (95.3) [92.3 - 97.3]
False	3 (0.9)
I don't know	12 (3.8)
7c: TIRF medicines may be used in opioid non-tolerant patients.	
True	28 (8.8)
False[2]	278 (87.4) [83.3 - 90.9]

Table 6.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys	
Question	**Pharmacists (N=318) n (%) [95% CI][1]**
I don't know	12 (3.8)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	
True[2]	267 (84.0) [79.5 - 87.8]
False	34 (10.7)
I don't know	17 (5.3)
Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:	
11a: 8 mg oral hydromorphone/day	
True[2]	237 (74.5) [69.4 - 79.2]
False	38 (11.9)
I don't know	43 (13.5)
11b: 60 mg oral morphine/day	
True[2]	280 (88.1) [84.0 - 91.4]
False	13 (4.1)
I don't know	25 (7.9)
11c: 30 mg oral oxycodone/day	
True[2]	247 (77.7) [72.7 - 82.1]
False	37 (11.6)
I don't know	34 (10.7)
11d: 25 mcg transdermal fentanyl/hour	
True[2]	253 (79.6) [74.7 - 83.9]
False	39 (12.3)
I don't know	26 (8.2)
11e: 25 mg oral oxymorphone/day	
True[2]	229 (72.0) [66.7 - 76.9]
False	30 (9.4)
I don't know	59 (18.6)

Table 6.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys	
Question	**Pharmacists (N=318) n (%) [95% CI][1]**
11f: An equianalgesic dose of another oral opioid	
True[2]	207 (65.1) [59.6 - 70.3]
False	51 (16.0)
I don't know	60 (18.9)
Question 12: Please answer True, False, or I don't know for the following statement about TIRF medicines:	
TIRF medicines should only be taken by patients who are opioid tolerant.	
True[2]	304 (95.6) [92.7 - 97.6]
False	12 (3.8)
I don't know	2 (0.6)

Source: Appendix B: Survey Tables, Table 6.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.1: Responses to Questions Linked to Key Risk Message #1 by Reading Full Prescribing Information or Medication Guide - Completed Surveys

Question	Reading Full Prescribing Information or Medication Guide: Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Reading Full Prescribing Information or Medication Guide: Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer		
True[2]	268 (96.1) [93.1 - 98.0]	36 (92.3) [79.1 - 98.4]
False	8 (2.9)	2 (5.1)
I don't know	3 (1.1)	1 (2.6)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
True	29 (10.4)	1 (2.6)
False[2]	242 (86.7) [82.2 - 90.5]	36 (92.3) [79.1 - 98.4]
I don't know	8 (2.9)	2 (5.1)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	40 (14.3)	6 (15.4)
False[2]	232 (83.2) [78.2 - 87.4]	29 (74.4) [57.9 - 87.0]
I don't know	7 (2.5)	4 (10.3)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True[2]	249 (89.2) [85.0 - 92.6]	32 (82.1) [66.5 - 92.5]
False	20 (7.2)	3 (7.7)
I don't know	10 (3.6)	4 (10.3)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[2]	269 (96.4) [93.5 - 98.3]	34 (87.2) [72.6 - 95.7]
False	2 (0.7)	1 (2.6)
I don't know	8 (2.9)	4 (10.3)
7c: TIRF medicines may be used in opioid non-tolerant patients.		

Table 6.1.1: Responses to Questions Linked to Key Risk Message #1 by Reading Full Prescribing Information or Medication Guide - Completed Surveys		
	Reading Full Prescribing Information or Medication Guide	
Question	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
True	24 (8.6)	4 (10.3)
False[2]	247 (88.5) [84.2 - 92.0]	31 (79.5) [63.5 - 90.7]
I don't know	8 (2.9)	4 (10.3)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True[2]	237 (84.9) [80.2 - 88.9]	30 (76.9) [60.7 - 88.9]
False	31 (11.1)	3 (7.7)
I don't know	11 (3.9)	6 (15.4)
Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
11a: 8 mg oral hydromorphone/day		
True[2]	212 (76.0) [70.5 - 80.9]	25 (64.1) [47.2 - 78.8]
False	35 (12.5)	3 (7.7)
I don't know	32 (11.5)	11 (28.2)
11b: 60 mg oral morphine/day		
True[2]	252 (90.3) [86.2 - 93.5]	28 (71.8) [55.1 - 85.0]
False	13 (4.7)	0
I don't know	14 (5.0)	11 (28.2)
11c: 30 mg oral oxycodone/day		
True[2]	223 (79.9) [74.7 - 84.5]	24 (61.5) [44.6 - 76.6]
False	33 (11.8)	4 (10.3)
I don't know	23 (8.2)	11 (28.2)
11d: 25 mcg transdermal fentanyl/hour		
True[2]	230 (82.4) [77.5 - 86.7]	23 (59.0) [42.1 - 74.4]
False	34 (12.2)	5 (12.8)
I don't know	15 (5.4)	11 (28.2)

Table 6.1.1: Responses to Questions Linked to Key Risk Message #1 by Reading Full Prescribing Information or Medication Guide - Completed Surveys		
	Reading Full Prescribing Information or Medication Guide	
Question	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
11e: 25 mg oral oxymorphone/day		
True[2]	208 (74.6) [69.0 - 79.6]	21 (53.8) [37.2 - 69.9]
False	25 (9.0)	5 (12.8)
I don't know	46 (16.5)	13 (33.3)
11f: An equianalgesic dose of another oral opioid		
True[2]	189 (67.7) [61.9 - 73.2]	18 (46.2) [30.1 - 62.8]
False	43 (15.4)	8 (20.5)
I don't know	47 (16.8)	13 (33.3)
Question 12: Please answer True, False, or I don't know for the following statement about TIRF medicines:		
TIRF medicines should only be taken by patients who are opioid tolerant.		
True[2]	268 (96.1) [93.1 - 98.0]	36 (92.3) [79.1 - 98.4]
False	10 (3.6)	2 (5.1)
I don't know	1 (0.4)	1 (2.6)

Source: Appendix B: Survey Tables, Table 6.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.2: Responses to Questions Linked to Key Risk Message #1 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=314) n (%) [95% CI][1]	Telephone (N=4) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer		
True[2]	301 (95.9) [93.0 - 97.8]	3 (75.0) [19.4 - 99.4]
False	9 (2.9)	1 (25.0)
I don't know	4 (1.3)	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
True	28 (8.9)	2 (50.0)
False[2]	276 (87.9) [83.8 - 91.3]	2 (50.0) [6.8 - 93.2]
I don't know	10 (3.2)	0
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	45 (14.3)	1 (25.0)
False[2]	258 (82.2) [77.5 - 86.2]	3 (75.0) [19.4 - 99.4]
I don't know	11 (3.5)	0
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True[2]	277 (88.2) [84.1 - 91.6]	4 (100.0) [39.8 - 100.0]
False	23 (7.3)	0
I don't know	14 (4.5)	0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[2]	299 (95.2) [92.2 - 97.3]	4 (100.0) [39.8 - 100.0]
False	3 (1.0)	0
I don't know	12 (3.8)	0
7c: TIRF medicines may be used in opioid non-tolerant patients.		
True	27 (8.6)	1 (25.0)

Table 6.1.2: Responses to Questions Linked to Key Risk Message #1 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=314) n (%) [95% CI][1]	Telephone (N=4) n (%) [95% CI][1]
False[2]	275 (87.6) [83.4 - 91.0]	3 (75.0) [19.4 - 99.4]
I don't know	12 (3.8)	0
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True[2]	263 (83.8) [79.2 - 87.7]	4 (100.0) [39.8 - 100.0]
False	34 (10.8)	0
I don't know	17 (5.4)	0
Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
11a: 8 mg oral hydromorphone/day		
True[2]	234 (74.5) [69.3 - 79.2]	3 (75.0) [19.4 - 99.4]
False	38 (12.1)	0
I don't know	42 (13.4)	1 (25.0)
11b: 60 mg oral morphine/day		
True[2]	276 (87.9) [83.8 - 91.3]	4 (100.0) [39.8 - 100.0]
False	13 (4.1)	0
I don't know	25 (8.0)	0
11c: 30 mg oral oxycodone/day		
True[2]	244 (77.7) [72.7 - 82.2]	3 (75.0) [19.4 - 99.4]
False	36 (11.5)	1 (25.0)
I don't know	34 (10.8)	0
11d: 25 mcg transdermal fentanyl/hour		
True[2]	250 (79.6) [74.7 - 83.9]	3 (75.0) [19.4 - 99.4]
False	39 (12.4)	0
I don't know	25 (8.0)	1 (25.0)
11e: 25 mg oral oxymorphone/day		
True[2]	225 (71.7) [66.3 - 76.6]	4 (100.0) [39.8 - 100.0]

Table 6.1.2: Responses to Questions Linked to Key Risk Message #1 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=314) n (%) [95% CI][1]	Telephone (N=4) n (%) [95% CI][1]
False	30 (9.6)	0
I don't know	59 (18.8)	0
11f: An equianalgesic dose of another oral opioid		
True[2]	205 (65.3) [59.7 - 70.5]	2 (50.0) [6.8 - 93.2]
False	51 (16.2)	0
I don't know	58 (18.5)	2 (50.0)
Question 12: Please answer True, False, or I don't know for the following statement about TIRF medicines:		
TIRF medicines should only be taken by patients who are opioid tolerant.		
True[2]	301 (95.9) [93.0 - 97.8]	3 (75.0) [19.4 - 99.4]
False	11 (3.5)	1 (25.0)
I don't know	2 (0.6)	0

Source: Appendix B: Survey Tables, Table 6.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.3: Responses to Questions Linked to Key Risk Message #1 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer				
True[2]	37 (100.0) [90.5 - 100.0]	48 (94.1) [83.8 - 98.8]	85 (93.4) [86.2 - 97.5]	127 (96.2) [91.4 - 98.8]
False	0	2 (3.9)	4 (4.4)	4 (3.0)
I don't know	0	1 (2.0)	2 (2.2)	1 (0.8)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
True	4 (10.8)	3 (5.9)	6 (6.6)	17 (12.9)
False[2]	31 (83.8) [68.0 - 93.8]	47 (92.2) [81.1 - 97.8]	83 (91.2) [83.4 - 96.1]	111 (84.1) [76.7 - 89.9]
I don't know	2 (5.4)	1 (2.0)	2 (2.2)	4 (3.0)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
True	4 (10.8)	6 (11.8)	14 (15.4)	21 (15.9)
False[2]	31 (83.8) [68.0 - 93.8]	44 (86.3) [73.7 - 94.3]	73 (80.2) [70.6 - 87.8]	108 (81.8) [74.2 - 88.0]
I don't know	2 (5.4)	1 (2.0)	4 (4.4)	3 (2.3)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
True[2]	36 (97.3) [85.8 - 99.9]	51 (100.0) [93.0 - 100.0]	79 (86.8) [78.1 - 93.0]	109 (82.6) [75.0 - 88.6]
False	0	0	8 (8.8)	15 (11.4)

Table 6.1.3: Responses to Questions Linked to Key Risk Message #1 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
I don't know	1 (2.7)	0	4 (4.4)	8 (6.1)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True[2]	37 (100.0) [90.5 - 100.0]	51 (100.0) [93.0 - 100.0]	88 (96.7) [90.7 - 99.3]	121 (91.7) [85.6 - 95.8]
False	0	0	0	3 (2.3)
I don't know	0	0	3 (3.3)	8 (6.1)
7c: TIRF medicines may be used in opioid non-tolerant patients.				
True	3 (8.1)	0	6 (6.6)	19 (14.4)
False[2]	33 (89.2) [74.6 - 97.0]	51 (100.0) [93.0 - 100.0]	81 (89.0) [80.7 - 94.6]	107 (81.1) [73.3 - 87.4]
I don't know	1 (2.7)	0	4 (4.4)	6 (4.5)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True[2]	29 (78.4) [61.8 - 90.2]	43 (84.3) [71.4 - 93.0]	82 (90.1) [82.1 - 95.4]	107 (81.1) [73.3 - 87.4]
False	5 (13.5)	5 (9.8)	6 (6.6)	18 (13.6)
I don't know	3 (8.1)	3 (5.9)	3 (3.3)	7 (5.3)
Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:				
11a: 8 mg oral hydromorphone/day				
True[2]	32 (86.5) [71.2 - 95.5]	37 (72.5) [58.3 - 84.1]	66 (72.5) [62.2 - 81.4]	96 (72.7) [64.3 - 80.1]

Table 6.1.3: Responses to Questions Linked to Key Risk Message #1 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
False	2 (5.4)	7 (13.7)	9 (9.9)	19 (14.4)
I don't know	3 (8.1)	7 (13.7)	16 (17.6)	17 (12.9)
11b: 60 mg oral morphine/day				
True[2]	35 (94.6) [81.8 - 99.3]	41 (80.4) [66.9 - 90.2]	79 (86.8) [78.1 - 93.0]	119 (90.2) [83.7 - 94.7]
False	0	5 (9.8)	3 (3.3)	4 (3.0)
I don't know	2 (5.4)	5 (9.8)	9 (9.9)	9 (6.8)
11c: 30 mg oral oxycodone/day				
True[2]	30 (81.1) [64.8 - 92.0]	36 (70.6) [56.2 - 82.5]	73 (80.2) [70.6 - 87.8]	102 (77.3) [69.2 - 84.1]
False	5 (13.5)	7 (13.7)	6 (6.6)	19 (14.4)
I don't know	2 (5.4)	8 (15.7)	12 (13.2)	11 (8.3)
11d: 25 mcg transdermal fentanyl/hour				
True[2]	31 (83.8) [68.0 - 93.8]	42 (82.4) [69.1 - 91.6]	77 (84.6) [75.5 - 91.3]	96 (72.7) [64.3 - 80.1]
False	3 (8.1)	5 (9.8)	6 (6.6)	25 (18.9)
I don't know	3 (8.1)	4 (7.8)	8 (8.8)	11 (8.3)
11e: 25 mg oral oxymorphone/day				
True[2]	30 (81.1) [64.8 - 92.0]	35 (68.6) [54.1 - 80.9]	63 (69.2) [58.7 - 78.5]	97 (73.5) [65.1 - 80.8]
False	4 (10.8)	4 (7.8)	7 (7.7)	14 (10.6)
I don't know	3 (8.1)	12 (23.5)	21 (23.1)	21 (15.9)

Table 6.1.3: Responses to Questions Linked to Key Risk Message #1 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
11f: An equianalgesic dose of another oral opioid				
True[2]	28 (75.7) [58.8 - 88.2]	35 (68.6) [54.1 - 80.9]	57 (62.6) [51.9 - 72.6]	83 (62.9) [54.0 - 71.1]
False	3 (8.1)	9 (17.6)	14 (15.4)	24 (18.2)
I don't know	6 (16.2)	7 (13.7)	20 (22.0)	25 (18.9)
Question 12: Please answer True, False, or I don't know for the following statement about TIRF medicines:				
TIRF medicines should only be taken by patients who are opioid tolerant.				
True[2]	37 (100.0) [90.5 - 100.0]	50 (98.0) [89.6 - 100.0]	88 (96.7) [90.7 - 99.3]	122 (92.4) [86.5 - 96.3]
False	0	1 (2.0)	2 (2.2)	9 (6.8)
I don't know	0	0	1 (1.1)	1 (0.8)

Source: Appendix B: Survey Tables, Table 6.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.1.4: Responses to Questions Linked to Key Risk Message #1 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:					
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer					
True[2]	55 (91.7) [81.6 - 97.2]	142 (95.3) [90.6 - 98.1]	37 (97.4) [86.2 - 99.9]	46 (97.9) [88.7 - 99.9]	24 (100.0) [85.8 - 100.0]
False	3 (5.0)	5 (3.4)	1 (2.6)	1 (2.1)	0
I don't know	2 (3.3)	2 (1.3)	0	0	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before					
True	5 (8.3)	12 (8.1)	6 (15.8)	5 (10.6)	2 (8.3)
False[2]	53 (88.3) [77.4 - 95.2]	132 (88.6) [82.4 - 93.2]	30 (78.9) [62.7 - 90.4]	42 (89.4) [76.9 - 96.5]	21 (87.5) [67.6 - 97.3]
I don't know	2 (3.3)	5 (3.4)	2 (5.3)	0	1 (4.2)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy					
True	7 (11.7)	22 (14.8)	7 (18.4)	9 (19.1)	1 (4.2)
False[2]	50 (83.3) [71.5 - 91.7]	121 (81.2) [74.0 - 87.1]	30 (78.9) [62.7 - 90.4]	37 (78.7) [64.3 - 89.3]	23 (95.8) [78.9 - 99.9]
I don't know	3 (5.0)	6 (4.0)	1 (2.6)	1 (2.1)	0
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.					
True[2]	56 (93.3) [83.8 - 98.2]	131 (87.9) [81.6 - 92.7]	30 (78.9) [62.7 - 90.4]	42 (89.4) [76.9 - 96.5]	22 (91.7) [73.0 - 99.0]

Table 6.1.4: Responses to Questions Linked to Key Risk Message #1 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
False	3 (5.0)	12 (8.1)	5 (13.2)	3 (6.4)	0
I don't know	1 (1.7)	6 (4.0)	3 (7.9)	2 (4.3)	2 (8.3)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.					
True[2]	57 (95.0) [86.1 - 99.0]	142 (95.3) [90.6 - 98.1]	37 (97.4) [86.2 - 99.9]	45 (95.7) [85.5 - 99.5]	22 (91.7) [73.0 - 99.0]
False	0	3 (2.0)	0	0	0
I don't know	3 (5.0)	4 (2.7)	1 (2.6)	2 (4.3)	2 (8.3)
7c: TIRF medicines may be used in opioid non-tolerant patients.					
True	2 (3.3)	16 (10.7)	4 (10.5)	6 (12.8)	0
False[2]	56 (93.3) [83.8 - 98.2]	128 (85.9) [79.3 - 91.1]	33 (86.8) [71.9 - 95.6]	39 (83.0) [69.2 - 92.4]	22 (91.7) [73.0 - 99.0]
I don't know	2 (3.3)	5 (3.4)	1 (2.6)	2 (4.3)	2 (8.3)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.					
True[2]	48 (80.0) [67.7 - 89.2]	131 (87.9) [81.6 - 92.7]	33 (86.8) [71.9 - 95.6]	38 (80.9) [66.7 - 90.9]	17 (70.8) [48.9 - 87.4]
False	8 (13.3)	12 (8.1)	4 (10.5)	7 (14.9)	3 (12.5)
I don't know	4 (6.7)	6 (4.0)	1 (2.6)	2 (4.3)	4 (16.7)
Question 11: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:					

Table 6.1.4: Responses to Questions Linked to Key Risk Message #1 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
11a: 8 mg oral hydromorphone/day					
True[2]	48 (80.0) [67.7 - 89.2]	110 (73.8) [66.0 - 80.7]	26 (68.4) [51.3 - 82.5]	38 (80.9) [66.7 - 90.9]	15 (62.5) [40.6 - 81.2]
False	3 (5.0)	18 (12.1)	6 (15.8)	7 (14.9)	4 (16.7)
I don't know	9 (15.0)	21 (14.1)	6 (15.8)	2 (4.3)	5 (20.8)
11b: 60 mg oral morphine/day					
True[2]	50 (83.3) [71.5 - 91.7]	129 (86.6) [80.0 - 91.6]	36 (94.7) [82.3 - 99.4]	44 (93.6) [82.5 - 98.7]	21 (87.5) [67.6 - 97.3]
False	2 (3.3)	7 (4.7)	2 (5.3)	2 (4.3)	0
I don't know	8 (13.3)	13 (8.7)	0	1 (2.1)	3 (12.5)
11c: 30 mg oral oxycodone/day					
True[2]	43 (71.7) [58.6 - 82.5]	115 (77.2) [69.6 - 83.7]	34 (89.5) [75.2 - 97.1]	39 (83.0) [69.2 - 92.4]	16 (66.7) [44.7 - 84.4]
False	7 (11.7)	19 (12.8)	2 (5.3)	6 (12.8)	3 (12.5)
I don't know	10 (16.7)	15 (10.1)	2 (5.3)	2 (4.3)	5 (20.8)
11d: 25 mcg transdermal fentanyl/hour					
True[2]	44 (73.3) [60.3 - 83.9]	116 (77.9) [70.3 - 84.2]	33 (86.8) [71.9 - 95.6]	42 (89.4) [76.9 - 96.5]	18 (75.0) [53.3 - 90.2]
False	7 (11.7)	23 (15.4)	3 (7.9)	3 (6.4)	3 (12.5)
I don't know	9 (15.0)	10 (6.7)	2 (5.3)	2 (4.3)	3 (12.5)

Table 6.1.4: Responses to Questions Linked to Key Risk Message #1 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
11e: 25 mg oral oxymorphone/day					
True[2]	38 (63.3) [49.9 - 75.4]	108 (72.5) [64.6 - 79.5]	30 (78.9) [62.7 - 90.4]	38 (80.9) [66.7 - 90.9]	15 (62.5) [40.6 - 81.2]
False	4 (6.7)	17 (11.4)	5 (13.2)	3 (6.4)	1 (4.2)
I don't know	18 (30.0)	24 (16.1)	3 (7.9)	6 (12.8)	8 (33.3)
11f: An equianalgesic dose of another oral opioid					
True[2]	38 (63.3) [49.9 - 75.4]	95 (63.8) [55.5 - 71.5]	25 (65.8) [48.6 - 80.4]	36 (76.6) [62.0 - 87.7]	13 (54.2) [32.8 - 74.4]
False	7 (11.7)	20 (13.4)	7 (18.4)	9 (19.1)	8 (33.3)
I don't know	15 (25.0)	34 (22.8)	6 (15.8)	2 (4.3)	3 (12.5)
Question 12: Please answer True, False, or I don't know for the following statement about TIRF medicines:					
TIRF medicines should only be taken by patients who are opioid tolerant.					
True[2]	57 (95.0) [86.1 - 99.0]	141 (94.6) [89.7 - 97.7]	37 (97.4) [86.2 - 99.9]	46 (97.9) [88.7 - 99.9]	23 (95.8) [78.9 - 99.9]
False	2 (3.3)	7 (4.7)	1 (2.6)	1 (2.1)	1 (4.2)
I don't know	1 (1.7)	1 (0.7)	0	0	0

Source: Appendix B: Survey Tables, Table 6.1.4
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 6.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys	
Correct Responses	**Pharmacists (N=318) n (%)**
0 correct responses	0
1 correct response	1 (0.3)
2 correct responses	1 (0.3)
3 correct responses	0
4 correct responses	2 (0.6)
5 correct responses	3 (0.9)
6 correct responses	4 (1.3)
7 correct responses	6 (1.9)
8 correct responses	25 (7.9)
9 correct responses	13 (4.1)
10 correct responses	31 (9.7)
11 correct responses	33 (10.4)
12 correct responses	38 (11.9)
13 correct responses	63 (19.8)
14 correct responses	98 (30.8)

Source: Appendix B: Survey Tables, Table 6.2

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys	
Question	**Pharmacists (N=318) n (%) [95% CI][1]**
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	
True	82 (25.8)
False[2]	197 (61.9) [56.4 - 67.3]
I don't know	39 (12.3)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	
True	34 (10.7)
False[2]	256 (80.5) [75.7 - 84.7]
I don't know	28 (8.8)
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.	
True[2]	131 (41.2) [35.7 - 46.8]
False	151 (47.5)
I don't know	36 (11.3)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.	
9a: Acute or postoperative pain	
Yes	35 (11.0)
No[2]	273 (85.8) [81.5 - 89.5]
I don't know	10 (3.1)
9b: Headache or migraine pain	
Yes	7 (2.2)
No[2]	300 (94.3) [91.2 - 96.6]
I don't know	11 (3.5)
9c: Dental pain	
Yes	2 (0.6)

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys	
Question	**Pharmacists (N=318) n (%) [95% CI][1]**
No[2]	306 (96.2) [93.5 - 98.0]
I don't know	10 (3.1)
9d: Breakthrough pain from cancer	
Yes[2]	292 (91.8) [88.2 - 94.6]
No	22 (6.9)
I don't know	4 (1.3)
9e: Chronic non-cancer pain	
Yes	138 (43.4)
No[2]	162 (50.9) [45.3 - 56.6]
I don't know	18 (5.7)

Source: Appendix B: Survey Tables, Table 7.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.1: Responses to Questions Linked to Key Risk Message #2 by Reading Full Prescribing Information or Medication Guide - Completed Surveys		
	Reading Full Prescribing Information or Medication Guide	
Question	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.		
True	73 (26.2)	9 (23.1)
False[2]	175 (62.7) [56.8 - 68.4]	22 (56.4) [39.6 - 72.2]
I don't know	31 (11.1)	8 (20.5)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.		
True	31 (11.1)	3 (7.7)
False[2]	230 (82.4) [77.5 - 86.7]	26 (66.7) [49.8 - 80.9]
I don't know	18 (6.5)	10 (25.6)
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.		
True[2]	118 (42.3) [36.4 - 48.3]	13 (33.3) [19.1 - 50.2]
False	134 (48.0)	17 (43.6)
I don't know	27 (9.7)	9 (23.1)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
Yes	29 (10.4)	6 (15.4)
No[2]	244 (87.5) [83.0 - 91.1]	29 (74.4) [57.9 - 87.0]
I don't know	6 (2.2)	4 (10.3)
9b: Headache or migraine pain		
Yes	6 (2.2)	1 (2.6)
No[2]	267 (95.7) [92.6 - 97.8]	33 (84.6) [69.5 - 94.1]
I don't know	6 (2.2)	5 (12.8)
9c: Dental pain		

Table 7.1.1: Responses to Questions Linked to Key Risk Message #2 by Reading Full Prescribing Information or Medication Guide - Completed Surveys

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
Yes	2 (0.7)	0
No[2]	272 (97.5) [94.9 - 99.0]	34 (87.2) [72.6 - 95.7]
I don't know	5 (1.8)	5 (12.8)
9d: Breakthrough pain from cancer		
Yes[2]	258 (92.5) [88.7 - 95.3]	34 (87.2) [72.6 - 95.7]
No	19 (6.8)	3 (7.7)
I don't know	2 (0.7)	2 (5.1)
9e: Chronic non-cancer pain		
Yes	117 (41.9)	21 (53.8)
No[2]	150 (53.8) [47.7 - 59.7]	12 (30.8) [17.0 - 47.6]
I don't know	12 (4.3)	6 (15.4)

Source: Appendix B: Survey Tables, Table 7.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.2: Responses to Questions Linked to Key Risk Message #2 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=314) n (%) [95% CI][1]	Telephone (N=4) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.		
True	80 (25.5)	2 (50.0)
False[2]	196 (62.4) [56.8 - 67.8]	1 (25.0) [0.6 - 80.6]
I don't know	38 (12.1)	1 (25.0)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.		
True	32 (10.2)	2 (50.0)
False[2]	254 (80.9) [76.1 - 85.1]	2 (50.0) [6.8 - 93.2]
I don't know	28 (8.9)	0
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.		
True[2]	130 (41.4) [35.9 - 47.1]	1 (25.0) [0.6 - 80.6]
False	149 (47.5)	2 (50.0)
I don't know	35 (11.1)	1 (25.0)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
Yes	33 (10.5)	2 (50.0)
No[2]	272 (86.6) [82.4 - 90.2]	1 (25.0) [0.6 - 80.6]
I don't know	9 (2.9)	1 (25.0)
9b: Headache or migraine pain		
Yes	5 (1.6)	2 (50.0)
No[2]	298 (94.9) [91.9 - 97.1]	2 (50.0) [6.8 - 93.2]
I don't know	11 (3.5)	0
9c: Dental pain		
Yes	1 (0.3)	1 (25.0)

Table 7.1.2: Responses to Questions Linked to Key Risk Message #2 by Modality to Complete Survey - Completed Surveys

Question	Modality to Complete Survey	
	Internet (N=314) n (%) [95% CI][1]	Telephone (N=4) n (%) [95% CI][1]
No[2]	304 (96.8) [94.2 - 98.5]	2 (50.0) [6.8 - 93.2]
I don't know	9 (2.9)	1 (25.0)
9d: Breakthrough pain from cancer		
Yes[2]	290 (92.4) [88.8 - 95.0]	2 (50.0) [6.8 - 93.2]
No	21 (6.7)	1 (25.0)
I don't know	3 (1.0)	1 (25.0)
9e: Chronic non-cancer pain		
Yes	136 (43.3)	2 (50.0)
No[2]	161 (51.3) [45.6 - 56.9]	1 (25.0) [0.6 - 80.6]
I don't know	17 (5.4)	1 (25.0)

Source: Appendix B: Survey Tables, Table 7.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.3: Responses to Questions Linked to Key Risk Message #2 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.				
True	7 (18.9)	7 (13.7)	26 (28.6)	41 (31.1)
False[2]	23 (62.2) [44.8 - 77.5]	36 (70.6) [56.2 - 82.5]	61 (67.0) [56.4 - 76.5]	74 (56.1) [47.2 - 64.7]
I don't know	7 (18.9)	8 (15.7)	4 (4.4)	17 (12.9)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.				
True	4 (10.8)	5 (9.8)	10 (11.0)	14 (10.6)
False[2]	29 (78.4) [61.8 - 90.2]	42 (82.4) [69.1 - 91.6]	75 (82.4) [73.0 - 89.6]	106 (80.3) [72.5 - 86.7]
I don't know	4 (10.8)	4 (7.8)	6 (6.6)	12 (9.1)
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.				
True[2]	21 (56.8) [39.5 - 72.9]	25 (49.0) [34.8 - 63.4]	45 (49.5) [38.8 - 60.1]	37 (28.0) [20.6 - 36.5]
False	13 (35.1)	23 (45.1)	38 (41.8)	74 (56.1)
I don't know	3 (8.1)	3 (5.9)	8 (8.8)	21 (15.9)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
Yes	4 (10.8)	5 (9.8)	8 (8.8)	18 (13.6)

Table 7.1.3: Responses to Questions Linked to Key Risk Message #2 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
No[2]	30 (81.1) [64.8 - 92.0]	46 (90.2) [78.6 - 96.7]	79 (86.8) [78.1 - 93.0]	111 (84.1) [76.7 - 89.9]
I don't know	3 (8.1)	0	4 (4.4)	3 (2.3)
9b: Headache or migraine pain				
Yes	0	0	4 (4.4)	3 (2.3)
No[2]	36 (97.3) [85.8 - 99.9]	48 (94.1) [83.8 - 98.8]	83 (91.2) [83.4 - 96.1]	126 (95.5) [90.4 - 98.3]
I don't know	1 (2.7)	3 (5.9)	4 (4.4)	3 (2.3)
9c: Dental pain				
Yes	0	0	0	2 (1.5)
No[2]	35 (94.6) [81.8 - 99.3]	51 (100.0) [93.0 - 100.0]	85 (93.4) [86.2 - 97.5]	128 (97.0) [92.4 - 99.2]
I don't know	2 (5.4)	0	6 (6.6)	2 (1.5)
9d: Breakthrough pain from cancer				
Yes[2]	35 (94.6) [81.8 - 99.3]	44 (86.3) [73.7 - 94.3]	87 (95.6) [89.1 - 98.8]	119 (90.2) [83.7 - 94.7]
No	2 (5.4)	6 (11.8)	3 (3.3)	11 (8.3)
I don't know	0	1 (2.0)	1 (1.1)	2 (1.5)
9e: Chronic non-cancer pain				
Yes	17 (45.9)	19 (37.3)	40 (44.0)	59 (44.7)
No[2]	18 (48.6) [31.9 - 65.6]	27 (52.9) [38.5 - 67.1]	44 (48.4) [37.7 - 59.1]	69 (52.3) [43.4 - 61.0]

Table 7.1.3: Responses to Questions Linked to Key Risk Message #2 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
I don't know	2 (5.4)	5 (9.8)	7 (7.7)	4 (3.0)

Source: Appendix B: Survey Tables, Table 7.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.4: Responses to Questions Linked to Key Risk Message #2 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.					
True	13 (21.7)	32 (21.5)	12 (31.6)	16 (34.0)	9 (37.5)
False[2]	39 (65.0) [51.6 - 76.9]	96 (64.4) [56.2 - 72.1]	24 (63.2) [46.0 - 78.2]	28 (59.6) [44.3 - 73.6]	10 (41.7) [22.1 - 63.4]
I don't know	8 (13.3)	21 (14.1)	2 (5.3)	3 (6.4)	5 (20.8)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.					
True	7 (11.7)	18 (12.1)	4 (10.5)	2 (4.3)	3 (12.5)
False[2]	48 (80.0) [67.7 - 89.2]	115 (77.2) [69.6 - 83.7]	31 (81.6) [65.7 - 92.3]	44 (93.6) [82.5 - 98.7]	18 (75.0) [53.3 - 90.2]
I don't know	5 (8.3)	16 (10.7)	3 (7.9)	1 (2.1)	3 (12.5)
6c: A patient must stop taking their TIRF medicine if they stop taking their around-the-clock opioid pain medicine.					
True[2]	26 (43.3) [30.6 - 56.8]	65 (43.6) [35.5 - 52.0]	14 (36.8) [21.8 - 54.0]	18 (38.3) [24.5 - 53.6]	8 (33.3) [15.6 - 55.3]
False	26 (43.3)	67 (45.0)	21 (55.3)	25 (53.2)	12 (50.0)
I don't know	8 (13.3)	17 (11.4)	3 (7.9)	4 (8.5)	4 (16.7)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indications can TIRF medicines be prescribed to opioid tolerant patients? Please answer Yes, No, or I don't know for each option.					
9a: Acute or postoperative pain					

Table 7.1.4: Responses to Questions Linked to Key Risk Message #2 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
Yes	11 (18.3)	12 (8.1)	3 (7.9)	6 (12.8)	3 (12.5)
No[2]	47 (78.3) [65.8 - 87.9]	131 (87.9) [81.6 - 92.7]	34 (89.5) [75.2 - 97.1]	41 (87.2) [74.3 - 95.2]	20 (83.3) [62.6 - 95.3]
I don't know	2 (3.3)	6 (4.0)	1 (2.6)	0	1 (4.2)
9b: Headache or migraine pain					
Yes	0	3 (2.0)	3 (7.9)	1 (2.1)	0
No[2]	56 (93.3) [83.8 - 98.2]	142 (95.3) [90.6 - 98.1]	35 (92.1) [78.6 - 98.3]	44 (93.6) [82.5 - 98.7]	23 (95.8) [78.9 - 99.9]
I don't know	4 (6.7)	4 (2.7)	0	2 (4.3)	1 (4.2)
9c: Dental pain					
Yes	0	0	1 (2.6)	1 (2.1)	0
No[2]	56 (93.3) [83.8 - 98.2]	145 (97.3) [93.3 - 99.3]	36 (94.7) [82.3 - 99.4]	46 (97.9) [88.7 - 99.9]	23 (95.8) [78.9 - 99.9]
I don't know	4 (6.7)	4 (2.7)	1 (2.6)	0	1 (4.2)
9d: Breakthrough pain from cancer					
Yes[2]	53 (88.3) [77.4 - 95.2]	140 (94.0) [88.8 - 97.2]	35 (92.1) [78.6 - 98.3]	41 (87.2) [74.3 - 95.2]	23 (95.8) [78.9 - 99.9]
No	6 (10.0)	7 (4.7)	3 (7.9)	5 (10.6)	1 (4.2)
I don't know	1 (1.7)	2 (1.3)	0	1 (2.1)	0
9e: Chronic non-cancer pain					

Table 7.1.4: Responses to Questions Linked to Key Risk Message #2 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
Yes	20 (33.3)	67 (45.0)	21 (55.3)	18 (38.3)	12 (50.0)
No[2]	33 (55.0) [41.6 - 67.9]	75 (50.3) [42.0 - 58.6]	16 (42.1) [26.3 - 59.2]	29 (61.7) [46.4 - 75.5]	9 (37.5) [18.8 - 59.4]
I don't know	7 (11.7)	7 (4.7)	1 (2.6)	0	3 (12.5)

Source: Appendix B: Survey Tables, Table 7.1.4
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys	
Correct Responses	**Pharmacists (N=318) n (%)**
0 correct responses	1 (0.3)
1 correct response	3 (0.9)
2 correct responses	6 (1.9)
3 correct responses	8 (2.5)
4 correct responses	38 (11.9)
5 correct responses	54 (17.0)
6 correct responses	71 (22.3)
7 correct responses	66 (20.8)
8 correct responses	71 (22.3)

Source: Appendix B: Survey Tables, Table 7.2

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys	
Question	**Pharmacists (N=318) n (%) [95% CI][1]**
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	
True[2]	312 (98.1) [95.9 - 99.3]
False	4 (1.3)
I don't know	2 (0.6)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a: A personal history of psychiatric illness	
Yes[2]	247 (77.7) [72.7 - 82.1]
No	42 (13.2)
I don't know	29 (9.1)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	
Yes[2]	314 (98.7) [96.8 - 99.7]
No	1 (0.3)
I don't know	3 (0.9)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.	
True[2]	298 (93.7) [90.5 - 96.1]
False	12 (3.8)
I don't know	8 (2.5)
Question 13: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.	
13a: Misuse	
True[2]	314 (98.7) [96.8 - 99.7]
False	3 (0.9)
I don't know	1 (0.3)
13b: Abuse	

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys	
Question	**Pharmacists (N=318) n (%) [95% CI][1]**
True[2]	315 (99.1) [97.3 - 99.8]
False	2 (0.6)
I don't know	1 (0.3)
13c: Addiction	
True[2]	314 (98.7) [96.8 - 99.7]
False	3 (0.9)
I don't know	1 (0.3)
13d: Overdose	
True[2]	316 (99.4) [97.7 - 99.9]
False	1 (0.3)
I don't know	1 (0.3)
13e: Hypothyroidism	
True	10 (3.1)
False[2]	267 (84.0) [79.5 - 87.8]
I don't know	41 (12.9)
13f: Infection	
True	15 (4.7)
False[2]	284 (89.3) [85.4 - 92.5]
I don't know	19 (6.0)

Source: Appendix B: Survey Tables, Table 8.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.1: Responses to Questions Linked to Key Risk Message #3 by Reading Full Prescribing Information or Medication Guide - Completed Surveys		
	Reading Full Prescribing Information or Medication Guide	
Question	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True[2]	274 (98.2) [95.9 - 99.4]	38 (97.4) [86.5 - 99.9]
False	3 (1.1)	1 (2.6)
I don't know	2 (0.7)	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8a: A personal history of psychiatric illness		
Yes[2]	219 (78.5) [73.2 - 83.2]	28 (71.8) [55.1 - 85.0]
No	38 (13.6)	4 (10.3)
I don't know	22 (7.9)	7 (17.9)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes[2]	276 (98.9) [96.9 - 99.8]	38 (97.4) [86.5 - 99.9]
No	1 (0.4)	0
I don't know	2 (0.7)	1 (2.6)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[2]	264 (94.6) [91.3 - 97.0]	34 (87.2) [72.6 - 95.7]
False	9 (3.2)	3 (7.7)
I don't know	6 (2.2)	2 (5.1)
Question 13: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.		
13a: Misuse		
True[2]	277 (99.3) [97.4 - 99.9]	37 (94.9) [82.7 - 99.4]
False	2 (0.7)	1 (2.6)

Table 8.1.1: Responses to Questions Linked to Key Risk Message #3 by Reading Full Prescribing Information or Medication Guide - Completed Surveys

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
I don't know	0	1 (2.6)
13b: Abuse		
True[2]	278 (99.6) [98.0 - 100.0]	37 (94.9) [82.7 - 99.4]
False	1 (0.4)	1 (2.6)
I don't know	0	1 (2.6)
13c: Addiction		
True[2]	278 (99.6) [98.0 - 100.0]	36 (92.3) [79.1 - 98.4]
False	1 (0.4)	2 (5.1)
I don't know	0	1 (2.6)
13d: Overdose		
True[2]	279 (100.0) [98.7 - 100.0]	37 (94.9) [82.7 - 99.4]
False	0	1 (2.6)
I don't know	0	1 (2.6)
13e: Hypothyroidism		
True	8 (2.9)	2 (5.1)
False[2]	238 (85.3) [80.6 - 89.2]	29 (74.4) [57.9 - 87.0]
I don't know	33 (11.8)	8 (20.5)
13f: Infection		
True	15 (5.4)	0
False[2]	250 (89.6) [85.4 - 92.9]	34 (87.2) [72.6 - 95.7]
I don't know	14 (5.0)	5 (12.8)

Source: Appendix B: Survey Tables, Table 8.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.2: Responses to Questions Linked to Key Risk Message #3 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=314) n (%) [95% CI][1]	Telephone (N=4) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True[2]	308 (98.1) [95.9 - 99.3]	4 (100.0) [39.8 - 100.0]
False	4 (1.3)	0
I don't know	2 (0.6)	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8a: A personal history of psychiatric illness		
Yes[2]	245 (78.0) [73.0 - 82.5]	2 (50.0) [6.8 - 93.2]
No	41 (13.1)	1 (25.0)
I don't know	28 (8.9)	1 (25.0)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes[2]	311 (99.0) [97.2 - 99.8]	3 (75.0) [19.4 - 99.4]
No	1 (0.3)	0
I don't know	2 (0.6)	1 (25.0)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[2]	294 (93.6) [90.3 - 96.1]	4 (100.0) [39.8 - 100.0]
False	12 (3.8)	0
I don't know	8 (2.5)	0
Question 13: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.		
13a: Misuse		
True[2]	311 (99.0) [97.2 - 99.8]	3 (75.0) [19.4 - 99.4]
False	2 (0.6)	1 (25.0)
I don't know	1 (0.3)	0

Table 8.1.2: Responses to Questions Linked to Key Risk Message #3 by Modality to Complete Survey - Completed Surveys

Question	Modality to Complete Survey	
	Internet (N=314) n (%) [95% CI][1]	Telephone (N=4) n (%) [95% CI][1]
13b: Abuse		
True[2]	312 (99.4) [97.7 - 99.9]	3 (75.0) [19.4 - 99.4]
False	1 (0.3)	1 (25.0)
I don't know	1 (0.3)	0
13c: Addiction		
True[2]	310 (98.7) [96.8 - 99.7]	4 (100.0) [39.8 - 100.0]
False	3 (1.0)	0
I don't know	1 (0.3)	0
13d: Overdose		
True[2]	312 (99.4) [97.7 - 99.9]	4 (100.0) [39.8 - 100.0]
False	1 (0.3)	0
I don't know	1 (0.3)	0
13e: Hypothyroidism		
True	9 (2.9)	1 (25.0)
False[2]	265 (84.4) [79.9 - 88.2]	2 (50.0) [6.8 - 93.2]
I don't know	40 (12.7)	1 (25.0)
13f: Infection		
True	13 (4.1)	2 (50.0)
False[2]	282 (89.8) [85.9 - 92.9]	2 (50.0) [6.8 - 93.2]
I don't know	19 (6.1)	0

Source: Appendix B: Survey Tables, Table 8.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.3: Responses to Questions Linked to Key Risk Message #3 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True[2]	37 (100.0) [90.5 - 100.0]	51 (100.0) [93.0 - 100.0]	90 (98.9) [94.0 - 100.0]	128 (97.0) [92.4 - 99.2]
False	0	0	1 (1.1)	3 (2.3)
I don't know	0	0	0	1 (0.8)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes[2]	33 (89.2) [74.6 - 97.0]	39 (76.5) [62.5 - 87.2]	75 (82.4) [73.0 - 89.6]	94 (71.2) [62.7 - 78.8]
No	2 (5.4)	7 (13.7)	8 (8.8)	25 (18.9)
I don't know	2 (5.4)	5 (9.8)	8 (8.8)	13 (9.8)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes[2]	37 (100.0) [90.5 - 100.0]	51 (100.0) [93.0 - 100.0]	89 (97.8) [92.3 - 99.7]	130 (98.5) [94.6 - 99.8]
No	0	0	1 (1.1)	0
I don't know	0	0	1 (1.1)	2 (1.5)
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True[2]	36 (97.3) [85.8 - 99.9]	49 (96.1) [86.5 - 99.5]	86 (94.5) [87.6 - 98.2]	120 (90.9) [84.7 - 95.2]
False	0	2 (3.9)	4 (4.4)	6 (4.5)

Table 8.1.3: Responses to Questions Linked to Key Risk Message #3 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
I don't know	1 (2.7)	0	1 (1.1)	6 (4.5)
Question 13: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.				
13a: Misuse				
True[2]	37 (100.0) [90.5 - 100.0]	51 (100.0) [93.0 - 100.0]	90 (98.9) [94.0 - 100.0]	129 (97.7) [93.5 - 99.5]
False	0	0	0	3 (2.3)
I don't know	0	0	1 (1.1)	0
13b: Abuse				
True[2]	37 (100.0) [90.5 - 100.0]	51 (100.0) [93.0 - 100.0]	90 (98.9) [94.0 - 100.0]	130 (98.5) [94.6 - 99.8]
False	0	0	0	2 (1.5)
I don't know	0	0	1 (1.1)	0
13c: Addiction				
True[2]	37 (100.0) [90.5 - 100.0]	51 (100.0) [93.0 - 100.0]	90 (98.9) [94.0 - 100.0]	129 (97.7) [93.5 - 99.5]
False	0	0	0	3 (2.3)
I don't know	0	0	1 (1.1)	0
13d: Overdose				
True[2]	37 (100.0) [90.5 - 100.0]	51 (100.0) [93.0 - 100.0]	90 (98.9) [94.0 - 100.0]	131 (99.2) [95.9 - 100.0]
False	0	0	0	1 (0.8)

Table 8.1.3: Responses to Questions Linked to Key Risk Message #3 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
I don't know	0	0	1 (1.1)	0
13e: Hypothyroidism				
True	1 (2.7)	3 (5.9)	2 (2.2)	4 (3.0)
False[2]	32 (86.5) [71.2 - 95.5]	46 (90.2) [78.6 - 96.7]	76 (83.5) [74.3 - 90.5]	107 (81.1) [73.3 - 87.4]
I don't know	4 (10.8)	2 (3.9)	13 (14.3)	21 (15.9)
13f: Infection				
True	3 (8.1)	2 (3.9)	5 (5.5)	4 (3.0)
False[2]	32 (86.5) [71.2 - 95.5]	47 (92.2) [81.1 - 97.8]	79 (86.8) [78.1 - 93.0]	121 (91.7) [85.6 - 95.8]
I don't know	2 (5.4)	2 (3.9)	7 (7.7)	7 (5.3)

Source: Appendix B: Survey Tables, Table 8.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.4: Responses to Questions Linked to Key Risk Message #3 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.					
True[2]	60 (100.0) [94.0 - 100.0]	145 (97.3) [93.3 - 99.3]	37 (97.4) [86.2 - 99.9]	47 (100.0) [92.5 - 100.0]	23 (95.8) [78.9 - 99.9]
False	0	2 (1.3)	1 (2.6)	0	1 (4.2)
I don't know	0	2 (1.3)	0	0	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.					
8a: A personal history of psychiatric illness					
Yes[2]	52 (86.7) [75.4 - 94.1]	116 (77.9) [70.3 - 84.2]	30 (78.9) [62.7 - 90.4]	30 (63.8) [48.5 - 77.3]	19 (79.2) [57.8 - 92.9]
No	3 (5.0)	19 (12.8)	6 (15.8)	12 (25.5)	2 (8.3)
I don't know	5 (8.3)	14 (9.4)	2 (5.3)	5 (10.6)	3 (12.5)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse					
Yes[2]	59 (98.3) [91.1 - 100.0]	146 (98.0) [94.2 - 99.6]	38 (100.0) [90.7 - 100.0]	47 (100.0) [92.5 - 100.0]	24 (100.0) [85.8 - 100.0]
No	1 (1.7)	0	0	0	0
I don't know	0	3 (2.0)	0	0	0
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
10a: TIRF medicines can be abused in a manner similar to other opioid agonists.					

Table 8.1.4: Responses to Questions Linked to Key Risk Message #3 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
True[2]	58 (96.7) [88.5 - 99.6]	140 (94.0) [88.8 - 97.2]	36 (94.7) [82.3 - 99.4]	41 (87.2) [74.3 - 95.2]	23 (95.8) [78.9 - 99.9]
False	2 (3.3)	4 (2.7)	1 (2.6)	4 (8.5)	1 (4.2)
I don't know	0	5 (3.4)	1 (2.6)	2 (4.3)	0
Question 13: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.					
13a: Misuse					
True[2]	60 (100.0) [94.0 - 100.0]	147 (98.7) [95.2 - 99.8]	37 (97.4) [86.2 - 99.9]	46 (97.9) [88.7 - 99.9]	24 (100.0) [85.8 - 100.0]
False	0	1 (0.7)	1 (2.6)	1 (2.1)	0
I don't know	0	1 (0.7)	0	0	0
13b: Abuse					
True[2]	60 (100.0) [94.0 - 100.0]	147 (98.7) [95.2 - 99.8]	37 (97.4) [86.2 - 99.9]	47 (100.0) [92.5 - 100.0]	24 (100.0) [85.8 - 100.0]
False	0	1 (0.7)	1 (2.6)	0	0
I don't know	0	1 (0.7)	0	0	0
13c: Addiction					
True[2]	60 (100.0) [94.0 - 100.0]	146 (98.0) [94.2 - 99.6]	38 (100.0) [90.7 - 100.0]	46 (97.9) [88.7 - 99.9]	24 (100.0) [85.8 - 100.0]
False	0	2 (1.3)	0	1 (2.1)	0
I don't know	0	1 (0.7)	0	0	0

Table 8.1.4: Responses to Questions Linked to Key Risk Message #3 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
13d: Overdose					
True[2]	60 (100.0) [94.0 - 100.0]	147 (98.7) [95.2 - 99.8]	38 (100.0) [90.7 - 100.0]	47 (100.0) [92.5 - 100.0]	24 (100.0) [85.8 - 100.0]
False	0	1 (0.7)	0	0	0
I don't know	0	1 (0.7)	0	0	0
13e: Hypothyroidism					
True	0	2 (1.3)	2 (5.3)	5 (10.6)	1 (4.2)
False[2]	54 (90.0) [79.5 - 96.2]	122 (81.9) [74.7 - 87.7]	32 (84.2) [68.7 - 94.0]	38 (80.9) [66.7 - 90.9]	21 (87.5) [67.6 - 97.3]
I don't know	6 (10.0)	25 (16.8)	4 (10.5)	4 (8.5)	2 (8.3)
13f: Infection					
True	0	3 (2.0)	3 (7.9)	8 (17.0)	1 (4.2)
False[2]	57 (95.0) [86.1 - 99.0]	136 (91.3) [85.5 - 95.3]	33 (86.8) [71.9 - 95.6]	37 (78.7) [64.3 - 89.3]	21 (87.5) [67.6 - 97.3]
I don't know	3 (5.0)	10 (6.7)	2 (5.3)	2 (4.3)	2 (8.3)

Source: Appendix B: Survey Tables, Table 8.1.4
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys	
Correct Responses	**Pharmacists (N=318) n (%)**
0 correct responses	0
1 correct response	0
2 correct responses	0
3 correct responses	1 (0.3)
4 correct responses	0
5 correct responses	1 (0.3)
6 correct responses	4 (1.3)
7 correct responses	8 (2.5)
8 correct responses	32 (10.1)
9 correct responses	83 (26.1)
10 correct responses	189 (59.4)

Source: Appendix B: Survey Tables, Table 8.2

Table 9.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys	
Question	**Pharmacists (N=318) n (%) [95% CI][1]**
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
10b: TIRF medicines are interchangeable with each other regardless of route of administration.	
True	6 (1.9)
False[2]	305 (95.9) [93.1 - 97.8]
I don't know	7 (2.2)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	
True[2]	296 (93.1) [89.7 - 95.6]
False	10 (3.1)
I don't know	12 (3.8)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	
True[2]	283 (89.0) [85.0 - 92.2]
False	16 (5.0)
I don't know	19 (6.0)
Question 16: Please answer True, False, or I don't know for each statement about TIRF medicines.	
16c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.	
True	10 (3.1)
False[2]	304 (95.6) [92.7 - 97.6]
I don't know	4 (1.3)

Source: Appendix B: Survey Tables, Table 9.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.1: Responses to Questions Linked to Key Risk Message #4 by Reading Full Prescribing Information or Medication Guide - Completed Surveys

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=279) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=39) n (%) [95% CI][1]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	6 (2.2)	0
False[2]	269 (96.4) [93.5 - 98.3]	36 (92.3) [79.1 - 98.4]
I don't know	4 (1.4)	3 (7.7)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True[2]	262 (93.9) [90.4 - 96.4]	34 (87.2) [72.6 - 95.7]
False	10 (3.6)	0
I don't know	7 (2.5)	5 (12.8)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2]	253 (90.7) [86.6 - 93.8]	30 (76.9) [60.7 - 88.9]
False	15 (5.4)	1 (2.6)
I don't know	11 (3.9)	8 (20.5)
Question 16: Please answer True, False, or I don't know for each statement about TIRF medicines.		
16c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.		
True	10 (3.6)	0
False[2]	267 (95.7) [92.6 - 97.8]	37 (94.9) [82.7 - 99.4]
I don't know	2 (0.7)	2 (5.1)

Source: Appendix B: Survey Tables, Table 9.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.2: Responses to Questions Linked to Key Risk Message #4 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=314) n (%) [95% CI][1]	Telephone (N=4) n (%) [95% CI][1]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
10b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	5 (1.6)	1 (25.0)
False[2]	302 (96.2) [93.4 - 98.0]	3 (75.0) [19.4 - 99.4]
I don't know	7 (2.2)	0
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True[2]	292 (93.0) [89.6 - 95.6]	4 (100.0) [39.8 - 100.0]
False	10 (3.2)	0
I don't know	12 (3.8)	0
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2]	279 (88.9) [84.8 - 92.1]	4 (100.0) [39.8 - 100.0]
False	16 (5.1)	0
I don't know	19 (6.1)	0
Question 16: Please answer True, False, or I don't know for each statement about TIRF medicines.		
16c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.		
True	9 (2.9)	1 (25.0)
False[2]	301 (95.9) [93.0 - 97.8]	3 (75.0) [19.4 - 99.4]
I don't know	4 (1.3)	0

Source: Appendix B: Survey Tables, Table 9.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.3: Responses to Questions Linked to Key Risk Message #4 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
10b: TIRF medicines are interchangeable with each other regardless of route of administration.				
True	0	0	1 (1.1)	4 (3.0)
False[2]	36 (97.3) [85.8 - 99.9]	51 (100.0) [93.0 - 100.0]	88 (96.7) [90.7 - 99.3]	124 (93.9) [88.4 - 97.3]
I don't know	1 (2.7)	0	2 (2.2)	4 (3.0)
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True[2]	37 (100.0) [90.5 - 100.0]	51 (100.0) [93.0 - 100.0]	83 (91.2) [83.4 - 96.1]	118 (89.4) [82.8 - 94.1]
False	0	0	5 (5.5)	5 (3.8)
I don't know	0	0	3 (3.3)	9 (6.8)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True[2]	36 (97.3) [85.8 - 99.9]	46 (90.2) [78.6 - 96.7]	81 (89.0) [80.7 - 94.6]	115 (87.1) [80.2 - 92.3]
False	0	3 (5.9)	5 (5.5)	6 (4.5)
I don't know	1 (2.7)	2 (3.9)	5 (5.5)	11 (8.3)
Question 16: Please answer True, False, or I don't know for each statement about TIRF medicines.				
16c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.				
True	2 (5.4)	2 (3.9)	1 (1.1)	5 (3.8)
False[2]	34 (91.9) [78.1 - 98.3]	49 (96.1) [86.5 - 99.5]	88 (96.7) [90.7 - 99.3]	126 (95.5) [90.4 - 98.3]

Table 9.1.3: Responses to Questions Linked to Key Risk Message #4 by Time Practicing as Pharmacist - Completed Surveys				
	Time Practicing as Pharmacist			
Question	Less than 3 years (N=37) n (%) [95% CI][1]	3 to 5 years (N=51) n (%) [95% CI][1]	6 to 15 years (N=91) n (%) [95% CI][1]	More than 15 years (N=132) n (%) [95% CI][1]
I don't know	1 (2.7)	0	2 (2.2)	1 (0.8)

Source: Appendix B: Survey Tables, Table 9.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.4: Responses to Questions Linked to Key Risk Message #4 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
Question 10: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
10b: TIRF medicines are interchangeable with each other regardless of route of administration.					
True	0	2 (1.3)	3 (7.9)	1 (2.1)	0
False[2]	56 (93.3) [83.8 - 98.2]	144 (96.6) [92.3 - 98.9]	35 (92.1) [78.6 - 98.3]	46 (97.9) [88.7 - 99.9]	24 (100.0) [85.8 - 100.0]
I don't know	4 (6.7)	3 (2.0)	0	0	0
10c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.					
True[2]	53 (88.3) [77.4 - 95.2]	136 (91.3) [85.5 - 95.3]	38 (100.0) [90.7 - 100.0]	46 (97.9) [88.7 - 99.9]	23 (95.8) [78.9 - 99.9]
False	4 (6.7)	5 (3.4)	0	1 (2.1)	0
I don't know	3 (5.0)	8 (5.4)	0	0	1 (4.2)
10d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.					
True[2]	51 (85.0) [73.4 - 92.9]	132 (88.6) [82.4 - 93.2]	37 (97.4) [86.2 - 99.9]	44 (93.6) [82.5 - 98.7]	19 (79.2) [57.8 - 92.9]
False	2 (3.3)	10 (6.7)	1 (2.6)	1 (2.1)	2 (8.3)
I don't know	7 (11.7)	7 (4.7)	0	2 (4.3)	3 (12.5)
Question 16: Please answer True, False, or I don't know for each statement about TIRF medicines.					
16c: TIRF medicines with the same route of administration can be substituted with each other if the pharmacy is out of stock for one product.					
True	1 (1.7)	5 (3.4)	3 (7.9)	1 (2.1)	0

Table 9.1.4: Responses to Questions Linked to Key Risk Message #4 by Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Dispensing TIRF Medicines per Month Within the Last 6 Months				
	None (N=60) n (%) [95% CI][1]	1 - 2 times per month (N=149) n (%) [95% CI][1]	3 - 5 times per month (N=38) n (%) [95% CI][1]	More than 5 times per month (N=47) n (%) [95% CI][1]	I don't remember (N=24) n (%) [95% CI][1]
False[2]	58 (96.7) [88.5 - 99.6]	143 (96.0) [91.4 - 98.5]	35 (92.1) [78.6 - 98.3]	46 (97.9) [88.7 - 99.9]	22 (91.7) [73.0 - 99.0]
I don't know	1 (1.7)	1 (0.7)	0	0	2 (8.3)

Source: Appendix B: Survey Tables, Table 9.1.4
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys	
Correct Responses	**Pharmacists (N=318) n (%)**
0 correct responses	0
1 correct response	6 (1.9)
2 correct responses	8 (2.5)
3 correct responses	50 (15.7)
4 correct responses	254 (79.9)

Source: Appendix B: Survey Tables, Table 9.2

Table 10: Average Knowledge Scores - Completed Surveys	
	Score [95% CI][1]
KRM #1	83.8 [81.8, 85.7]
KRM #2	75.4 [73.1, 77.6]
KRM #3	93.7 [92.7, 94.8]
KRM #4	93.4 [91.7, 95.0]
Overall Knowledge Score	85.7 [84.4, 87.0]

Source: Appendix B: Survey Tables, Table 10
[1] 95% CIs are constructed based on normal distribution function.

Listing 1: Listing of Verbatim Responses to Question #26 (Questions about the Full Prescribing Information or the Medication Guide) - Completed Surveys
Verbatim Responses
How often do you have to renew the TIRF?
How to use Lazanda and Subsys devices
Various kinetic questions
We've seen prescriptions come through where the patient does not have cancer, but they are on Subsys, so that just kind of worries us.
When does one have to not give the Package Insert?
would like to know more about the requirements for prescribing

Listing 2: Listing of Adverse Events and/or Product Complaints Reported by Modality	
Verbatim Text	**Modality of Report**
How often do you have to renew the TIRF?	Internet
How to use Lazanda and Subsys devices	Internet
We've seen prescriptions come through where the patient does not have cancer, but they are on Subsys, so that just kind of worries us.	Telephone
When does one have to not give the Package Insert?	Internet
would like to know more about the requirements for prescribing	Internet

4.4 Prescriber KAB Report

Title: **Transmucosal Immediate Release Fentanyl (TIRF) REMS Assessment**

Quantitative Testing of Prescriber Knowledge, Attitudes, and Behavior (KAB) about TIRF Products Safety and Use Information

Document Number: Wave 5, 60-Month REMS Assessment Report
Version 1.0

Survey Time Period: 26 September 2016 to 20 December 2016

Product Name: Transmucosal Immediate Release Fentanyl

Sponsor: **TIRF REMS Industry Group (TRIG) of Companies**:

Actavis Laboratories FL, Inc.

BioDelivery Sciences International, Inc. (BDSI)

Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)

Depomed, Inc.

Insys Therapeutics, Inc.

Mallinckrodt Pharmaceuticals

Mylan, Inc.

Par Pharmaceutical, Inc.

Sentynl Therapeutics, Inc.

Date: 10 February 2017

Confidentiality Statement

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LIST OF ABBREVIATIONS

BDSI	BioDelivery Sciences International, Inc.
CI	Confidence Interval
DoD	Department of Defense
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
ISI	Important Safety Information
HCP	Healthcare Professional
KAB	Knowledge, Attitudes, and Behavior
KRM	Key Risk Message
N/A	Not Applicable or Not Available
NIH	National Institutes of Health
PI	Prescribing Information
PPAF	Patient-Prescriber Agreement Form
REMS	Risk Evaluation and Mitigation Strategy
SCC	Survey Coordinating Center
SD	Standard Deviation
TIRF	Transmucosal Immediate Release Fentanyl
TIRF medicines	Transmucosal Immediate Release Fentanyl products
TIRF REMS Access program	REMS program for TIRF medicines
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States
USPS	United States Postal Service
VA	Department of Veterans Affairs

EXECUTIVE SUMMARY

The 60-month Knowledge, Attitudes, and Behavior (KAB) survey for prescribers who prescribe Transmucosal Immediate Release Fentanyl (TIRF) medicines was conducted as part of the 60-Month TIRF Risk Evaluation and Mitigation Strategy (REMS) Access program assessment. On 21 July 2016, the United States (US) Food and Drug Administration (FDA) provided feedback on the prescriber survey. After careful review of the requested changes, the TIRF REMS Industry Group (TRIG) notified FDA that in order to incorporate all changes, an extension for report submission would be required. As proposed by FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month KAB survey results were planned for a separate submission from the overall assessment report on or before 17 February 2017. The 60-month KAB survey for prescribers launched on 26 September 2016 and closed on 20 December 2016.

Subjects were recruited from a random sample of prescribers who were enrolled in the TIRF REMS Access program and who had prescribed a TIRF medicine in the last 6 months. From total of 524 respondents who accessed the survey, 313 prescribers (59.7%) met eligibility criteria, and of those who met eligibility criteria, 294 (93.9%) completed the survey.

On 21 July 2016, FDA provided feedback on the KAB survey for prescribers. Changes to the 60-month KAB Survey for Prescribers based on FDA feedback included the addition of 3 survey questions, the revision of 1 survey question, and a change to the recruitment strategy to limit the survey to prescribers who have prescribed TIRF medicines in the past 6 months. The change to Question 9 (*Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved*), and the addition of Question 21 (*TIRF medicines should only be taken by patients who are opioid tolerant*) and Question 22 (*Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements*) are discussed with the key risk message results below. Question 32 (*How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know)* included 3 response items about prescriber reported activity. For each item, most prescribers selected *always* or *only with the first prescription*; and few prescribers selected *sometimes*, *never*, or *I don't know*.

The overall knowledge score of 89.1 (95% confidence interval [CI]: 88.0 90.2) for the survey indicates a high percentage of respondents demonstrated understanding of the key risk messages. The average knowledge score was greater than 86 for all 4 key risk messages. Of the 38 questions/items included as part of key risk messages, 28 questions/items had a correct response rate >80% and 10 questions/items had a correct response rate between 65% and 80%. None of the questions/items had a correct response rate that fell below the desired level of understanding of 65%.

When comparing correct response rates from the 12-month KAB survey through the 60-month KAB survey, knowledge and understanding of the key risk message questions has generally remained stable or improved over time. Correct response rates for 4 of the 5 items

of the revised Question 9 were similar compared to the 48-month survey; however, the item pertaining to a response of 'chronic non-cancer pain' had a notably improved correct response rate. In addition, the 2 new survey questions (Question 21 and Question 22 [6 separate response items]) that were added as part of key risk messages for the 60-month survey based on FDA feedback had a correct response rate of >96% for 5 questions/items and >78% for 2 items.

1. PRESCRIBER SURVEY BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate release opioid analgesics indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® [fentanyl citrate oral transmucosal lozenge] and equivalent generics) who are receiving and already tolerant to opioid therapy for their underlying persistent cancer pain. The FDA has determined that a shared system REMS is required to mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access program was approved by the FDA on 28 December 2011. This report describes the results from the prescriber surveys conducted for the 60-month TIRF REMS Access program assessment, and reflects the REMS reporting period of 29 October 2016 to 28 October 2016. The 60-month KAB survey for prescribers launched on 26 September 2016 and closed on 20 December 2016.

The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and (where applicable) their respective generic equivalents. The TRIG includes Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan, Inc.; Par Pharmaceutical, Inc.; and Sentynl Therapeutics, Inc. One company joined the TRIG during the reporting period: Sentynl Therapeutics, Inc. replaced Galena Biopharma, Inc. on 09 January 2016.

The TIRF REMS Access program consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments. The goals of the TIRF REMS Access program are to mitigate the risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.

2. Preventing inappropriate conversion between TIRF medicines.

3. Preventing accidental exposure to children and others for whom it was not prescribed.

4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS Access program assessment is the conduct of quantitative evaluation surveys to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS Access program educational materials, Prescriber Enrollment Form, and Prescribing Information of each product. Administration of the surveys conducted among prescribers who are enrolled in the TIRF REMS Access program is described in the protocol (See Appendix A). Note: Protocol and survey question revisions from the 48-month assessment report are identified as tracked changes.

Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

1.1 Changes to the KAB Survey for Prescribers Based on FDA Feedback

On 21 July 2016, FDA provided feedback on the KAB survey for prescribers. After careful review of the requested changes, the TRIG notified FDA that in order to incorporate all changes, an extension for report submission would be required. As proposed by FDA on 29 July 2016 and agreed to by the TRIG on 01 August 2016, the 60-month KAB survey results were planned for a separate submission from the overall assessment report on or before 17 February 2017.

Specific updates made to the protocol and survey included:

- Changes to the recruitment strategy to:
  - Limit the survey to prescribers who have prescribed TIRF medicines in the past 6 months
- Addition of the following questions:
  - 21 (*TIRF medicines should only be taken by patients who are opioid tolerant*)
  - 32 (*How frequently do you perform the following activities when prescribing TIRF medicines?*
    - *32a Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed*
    - *32b Instruct the patient on how to use the TIRF medicine that was most recently prescribed*
    - *32c Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed*)
  - 22 (*Which of the following risks are associated with the use of TIRF medicines?*
    - *22a Misuse*
    - *22b Abuse*
    - *22c Addiction*
    - *22d Overdose*
    - *22e Hypothyroidism*
    - *22f Infection*)

- Revision to Question 9 (*For which indications do you prescribe TIRF medicines to opioid tolerant patients*) as it assumes that prescribers are only using TIRF medicines for opioid tolerant patients which may not be the case. Question was updated to: *Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved?*

All of the above requested changes were incorporated prior to survey launch on 26 September 2016.

2. PRESCRIBER SURVEY OBJECTIVES

The evaluation survey used a questionnaire to document the level of knowledge and assess the attitudes and behavior of prescribers regarding the following key information and risk messages communicated through the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.
2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II controlled substance, with abuse liability similar to other opioid analgesics.
4. TIRF medicines are not interchangeable with each other, regardless of route of administration.
5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

3. SURVEY METHODOLOGY

This section summarizes the survey design and the questions developed to test prescriber understanding of the key risk messages of the REMS. Full details of the survey design are in the protocol, provided in Appendix A.

3.1 Survey Sample

A sample of 300 healthcare professionals (HCPs) who are enrolled in the TIRF REMS Access program is proposed for each survey wave. The survey sample size was determined based on both practical and statistical considerations. The survey was written to reflect wording for both methods of survey administration: Internet-based and telephone.

3.1.1 Eligibility

Subjects were recruited from a random sample of prescribers who were enrolled in the TIRF REMS Access program and who had prescribed a TIRF medicine in the last 6 months. Respondents or respondents with immediate family members who had ever worked for any of the TRIG companies, RelayHealth, McKesson Specialty Care Solutions, United BioSource Corporation (UBC), or the FDA were not eligible to participate, nor were respondents who participated in the previous waves of the survey (annual waves from the 12-month TIRF REMS Access program assessment through the 48-month TIRF REMS Access program assessment).

3.1.2 Recruitment

Prescribers who were enrolled in the TIRF REMS Access program as of 02 September 2016 and who had prescribed a TIRF medicine in the last 6 months were recruited via an invitation letter sent via email and through the United States Postal Service (USPS) (Section 5.1.1 for more detail).

If the required number of completed surveys was not achieved within the expected timeframe of approximately 1 to 2 weeks after the first mailing, reminder letters were to be sent to non-responders from the original sample with subsequent follow-up to maximize participation. If these efforts did not result in the required number of completed surveys within 2 to 3 weeks, then a new sample of prescribers was to be randomly selected.

Each letter of invitation included a unique code needed to access the survey. The code was deactivated after the respondent had initiated the survey (whether or not the survey was completed). Respondents were given the option of taking the survey by telephone via the Survey Coordinating Center (SCC) or online via a secure website. The survey was estimated to take approximately 20 minutes to complete.

All respondents who completed the survey and provided their contact information were mailed a $125 gift card for participating, with the exception of prescribers who practiced in Massachusetts, Minnesota, or Vermont (due to state laws prohibiting it). The mailing also included a Thank You Letter, a copy of the Important Safety Information (ISI) and a copy of the correct answers to key risk message questions.

3.2 Questions and Statements on Key Risk Messages

The questions and statements comprising the knowledge survey were constructed to test the prescribers' understanding of the key risk messages of the REMS. The questions were to be answered either by selecting options from multiple-choice lists that included statements of the specific key risk messages or by choosing "Yes" or "True," "No" or "False," or "I Don't Know" regarding statements about TIRF medicines.

For statements or questions that use "True" or "Yes" versus "False" or "No" response options, the desired response for key risk messages is generally "True" or "Yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some

questions were formatted to have the respondent disagree with the statement as written by providing response options of "False" or "No" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the survey protocol (Appendix A).

3.2.1 Key Risk Message 1

Key Risk Message 1 refers to the prescriber's knowledge of the specific contraindications for TIRF medicine in opioid non-tolerant patients and under what conditions a patient is considered opioid tolerant.

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired Response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	***True***
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	***False***
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	***False***
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	***True***
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	***True***
7c	TIRF medicines may be used to treat opioid non-tolerant patients.	***False***
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	***True***
13	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:	
13a	8 mg oral hydromorphone/day	***True***
13b	60 mg oral morphine/day	***True***

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**Desired Response**
13c	30 mg oral oxycodone/day	***True***
13d	25 mcg transdermal fentanyl/hour	***True***
13e	25 mg oral oxymorphone/day	***True***
13f	An equianalgesic dose of another oral opioid	***True***
21	Please answer True, False, or I don't know for the following statement about TIRF medicines: TIRF medicines should only be taken by patients who are opioid tolerant.	***True***

3.2.2 Key Risk Message 2

Key Risk Message 2 refers to the prescriber's knowledge of the indications for prescribing TIRF medicines for the management of breakthrough pain in opioid-tolerant adult cancer patients, and the timing of administration of the TIRF medicine in relation to the around-the-clock opioid therapy to ensure the patient is considered opioid tolerant.

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired Response**
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a	According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	***False***
6b	According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain	***False***
9	Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	***No***
9b	Headache or migraine pain	***No***
9c	Dental pain	***No***
9d	Breakthrough pain from cancer	***Yes***

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.		
Question No.	**Question**	**Desired Response**
9e	Chronic non-cancer pain	***No***
15	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	***15b. Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.***
20	Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.	
20b	Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	***True***
20c	Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.	***False***

3.2.3 Key Risk Message 3

Key Risk Message 3 refers to the prescriber's knowledge of the risk factors for opioid abuse and importance in monitoring for signs of abuse in patients who take TIRF medicines.

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**Desired response**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	***True***
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	***Yes***
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	***Yes***
12	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12a	TIRF medicines can be abused in a manner similar to other opioid agonists.	***True***
22	Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.	
22a	Misuse	***True***
22b	Abuse	***True***
22c	Addiction	***True***
22d	Overdose	***True***
22e	Hypothyroidism	***False***
22f	Infection	***False***

3.2.4 Key Risk Message 4

Key Risk Message 4 refers to the prescriber's knowledge of the interchangeability of TIRF medicines based on route of administration, pharmacokinetic absorption, and dosage.

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired response**
12	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12b	TIRF medicines are interchangeable with each other regardless of route of administration.	***False***
12c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	***True***
12d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	***True***
16	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.	***16b. The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.***

3.3 Additional Questions

Additional questions in the survey include inclusion/exclusion questions to confirm respondent eligibility; questions on knowledge of safe use of TIRF medicines; questions about receipt/access to and reading the Full Prescribing Information and Medication Guide; questions about review and signing of the Patient-Prescriber Agreement Form (PPAF); and questions to collect demographic information. In addition, the following questions about behaviors (Question 14a-f and Question 32a-c) were asked after the key risk message questions.

Question No.	Question
14	How frequently do you perform the following activities when dispensing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know."
14a	Ask patients (or their caregivers) about the presence of children in the home
14b	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
14c	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
14d	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
14e	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
14f	Give patients (or their caregivers) the Medication Guide for their TIRF medicine
32	How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
32a	Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed.
32b	Instruct the patient on how to use the TIRF medicine that was most recently prescribed.
32c	Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed.

4. STATISTICAL METHODS

4.1 Study Population

4.1.1 All Respondents

The All Respondents population consisted of respondents that accessed the survey using a unique code. These respondents were used as the denominator for percentages in survey administration statistics unless otherwise specified.

4.1.2 Completed Surveys (Primary Population)

The primary population for analysis was all eligible prescribers who completed the survey. Eligible prescribers were defined as those respondents who answered Yes to Question 1 (agree to take part in survey) and Yes to Question 3 (enrolled in the TIRF REMS Access program), and No to Question 2 (participated in past survey) and No to Question 4 (worked for a TRIG company, UBC, RelayHealth, McKesson Specialty Care Solutions, or FDA). A survey was considered "completed" when an eligible prescriber answered all relevant questions.

4.1.3 General Population

The general population consisted of all prescribers who prescribed a TIRF medicine in the past 6 months as shown in IMS Health data (IMS data) and REMS switch provider data. These populations were used to compare the population represented in the survey to the general population to determine whether those completing the survey were representative of the prescribing population. It was assumed that the IMS data covered the majority of HCPs prescribing TIRF medicines in the outpatient setting and REMS switch provider data included all HCPs prescribing TIRF medicines in the outpatient setting. The analysis included calculation of p-values by a chi-square test.

4.2 Primary Analysis

Primary analyses were performed for all key risk messages. The primary analysis for a key risk message evaluated the number and percentage of correct responses for each individual question/item included in the key risk message. Confidence intervals (95% CI) were calculated using the exact binomial method around the percentage of correct responses.

Primary analyses were then stratified by questions/characteristics of interest:

1) Those who indicated they both received/had access to and read the Medication Guide and Full Prescribing Information versus those who did not receive/have access to or read the Full Prescribing Information or Medication Guide (Questions 23-26).
2) Medical degree of respondents (Question 36).
3) Whether the survey was completed via the Internet or telephone
4) Time practicing medicine (Question 37).
5) The number of times per month they prescribed TIRF medicines within the last 6 months (Question 33).
6) Respondents practicing in a Closed Healthcare System (Question 38).

Stratified analyses were conducted on all completed surveys.

4.3 Secondary Analyses

As an indicator of the overall level of comprehension of the entire key risk message, descriptive analyses of the number and percentage of responders who answered various proportions of the key risk message questions/items correctly are presented (e.g., the proportion who answered 1 question/item in the key risk message correctly, those who answered 2 questions/items correctly, those who answered 3 questions/items correctly, etc.).

A knowledge score was computed for each key risk message (KRM) and overall as a percentage for each respondent. The score was defined as the ratio of the number of correct responses to all KRM questions to the total number of possible correct responses to all KRM

questions. The average knowledge score was calculated as the mean of the sore across all completed surveys; 95% CIs were calculated based on the normal distribution function.

4.4 Prescriber Report of a Potential Adverse Event, Product Complaint, or Medical Information Request during the Survey

A prescriber may have reported a potential adverse event or other event experienced by a patient while taking a TIRF product either in free text fields while taking the online survey or while in conversation with the SCC Associate. If an event was mentioned to the SCC Associate, the Associate documented the event or complaint, the verbatim response, and the prescriber's contact information, if provided. The prescriber was also informed that a representative from the appropriate TIRF medicine sponsor might contact him/her to obtain additional information about the event. The Internet surveys were monitored for any comments recorded in the free text field. Information on all reports (Internet or telephone) that constituted an adverse event or other event was forwarded to the appropriate TIRF medicine sponsor for processing within 1 business day of awareness of the event as outlined in the Escalating Adverse Events, Product Complaints, and Medical Information Requests Identified During Execution of the Knowledge, Attitudes, and Behavior Survey Project Specific Procedure.

5. RESULTS

Results of the prescriber's responses to questions in the KAB survey are summarized in this section; the full set of summary tables and listings are provided in Appendix B.

5.1 Survey Participants

5.1.1 Survey Participant Administration Results

A total of 2848 prescribers were sent letters inviting them to participate in this survey (Table 1). A total of 8405 reminder letters were sent to non-responders (See Section 3.1 for survey methodology details). Most prescribers received more than 1 reminder letter. At the point of planned survey close date, the prescriber survey had still not met its goal of 300 survey completers; therefore, the survey fielding period was extended in an effort to meet the goal. The survey was closed on 20 December 2016 to allow for inclusion of results in the 17 February 2017 submission. A total of 294 prescribers completed the survey.

From the total of 524 respondents who accessed the survey, 313 prescribers (59.7%) met eligibility criteria, and of those who met eligibility criteria, 294 (93.9%) completed the survey. Of these 294 prescribers, 289 (98.3%) completed the survey online, and 5 (1.7%) completed it by telephone (Table 3).

Based on the TRIG Sponsors interpretation of state laws regarding prescriber reimbursement, respondents whose practices were based in Massachusetts, Vermont, and Minnesota were eligible to participate in the survey. However, they were not eligible to receive the

$125 honorarium. Three respondents who practiced in Massachusetts and 1 respondent who practiced in Minnesota participated in the survey.

Table 1. Survey Administration Statistics

Parameter, n (%)	
Number of invitations distributed	2848
Number of invitations returned as undeliverable	205
Number of reminder letters distributed	8405
All Respondents[1]	524 (19.8)
Eligible Respondents[2]	313 (59.7)
Completed survey[3]	294 (93.9)
Did not complete the survey[3]	19 (6.1)
Respondents not eligible[2], [4]	211 (40.3)

Source: Appendix B: Survey Tables, Table 1.1
[1] Number of unique respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[2] Percentage is based on the number of all respondents.
[3] Percentage is based on the number of eligible respondents.
[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

As shown in Table 2, of the 524 prescribers who accessed the survey, 501 prescribers answered at least 1 survey question and 23 respondents did not answer any of the survey questions (discontinued the survey before answering Question 1). During the screening process it was determined that 185 of the 501 respondents who answered at least 1 survey question were not eligible to participate in the survey because they either indicated they had participated in or did not know whether they participated in a survey about TIRF medicines before (160 respondents); were not enrolled or did not know whether they were enrolled in the TIRF REMS Access program (15 respondents); or indicated they or an immediate family member had worked for a TRIG company, UBC, or FDA in the past or did not know if they or an immediate family member had worked for a TRIG company, UBC, or FDA in the past, or preferred not to answer the question (10 respondents). In addition, 2 of the 501 prescribers who answered at least 1 survey question discontinued the survey at Question 2, and 1 prescriber discontinued at Question 3. Thus, there were 313 eligible participants (Table 2).

Table 2. Survey Participant Eligibility Results - All Respondents

Question	Prescribers (N=524) n (%)
Question 1: Do you agree to participate in this survey?	
Yes	501 (95.6)
No[1]	0
Discontinued	23 (4.4)
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.	
Yes[1]	70 (13.4)
No	339 (64.7)
I don't know[1]	90 (17.2)
Question not asked [2]	0
Discontinued	25 (4.8)
Question 3: Are you enrolled in the TIRF REMS Access program?	
Yes	323 (61.6)
No[1]	7 (1.3)
I don't know[1]	8 (1.5)
Question not asked [2]	160 (30.5)
Discontinued	26 (5.0)
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[3]	
Actavis Laboratories FL, Inc.[1]	0
Anesta LLC[1]	0
BioDelivery Services International, Inc. (BDSI)[1]	0
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	3 (0.6)
Depomed, Inc.[1]	3 (0.6)
Galena Biopharma, Inc.[1]	1 (0.2)
Insys Therapeutics, Inc.[1]	6 (1.1)
Mallinckrodt Pharmaceuticals[1]	1 (0.2)
McKesson Specialty Care Solutions[1]	0
Mylan Inc.[1]	0
Par Pharmaceuticals, Inc.[1]	0
RelayHealth[1]	0
Sentynl Therapeutics, Inc.[1]	0

Table 2. Survey Participant Eligibility Results - All Respondents

Question	Prescribers (N=524) n (%)
Teva Pharmaceuticals, Ltd.[1]	1 (0.2)
United BioSource Corporation[1]	0
FDA[1]	0
None of these apply[4]	313 (59.7)
I don't know[1]	0
Prefer not to answer[1]	2 (0.4)
Question not asked[2]	175 (33.4)
Discontinued	26 (5.0)

Source: Appendix B: Survey Tables, Table 1.2
Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.
[1] Ineligible to participate in the survey.
[2] Question not asked due to termination response from a previous question.
[3] More than one response can be selected, so percentages may not sum to 100%.
[4] Ineligible to participate in the survey if selected additionally to another response.

Prescribers taking the survey online took a mean of 18.91 minutes to complete it, while those taking it by telephone took a mean of 23.90 minutes (Table 3).

Table 3. Time to Complete Survey - Completed Surveys

	Telephone	Internet	Total[1]
Summary Statistic (minutes)			
N	5	289	294
Mean (SD)	23.90 (2.565)	18.91 (10.867)	18.99 (10.797)
Minimum	21.0	5.6	5.6
Median	25.42	16.02	16.17
Maximum	26.4	91.2	91.2
Category, n			
0 to <5 Minutes	0	0	0
5 to <10 Minutes	0	31	31
10 to <15 Minutes	0	95	95
15 to <20 Minutes	0	74	74
20 to <25 Minutes	2	36	38

Table 3. Time to Complete Survey - Completed Surveys

	Telephone	Internet	Total[1]
25 to <30 Minutes	3	22	25
30 Minutes or more	0	31	31

Source: Appendix B: Survey Tables, Table 1.3
[1] Number of eligible prescribers completing the survey.

5.1.2 Description of Eligible Prescribers who Completed the Survey

The demographic characteristics of prescribers who completed the survey are shown in Table 4.

More males than females participated in the survey (59.5% versus 38.8%) and most respondents (98.6%) did not practice within a closed healthcare system. Most respondents had prescribed a TIRF medicine 1 to 2 times per month (63.9%) or 3 to 5 times per month (21.8%) within the 6 months preceding the survey, and of the TIRF medicines prescribed within the last 6 months, Actiq® or generic Actiq® (56.6%) or Subsys® (53.8%) were most frequently prescribed.

Over half of prescribers identified their medical degree as MD (56.8%), and their medical specialty as pain management (58.8%). Most prescribers had practiced medicine for 11 years or longer (60.2%).

Of the survey respondents, 31.6% of respondents were from the West, 30.6% from the South, 21.1% from the Northeast, and 16.3% from the Midwest regions of the US (Table 4).

Table 4. Description of Eligible Prescribers - Completed Surveys

Question	Prescribers (N=294) n (%)
Question 33: On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?	
None	15 (5.1)
1 - 2 times per month	188 (63.9)
3 - 5 times per month	64 (21.8)
More than 5 times per month	21 (7.1)
I don't remember	6 (2.0)

Table 4. Description of Eligible Prescribers - Completed Surveys

Question	Prescribers (N=294) n (%)
Question 34: Please select the TIRF medicines that you have prescribed within the last 6 months. Please select all that apply.[1], [2]	
Abstral®	31 (11.1)
Actiq® or generic Actiq®	158 (56.6)
Fentora®	93 (33.3)
Lazanda®	32 (11.5)
Subsys®	150 (53.8)
N/A (Answered "None" to Question 33)	15
Question 35: What is your gender?	
Male	175 (59.5)
Female	114 (38.8)
Prefer not to answer	5 (1.7)
Question 36: What is your medical degree?	
MD	167 (56.8)
DO	26 (8.8)
Nurse Practitioner	53 (18.0)
Physician Assistant	46 (15.6)
Prefer not to answer	2 (0.7)
Question 37: In total, how many years have you been practicing medicine, since completing your education?	
Less than 3 years	26 (8.8)
3 - 5 years	49 (16.7)
6 - 10 years	42 (14.3)
11 - 15 years	43 (14.6)
More than 15 years	134 (45.6)
Prefer not to answer	0
Question 38: Do you practice in a closed healthcare system, such as: Kaiser, VA, DoD, or NIH?	
Yes	4 (1.4)
No	290 (98.6)

Table 4. Description of Eligible Prescribers - Completed Surveys

Question	Prescribers (N=294) n (%)
Geographic Distribution (based on Question 39 - In which state do you practice?)[3]	
Northeast	62 (21.1)
Midwest	48 (16.3)
South	90 (30.6)
West	93 (31.6)
Other	0
Prefer not to answer	1 (0.3)
Question 40: What is your medical specialty?	
Oncology	45 (15.3)
Primary care	29 (9.9)
Pain management	173 (58.8)
Other (please specify)[4]	46 (15.6)
No designated specialty	1 (0.3)

Source: Appendix B: Survey Tables, Table 2
[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[2] More than one response can be selected, so percentages may not sum to 100%
[3] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.
[4] Verbatim text for the question about medical specialty is presented in Listing 4.

5.1.2.1 Comparison of Survey Respondents to the General Population of TIRF Prescribers

A comparison of prescribers who completed the survey to the general population of prescribers based on REMS switch provider data is provided in Table 5. There were no statistically significant differences ($p<0.05$) observed in the demographics between the prescribers completing the survey compared with the general population of prescribers for questions on average number of times per month TIRF medicines have been prescribed, and geographic region (the only characteristics available from the switch provider data).

Table 5. Comparison of Survey Respondents to General Population of Prescribers (REMS Switch Provider Data)

Question	Prescribers Completing Survey (Self-Report) (N=294) n (%)	Prescribers Completing Survey (REMS Switch Provider Data) (N=294) n (%)	Prescribers of TIRF Medicines in the Past Six Months (REMS Switch Provider Data) (N=3045) n (%)	p-value
Average times per month TIRF medicines have been prescribed within the last 6 months[1]				
None	15 (5.1)	0	0	0.4088
1 - 2 times per month	188 (63.9)	163 (55.4)	1671 (54.9)	
3 - 5 times per month	64 (21.8)	98 (33.3)	951 (31.2)	
More than 5 times per month	21 (7.1)	33 (11.2)	423 (13.9)	
I don't remember	6 (2.0)	*N/A*	*N/A*	
TIRF medicines prescribed within the last 6 months[2]				
Abstral®	31 (11.1)	18 (6.1)	199 (6.5)	
Actiq® or generic Actiq®	158 (56.6)	166 (56.5)	1652 (54.3)	
Fentora®	93 (33.3)	74 (25.2)	824 (27.1)	
Lazanda®	32 (11.5)	30 (10.2)	273 (9.0)	
Subsys®	150 (53.8)	137 (46.6)	1406 (46.2)	
N/A (Answered "None" to Question 33)	15	*N/A*	*N/A*	
Geographic region[3]				
Northeast	62 (21.1)	59 (20.1)	581 (19.1)	0.8942
Midwest	48 (16.3)	48 (16.3)	466 (15.3)	
South	90 (30.6)	107 (36.4)	1116 (36.7)	
West	93 (31.6)	80 (27.2)	882 (29.0)	
Other	0	0	0	

Table 5. Comparison of Survey Respondents to General Population of Prescribers (REMS Switch Provider Data)

Question	Prescribers Completing Survey (Self-Report) (N=294) n (%)	Prescribers Completing Survey (REMS Switch Provider Data) (N=294) n (%)	Prescribers of TIRF Medicines in the Past Six Months (REMS Switch Provider Data) (N=3045) n (%)	p-value
Prefer not to answer	1 (0.3)	*N/A*	*N/A*	

Source: Appendix B: Survey Tables, Table 2b
Note: Switch provider data was provided by McKesson on September 6th, 2016. P-values are based on the REMS switch provider data comparing the survey completers vs. the prescribers of TIRF medicines in the last 6 months.
N/A = Not available.
[1] Based on Question 33.
[2] Based on Question 34.
[3] Based on Question 39; U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.

To provide a more comprehensive comparison of prescribers completing the survey and the general population of prescribers, additional data were obtained through IMS Health. This comparison of prescribers who completed the survey to the general population of prescribers based on IMS data is provided in Table 6.

In this analysis there were statistically significant differences ($p<0.05$) observed in the demographics between the prescribers completing the survey compared with the general population of prescribers on most questions with the exception of geographic distribution of practice location for which characteristics between groups were similar. It is important to note the sample size of the general population of prescribers (N[(b) (4)] affects the power of the test, and therefore, may mean that even small differences between groups resulted in significant p-values. Additionally, since the IMS data is compared to self-reported data, there may be reporting bias. For the questions that showed statistically significant differences between the groups, it is important to review the proportional differences between the groups for each response within a question. For example, there were differences between the prescribers completing the survey and the general population of prescribers for gender (response male; 59.5% vs. 71.2%), medical degree (response MD; 56.8% vs. 70.7%), and number of years practicing medicine (response more than 15 years; 45.6% vs. 61.4%), but the majority of responders in each group selected these responses. In addition, conflicting results were seen for the average prescribing frequency, indicating potential reporting bias. For differences specifically related to specialty, it is difficult to determine whether these are true differences or if this is impacted by reporting bias.

While the differences are statistically significant, these differences should not have a big impact on the primary objectives of the survey since a relevant uniform correlation of demographic characteristics and the knowledge of the key risk messages could not be detected.

Table 6. Comparison of Survey Respondents to General Population of Prescribers

Question	Prescribers Completing Survey (Self-Report) (N=294) n (%)	Prescribers of TIRF Medicines in the Past Six Months (IMS Data)[1] (N=(b) (4) n (%)	p-value
Average times per month TIRF medicines have been prescribed within the last 6 months[2]			
None	15 (5.1)	(b) (4)	<.0001
1 - 2 times per month	188 (63.9)		
3 - 5 times per month	64 (21.8)		
More than 5 times per month	21 (7.1)		
I don't remember	6 (2.0)		
TIRF medicines prescribed within the last 6 months[3]			
Abstral®	31 (11.1)		
Actiq® or generic Actiq®	158 (56.6)		
Fentora®	93 (33.3)		
Lazanda®	32 (11.5)		
Subsys®	150 (53.8)		
N/A (Answered "None" to Question 33)	15		
Gender[4]			
Male	175 (59.5)		0.0002
Female	114 (38.8)		
Prefer not to answer/Unknown	5 (1.7)		
Medical Degree[5]			
MD	167 (56.8)		<.0001
DO	26 (8.8)		
Nurse Practitioner	53 (18.0)		
Physician Assistant	46 (15.6)		
Others	*N/A*		
Prefer not to answer	2 (0.7)		

Table 6. Comparison of Survey Respondents to General Population of Prescribers

Question	Prescribers Completing Survey (Self-Report) (N=294) n (%)	Prescribers of TIRF Medicines in the Past Six Months (IMS Data)[1] (N=(b) (4) n (%)	p-value
Number of Years Practicing Medicine[6]		(b) (4)	
Less than 3 years	26 (8.8)		
3 - 5 years	49 (16.7)		
6 - 10 years	42 (14.3)		<.0001
11 - 15 years	43 (14.6)		
More than 15 years	134 (45.6)		
Prefer not to answer/Unknown	0		
Geographic Distribution of Practice Location[7]			
Northeast	62 (21.1)		
Midwest	48 (16.3)		
South	90 (30.6)		0.4771
West	93 (31.6)		
Other	0		
Prefer not to answer	1 (0.3)		
Medical Specialty[8]			
Oncology	28 (9.5)		
Primary care	24 (8.2)		
Pain management	108 (36.7)		<.0001
Other (please specify)	35 (11.9)		
No designated specialty[9]	0		

Table 6. Comparison of Survey Respondents to General Population of Prescribers

Question	Prescribers Completing Survey (Self-Report) (N=294) n (%)	Prescribers of TIRF Medicines in the Past Six Months (IMS Data)[1] (N(b) (4)) n (%)	p-value
NP/PA	99 (33.7)	(b) (4)	

Source: Appendix B: Survey Tables, Table 2a
Note: P-values are calculated by a chi-square test excluding prefer not to answer, other, and comparable categories. The question regarding TIRF medicine prescriptions filled in the last 6 months directed respondents to "select all that apply"; therefore, p-values were not calculated for the responses to this question.
N/A = Not available.
[1] Based on data from IMS provided on 07Dec2016. Data covered period of 01Mar2016 to 02Sep2016.
[2] Based on Question 33.
[3] Based on Question 34.
[4] Based on Question 35.
[5] Based on Question 36.
[6] Based on Question 37.
[7] Based on Question 39; U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.
[8] Based on Question 36/40. "NP/PA" for the survey data is calculated as the total number of prescribers who responded "Nurse Practitioner" or "Physician Assistant" to Question 36. The other categories for the survey data are based on responses to Question 40, for prescribers who are not categorized as "NP/PA."
[9] IMS data includes Not Applicable, Other Specialty, and Unspecified.

5.1.3 TIRF Medicines Educational Materials

Prescribers were asked about their access to educational materials for TIRF medicines, specifically the Full Prescribing Information and the Medication Guide (Table 7). Almost all prescribers reported they had received or had access to the Full Prescribing Information (96.9%) and the Medication Guide (95.9%). Of those with access to these materials, 87.0% indicated that they had read the Full Prescribing Information and 92.2% indicated that they had read the Medication Guide. Eight prescribers indicated they had questions about the information in the Full Prescribing Information or Medication Guide (provided in Listing 3).

Table 7. Responses to Questions about TIRF Educational Materials - Completed Surveys

Question	Prescribers (N=294) n (%)
Question 23: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?	
Yes	285 (96.9)
No	5 (1.7)
I don't know	4 (1.4)
Question 24: Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe?[1]	
Yes	248 (87.0)
No	31 (10.9)
I don't know	6 (2.1)
N/A (Answered "No" or "I don't know" to Question 23)	9
Question 25: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?	
Yes	282 (95.9)
No	4 (1.4)
I don't know	8 (2.7)
Question 26: Did you read the Medication Guide for the TIRF medicine(s) that you prescribe?[1]	
Yes	260 (92.2)
No	17 (6.0)
I don't know	5 (1.8)
N/A (Answered "No" or "I don't know" to Question 25)	12
Question 27: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?[2]	
Yes	8 (2.7)
No	264 (89.8)
I don't know	22 (7.5)

Source: Appendix B: Survey Tables, Table 4
[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[2] Verbatim text for questions about the Full Prescribing Information or Medication Guide is presented in Listing 3.

Additionally, most prescribers reported reviewing the PPAF with each patient or their caregiver (94.6%); and of those, 97.8% indicated they and the patient/caregiver sign the

PPAF and 89.9% indicated that they give a copy of the PPAF to the patient or the patient's caregiver (Table 8).

Table 8. Responses to Questions about the Patient-Prescriber Agreement Form - Completed Surveys

Question	Prescribers (N=294) n (%)
Question 29: Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?	
Yes	278 (94.6)
No	10 (3.4)
I don't know	6 (2.0)
Question 30: Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her?[1]	
Yes	272 (97.8)
No	2 (0.7)
I don't know	4 (1.4)
N/A (Answered "No" or "I don't know" to Question 29)	16
Question 31: Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?[1]	
Yes	250 (89.9)
No	15 (5.4)
I don't know	13 (4.7)
N/A (Answered "No" or "I don't know" to Question 29)	16

Source: Appendix B: Survey Tables, Table 5
[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

5.2 Key Risk Messages

5.2.1 Key Risk Message 1

Key Risk Message 1 states "TIRF medicines are contraindicated in opioid non-tolerant patients." Fourteen questions/items defined this key risk message (Table 9).

Almost all prescribers knew that patients with cancer who are considered opioid-tolerant are those who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer (94.9%, 95% CI: 91.7 97.1) and are those who are not currently taking opioid therapy are not opioid-tolerant (93.9%, 95% CI: 90.5 96.3). In addition, most understood that cancer patients with no known contraindications to the drug fentanyl, but who are not taking around-the-clock opioid therapy, are not considered opioid tolerant

(92.5%, 95% CI: 88.9 95.3). Nearly all prescribers (96.6%, 95% CI: 93.8 98.4) indicated TIRF medicines should only be taken by patients who are opioid tolerant.

Similarly, most prescribers knew that TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur (91.8%, 95% CI: 88.1 94.7), that death has occurred in opioid non-tolerant patients treated with some fentanyl products (95.6%, 95% CI: 92.6 97.6), and that TIRF medicines may not be used to treat opioid non-tolerant patients (88.4%, 95% CI: 84.2 91.9). In addition, 85.7% (95% CI: 81.2 89.5) of prescribers were aware that starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.

The majority of prescribers were aware of the regimens, taken for one week or longer, that defined an opioid-tolerant patient based on the labeling for TIRF medicines: 8 mg oral hydromorphone/day (71.8%, 95% CI: 66.3 76.8), 60 mg oral morphine/day (95.6%, 95% CI: 92.6 97.6), 30 mg oral oxycodone/day (82.0%, 95% CI: 77.1 86.2), 25 mcg transdermal fentanyl/hour (89.1%; 95% CI: 85.0 92.4), 25 mg oral oxymorphone/day (79.6 %, 95% CI: 74.5 84.0), and an equianalgesic dose of another oral opioid (65.6%, 95% CI: 59.9 71.1).

Table 9. Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Question	Prescribers (N=294) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	
True[2]	279 (94.9) [91.7 - 97.1]
False	11 (3.7)
I don't know	4 (1.4)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before	
True	16 (5.4)
False[2]	276 (93.9) [90.5 - 96.3]
I don't know	2 (0.7)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	
True	17 (5.8)
False[2]	272 (92.5) [88.9 - 95.3]
I don't know	5 (1.7)

Table 9. Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Question	Prescribers (N=294) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	
True[2]	270 (91.8) [88.1 - 94.7]
False	21 (7.1)
I don't know	3 (1.0)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	
True[2]	281 (95.6) [92.6 - 97.6]
False	3 (1.0)
I don't know	10 (3.4)
7c: TIRF medicines may be used to treat opioid non-tolerant patients.	
True	27 (9.2)
False[2]	260 (88.4) [84.2 - 91.9]
I don't know	7 (2.4)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	
True[2]	252 (85.7) [81.2 - 89.5]
False	37 (12.6)
I don't know	5 (1.7)
Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:	
13a: 8 mg oral hydromorphone/day	
True[2]	211 (71.8) [66.3 - 76.8]
False	69 (23.5)
I don't know	14 (4.8)
13b: 60 mg oral morphine/day	
True[2]	281 (95.6) [92.6 - 97.6]
False	6 (2.0)
I don't know	7 (2.4)
13c: 30 mg oral oxycodone/day	
True[2]	241 (82.0) [77.1 - 86.2]

Table 9. Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Question	Prescribers (N=294) n (%) [95% CI][1]
False	44 (15.0)
I don't know	9 (3.1)
13d: 25 mcg transdermal fentanyl/hour	
True[2]	262 (89.1) [85.0 - 92.4]
False	21 (7.1)
I don't know	11 (3.7)
13e: 25 mg oral oxymorphone/day	
True[2]	234 (79.6) [74.5 - 84.0]
False	33 (11.2)
I don't know	27 (9.2)
13f: An equianalgesic dose of another oral opioid	
True[2]	193 (65.6) [59.9 - 71.1]
False	56 (19.0)
I don't know	45 (15.3)
Question 21: Please answer True, False, or I don't know for the following statement about TIRF medicines:	
TIRF medicines should only be taken by patients who are opioid tolerant.	
True[2]	284 (96.6) [93.8 - 98.4]
False	8 (2.7)
I don't know	2 (0.7)

Source: Appendix B: Survey Tables, Table 7.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Overall, 32.7% of prescribers answered all questions/items of key risk message 1 correctly, 58.5% missed no more than 1 item and 71.8% missed no more than 2 items (Table 10).

Table 10. Secondary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys

Correct Responses	Prescribers (N=294) n (%)
0 correct responses	0
1 correct response	0
2 correct responses	0
3 correct responses	1 (0.3)
4 correct responses	0
5 correct responses	1 (0.3)
6 correct responses	1 (0.3)
7 correct responses	4 (1.4)
8 correct responses	9 (3.1)
9 correct responses	16 (5.4)
10 correct responses	23 (7.8)
11 correct responses	28 (9.5)
12 correct responses	39 (13.3)
13 correct responses	76 (25.9)
14 correct responses	96 (32.7)

Source: Appendix B: Survey Tables, Table 7.2

For Key Risk Message 1 Question 13, the analysis stratified by whether the Medication Guide and Full Prescribing Information was received/accessed and read showed an overall trend in favor of respondents who received and read the materials. Of note, the differences for Items 13a and 13c were significant (Table 11). Similarly for Question 13, there was trend toward lower correct response rate for prescribers practicing medicine less than 3 years when stratified by time practicing medicine (Table 12).

No other trends were evident when the results for Key Risk Message 1 were stratified by medical degree of respondents or number of times per month TIRF medicines were prescribed within the last 6 months. For sub-group analysis by modality used to complete the survey (internet versus telephone), and by those practicing in a closed healthcare system, sample sizes were too small to allow for meaningful interpretation (see Appendix B).

Table 11. Responses to Questions Linked to Key Risk Message #1 by Reading Full Prescribing Information or Medication Guide - Completed Surveys (Questions/Items with Apparent Trends)

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
13a: 8 mg oral hydromorphone/day		
True[2]	200 (74.6) [69.0 - 79.7]	11 (42.3) [23.4 - 63.1]
False	57 (21.3)	12 (46.2)
I don't know	11 (4.1)	3 (11.5)
13b: 60 mg oral morphine/day		
True[2]	258 (96.3) [93.2 - 98.2]	23 (88.5) [69.8 - 97.6]
False	6 (2.2)	0
I don't know	4 (1.5)	3 (11.5)
13c: 30 mg oral oxycodone/day		
True[2]	226 (84.3) [79.4 - 88.5]	15 (57.7) [36.9 - 76.6]
False	36 (13.4)	8 (30.8)
I don't know	6 (2.2)	3 (11.5)
13d: 25 mcg transdermal fentanyl/hour		
True[2]	242 (90.3) [86.1 - 93.6]	20 (76.9) [56.4 - 91.0]
False	19 (7.1)	2 (7.7)
I don't know	7 (2.6)	4 (15.4)
13e: 25 mg oral oxymorphone/day		
True[2]	218 (81.3) [76.2 - 85.8]	16 (61.5) [40.6 - 79.8]
False	26 (9.7)	7 (26.9)
I don't know	24 (9.0)	3 (11.5)
13f: An equianalgesic dose of another oral opioid		
True[2]	178 (66.4) [60.4 - 72.0]	15 (57.7) [36.9 - 76.6]
False	52 (19.4)	4 (15.4)
I don't know	38 (14.2)	7 (26.9)

Source: Appendix B: Survey Tables, Table 7.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 12. Responses to Questions Linked to Key Risk Message #1 by Time Practicing Medicine - Completed Surveys (Questions/Items with Apparent Trends)

Question	Time Practicing Medicine			
	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:				
13a: 8 mg oral hydromorphone/day				
True[2]	14 (53.8) [33.4 - 73.4]	35 (71.4) [56.7 - 83.4]	57 (67.1) [56.0 - 76.9]	105 (78.4) [70.4 - 85.0]
False	8 (30.8)	13 (26.5)	22 (25.9)	26 (19.4)
I don't know	4 (15.4)	1 (2.0)	6 (7.1)	3 (2.2)
13b: 60 mg oral morphine/day				
True[2]	23 (88.5) [69.8 - 97.6]	48 (98.0) [89.1 - 99.9]	79 (92.9) [85.3 - 97.4]	131 (97.8) [93.6 - 99.5]
False	0	1 (2.0)	4 (4.7)	1 (0.7)
I don't know	3 (11.5)	0	2 (2.4)	2 (1.5)
13c: 30 mg oral oxycodone/day				
True[2]	17 (65.4) [44.3 - 82.8]	40 (81.6) [68.0 - 91.2]	69 (81.2) [71.2 - 88.8]	115 (85.8) [78.7 - 91.2]
False	6 (23.1)	8 (16.3)	13 (15.3)	17 (12.7)
I don't know	3 (11.5)	1 (2.0)	3 (3.5)	2 (1.5)
13d: 25 mcg transdermal fentanyl/hour				
True[2]	20 (76.9) [56.4 - 91.0]	43 (87.8) [75.2 - 95.4]	79 (92.9) [85.3 - 97.4]	120 (89.6) [83.1 - 94.2]
False	2 (7.7)	4 (8.2)	3 (3.5)	12 (9.0)
I don't know	4 (15.4)	2 (4.1)	3 (3.5)	2 (1.5)

Table 12. Responses to Questions Linked to Key Risk Message #1 by Time Practicing Medicine - Completed Surveys (Questions/Items with Apparent Trends)

Question	Time Practicing Medicine			
	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
13e: 25 mg oral oxymorphone/day				
True[2]	17 (65.4) [44.3 - 82.8]	39 (79.6) [65.7 - 89.8]	68 (80.0) [69.9 - 87.9]	110 (82.1) [74.5 - 88.2]
False	5 (19.2)	8 (16.3)	7 (8.2)	13 (9.7)
I don't know	4 (15.4)	2 (4.1)	10 (11.8)	11 (8.2)
13f: An equianalgesic dose of another oral opioid				
True[2]	12 (46.2) [26.6 - 66.6]	35 (71.4) [56.7 - 83.4]	53 (62.4) [51.2 - 72.6]	93 (69.4) [60.9 - 77.1]
False	6 (23.1)	5 (10.2)	20 (23.5)	25 (18.7)
I don't know	8 (30.8)	9 (18.4)	12 (14.1)	16 (11.9)

Source: Appendix B: Survey Tables, Table 7.1.4
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

5.2.2 Key Risk Message 2

Key Risk Message 2 states "TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain." Ten questions/items defined this key risk message (Table 13).

The majority of prescribers (77.2%, 95% CI: 72.0 81.9) correctly indicated that according to the product labeling, a cancer patient may not start a TIRF medicine and an around-the-clock opioid at the same time, and 78.2% (95% CI: 73.1 82.8) correctly indicated that according to the product labeling, a cancer patient who had been on an around-the-clock opioid for one day may not start taking a TIRF medicine for breakthrough pain.

In addition, 99.3% of prescribers (95% CI:97.6 99.9) were aware that per the approved labeling, TIRF medicines are approved for use in patients with breakthrough pain from cancer, and not for patients with acute or postoperative pain (94.6%, 95% CI: 91.3 96.9), headache or migraine pain (93.9%, 95% CI: 90.5 96.3), dental pain (96.3%, 95% CI: 93.4 98.1), or chronic non-cancer pain (78.2%, 95% CI: 73.1 82.8). The 54 prescribers (18.4%) who stated that per the approved labeling for TIRF medicines, chronic non-cancer pain is an approved indication (Item 9e) were presented with 2 additional questions as requested by FDA. Question 10 addressed the type of chronic pain conditions they prescribe a TIRF medicine to treat (Table 14). The most frequently reported conditions were back pain (16.7%), chronic pain (14.8%), and cancer pain (11.1%). Question 11 addressed the reasons for selecting a TIRF medicine to treat these conditions (Table 15). The most frequently reported reasons were efficacy (24.1%), "I do not treat non-cancer patients" (13.0%), fast onset (11.1%), and that other types of treatments have failed (11.1%). Verbatim responses for Questions 10 and 11 can be found in Listing 1.1 and Listing 2.1, respectively (Appendix B).

Most prescribers (72.1%, 95% CI: 66.6 77.2) correctly indicated that a TIRF medicine should not be prescribed to an adult female with localized breast cancer who just completed a mastectomy and reconstructive surgery and who has persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks (Table 13).

Regarding reviewing the Medication Guide with the patient, a high percentage of prescribers (96.3%, 95% CI: 93.4 98.1) were aware that patients need to be informed that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain; and most (76.5%, 95% CI: 71.3 81.3) correctly indicated that patients should be instructed that if they stop taking their around-the-clock opioid medicine, they cannot continue to take their TIRF medicine.

Table 13. Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Question	Prescribers (N=294) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	
True	52 (17.7)
False[2]	227 (77.2) [72.0 - 81.9]
I don't know	15 (5.1)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	
True	54 (18.4)
False[2]	230 (78.2) [73.1 - 82.8]
I don't know	10 (3.4)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.	
9a: Acute or postoperative pain	
Yes	9 (3.1)
No[2]	278 (94.6) [91.3 - 96.9]
I don't know	7 (2.4)
9b: Headache or migraine pain	
Yes	6 (2.0)
No[2]	276 (93.9) [90.5 - 96.3]
I don't know	12 (4.1)
9c: Dental pain	
Yes	4 (1.4)
No[2]	283 (96.3) [93.4 - 98.1]
I don't know	7 (2.4)
9d: Breakthrough pain from cancer	
Yes[2]	292 (99.3) [97.6 - 99.9]
No	2 (0.7)
I don't know	0

Table 13. Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Question	Prescribers (N=294) n (%) [95% CI][1]
9e: Chronic non-cancer pain	
Yes	54 (18.4)
No[2]	230 (78.2) [73.1 - 82.8]
I don't know	10 (3.4)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	20 (6.8)
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.[2]	212 (72.1) [66.6 - 77.2]
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	18 (6.1)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	27 (9.2)
I don't know	17 (5.8)
Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.	
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	
True[2]	283 (96.3) [93.4 - 98.1]
False	8 (2.7)
I don't know	3 (1.0)
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.	
True	58 (19.7)
False[2]	225 (76.5) [71.3 - 81.3]
I don't know	11 (3.7)

Source: Appendix B: Survey Tables, Table 8.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 14. Types of Chronic Pain Conditions Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=54)[1] n (%)
Question 10: For what type(s) of chronic non-cancer pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?	
Total Number of Responses[2]	80
Back Pain	9 (16.7)
Chronic Pain	8 (14.8)
Cancer Pain	6 (11.1)
Not Applicable	6 (11.1)
Failed Back Syndrome	4 (7.4)
Arachnoiditis	2 (3.7)
Bone Pain	2 (3.7)
Breakthrough Pain	2 (3.7)
Degenerative Disc Disease	2 (3.7)
Failed Spine Surgery	2 (3.7)
Fibromyalgia	2 (3.7)
Neck Pain	2 (3.7)
Neuropathy	2 (3.7)
Orthopedic Pain	2 (3.7)
Post Laminectomy Syndrome	2 (3.7)
Reflex Sympathetic Distrophy	2 (3.7)
Spondylosis	2 (3.7)
AIDS	1 (1.9)
Arthritic Pain	1 (1.9)
Cannot be Categorized	1 (1.9)
Cervicalgia	1 (1.9)
Chronic Regional Pain Syndrome	1 (1.9)
Crohn's Disease	1 (1.9)
Dyspnea	1 (1.9)
Facial Pain	1 (1.9)
Failed Neck Syndrome	1 (1.9)
Headache	1 (1.9)
Intractable Pain	1 (1.9)

Table 14. Types of Chronic Pain Conditions Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=54)[1] n (%)
Knee Pain	1 (1.9)
Multiple Autoimmune Disease	1 (1.9)
Multiple Sclerosis	1 (1.9)
Neuralgia	1 (1.9)
Pancreatitis	1 (1.9)
Peripheral Neuropathic Pain	1 (1.9)
Phantom Limb Pain	1 (1.9)
Polyneuropathy	1 (1.9)
Rheumatoid Arthritis	1 (1.9)
Spinal Stenosis	1 (1.9)
Spine Pain	1 (1.9)
Torticollis	1 (1.9)

Source: Appendix B: Survey Tables, Table 12
[1] Number and percentages are based on the subset of completed surveys where prescribers responded "Yes" to prescribing TIRF medicines for chronic non-cancer pain (*Question 9e: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Chronic Non-Cancer Pain-"Yes"*) and were subsequently presented Question 10 and Question 11.
[2] Total number of responses may exceed the number of prescribers and percentages may not equal 100% as multiple responses were provided by some prescribers.

Table 15. Reasons for Selecting a TIRF Medicine Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=54)[1] n (%)
Question 11: Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?	
Total Number of Responses[2]	62
Efficacy	13 (24.1)
I Do Not Treat Non-Cancer Patients	7 (13.0)
Fast Onset	6 (11.1)
Other Treatments Have Failed	6 (11.1)
Not Applicable	5 (9.3)
Ease of Use	3 (5.6)

Table 15. Reasons for Selecting a TIRF Medicine Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=54)[1] n (%)
Exhausted Other Options	3 (5.6)
Lack of Tolerance of Other Options	3 (5.6)
Medication Was Initiated by Pain Specialist	3 (5.6)
No Reason Provided	3 (5.6)
Dosing Options	2 (3.7)
Patient Preference	2 (3.7)
Convenience	1 (1.9)
Insurance Issues	1 (1.9)
Long Lasting	1 (1.9)
Patient Lack of Tolerance of Other Options	1 (1.9)
Safety	1 (1.9)
Sustained Pain Relief	1 (1.9)

Source: Appendix B: Survey Tables, Table 13
[1] Number and percentages are based on the subset of completed surveys where prescribers responded "Yes" to prescribing TIRF medicines for chronic non-cancer pain (*Question 9e: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Chronic Non-Cancer Pain-"Yes"*) and were subsequently presented Question 10 and Question 11.
[2] Total number of responses may exceed the number of prescribers and percentages may not equal 100% as multiple responses were provided by some prescribers.

Overall, 33.3% of prescribers correctly answered all questions/items of Key Risk Message 2, 64.6% missed no more than 1 item, and 80.3% missed no more than 2 of the 10 items (Table 16).

Table 16. Secondary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Correct Responses	Prescribers (N=294) n (%)
0 correct responses	0
1 correct response	0
2 correct responses	2 (0.7)
3 correct responses	1 (0.3)
4 correct responses	3 (1.0)
5 correct responses	6 (2.0)

Table 16. Secondary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys

Correct Responses	Prescribers (N=294) n (%)
6 correct responses	11 (3.7)
7 correct responses	35 (11.9)
8 correct responses	46 (15.6)
9 correct responses	92 (31.3)
10 correct responses	98 (33.3)

Source: Appendix B: Survey Tables, Table 8.2

For Key Risk Message 2, Item 20c, the analysis stratified by whether the Medication Guide and Full Prescribing Information was received/accessed and read showed a meaningful trend favoring respondents who received and read the materials (Table 17). No other trends were evident when the results for Key Risk Message 2 were stratified by medical degree of respondents, time practicing medicine, or number of times per month TIRF medicines were prescribed within the last 6 months. For sub-group analysis by modality used to complete the survey (internet versus telephone), and by those practicing in a closed healthcare system, sample sizes were too small to allow for meaningful interpretation (see Appendix B).

Table 17. Responses to Questions Linked to Key Risk Message #2 by Reading Full Prescribing Information or Medication Guide - Completed Surveys (Questions/Items with Apparent Trends)

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.		
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.		
True	51 (19.0)	7 (26.9)
False[2]	210 (78.4) [72.9 - 83.1]	15 (57.7) [36.9 - 76.6]
I don't know	7 (2.6)	4 (15.4)

Source: Appendix B: Survey Tables, Table 8.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

5.2.3 Key Risk Message 3

Key Risk Message 3 states "TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics." Ten questions/items defined this key risk message (Table 18).

All prescribers (100.0%, 95% CI: 98.8 100.0) indicated that a personal history of past or current alcohol or drug abuse, or family history of drug use or alcohol abuse is a risk factor for opioid abuse. Almost all prescribers (99.0% 95% CI: 97.0 99.8) were aware that it is important to monitor for signs of abuse and addiction in patients who take TIRF medicines. In addition, most prescribers correctly indicated that a personal history of psychiatric illness is a risk factor for opioid abuse (86.1%, 95% CI: 81.6 89.8), and that TIRF medicines can be abused in a manner similar to other opioid agonists (95.9%, 95% CI: 93.0 97.9).

Almost all prescribers identified misuse (98.6%, 95% CI: 96.6 99.6), abuse (99.0%, 95% CI: 97.0 99.8), addiction (99.0%, 95% CI: 97.0 99.8), and overdose (99.3%, 95% CI: 97.6 99.9) as risks associated with the use of TIRF medicines. Most prescribers also correctly responded that hypothyroidism (78.9%, 95% CI: 73.8 83.4) and infection (86.1%, 95% CI: 81.6 89.8) are not risks associated with the use of TIRF medicines.

Table 18. Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Question	Prescribers (N=294) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	
True[2]	291 (99.0) [97.0 - 99.8]
False	3 (1.0)
I don't know	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a: A personal history of psychiatric illness	
Yes[2]	253 (86.1) [81.6 - 89.8]
No	27 (9.2)
I don't know	14 (4.8)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	
Yes[2]	294 (100.0) [98.8 - 100.0]
No	0
I don't know	0

Table 18. Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Question	Prescribers (N=294) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.	
True[2]	282 (95.9) [93.0 - 97.9]
False	10 (3.4)
I don't know	2 (0.7)
Question 22: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.	
22a: Misuse	
True[2]	290 (98.6) [96.6 - 99.6]
False	4 (1.4)
I don't know	0
22b: Abuse	
True[2]	291 (99.0) [97.0 - 99.8]
False	2 (0.7)
I don't know	1 (0.3)
22c: Addiction	
True[2]	291 (99.0) [97.0 - 99.8]
False	3 (1.0)
I don't know	0
22d: Overdose	
True[2]	292 (99.3) [97.6 - 99.9]
False	2 (0.7)
I don't know	0
22e: Hypothyroidism	
True	20 (6.8)
False[2]	232 (78.9) [73.8 - 83.4]
I don't know	42 (14.3)

Table 18. Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Question	Prescribers (N=294) n (%) [95% CI][1]
22f: Infection	
True	23 (7.8)
False[2]	253 (86.1) [81.6 - 89.8]
I don't know	18 (6.1)

Source: Appendix B: Survey Tables, Table 9.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Overall, 61.2% of prescribers correctly answered all questions/items of Key Risk Message 3, and 85.4% missed no more than 1 of the 10 items (Table 19).

Table 19. Secondary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Correct Responses	Prescribers (N=294) n (%)
0 correct responses	0
1 correct response	0
2 correct responses	0
3 correct responses	0
4 correct responses	0
5 correct responses	1 (0.3)
6 correct responses	2 (0.7)
7 correct responses	7 (2.4)
8 correct responses	33 (11.2)
9 correct responses	71 (24.1)
10 correct responses	180 (61.2)

Source: Appendix B: Survey Tables, Table 9.2

No trends were evident when the results for Key Risk Message 3 were stratified by whether the Medication Guide and Full Prescribing Information was received/accessed and read, medical degree of respondents, time practicing medicine, or number of times per month TIRF medicines were prescribed within the last 6 months. For sub-group analysis by modality used to complete the survey (internet versus telephone), and by those practicing in a

closed healthcare system, sample sizes were too small to allow for meaningful interpretation (see Appendix B).

5.2.4 Key Risk Message 4

Key Risk Message 4 states "TIRF medicines are not interchangeable with each other, regardless of route of administration." Four questions/items defined this key risk message (Table 20).

Almost all prescribers (92.2%; 95% CI: 88.5 95.0) understood TIRF medicines are not interchangeable with each other regardless of the route of administration, 96.3% (95% CI: 93.4 98.1) understood the conversion of one TIRF medicine to another may result in a fatal overdose, and 91.5% (95% CI: 87.7 94.4) understood that dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis. The majority of prescribers (78.6%, 95% CI: 73.4 83.1) correctly indicated that, when a patient wants to change his/her TIRF medicine, the prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

Table 20. Primary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Question	Prescribers (N=294) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12b: TIRF medicines are interchangeable with each other regardless of route of administration.	
True	15 (5.1)
False[2]	271 (92.2) [88.5 - 95.0]
I don't know	8 (2.7)
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	
True[2]	283 (96.3) [93.4 - 98.1]
False	5 (1.7)
I don't know	6 (2.0)
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	
True[2]	269 (91.5) [87.7 - 94.4]
False	11 (3.7)
I don't know	14 (4.8)

Table 20. Primary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Question	Prescribers (N=294) n (%) [95% CI][1]
Question 16: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.	
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	5 (1.7)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	231 (78.6) [73.4 - 83.1]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	25 (8.5)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	21 (7.1)
I don't know.	12 (4.1)

Source: Appendix B: Survey Tables, Table 10.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Overall, 70.1% of prescribers correctly answered all questions/items of Key Risk Message 4; 90.8% missed no more than 1 of the 4 items (Table 21).

Table 21. Secondary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Correct Responses	Prescribers (N=294) n (%)
0 correct responses	2 (0.7)
1 correct response	3 (1.0)
2 correct responses	22 (7.5)
3 correct responses	61 (20.7)
4 correct responses	206 (70.1)

Source: Appendix B: Survey Tables, Table 10.2

For Key Risk Message 4, for Question 16, the analysis stratified by whether the Medication Guide and Full Prescribing Information was received/accessed and read showed a significant difference favoring respondents who received and read the materials (Table 22). No other trends were evident when the results for Key Risk Message 4 were stratified by medical

degree of respondents, time practicing medicine, or number of times per month TIRF medicines were prescribed within the last 6 months. For sub-group analysis by modality used to complete the survey (internet versus telephone), and by those practicing in a closed healthcare system, sample sizes were too small to allow for meaningful interpretation (see Appendix B).

Table 22. Responses to Questions Linked to Key Risk Message #4 by Reading Full Prescribing Information or Medication Guide - Completed Surveys (Questions/Items with Apparent Trends)

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
Question 16: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.		
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	4 (1.5)	1 (3.8)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	217 (81.0) [75.8 - 85.5]	14 (53.8) [33.4 - 73.4]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	20 (7.5)	5 (19.2)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	18 (6.7)	3 (11.5)
I don't know.	9 (3.4)	3 (11.5)

Source: Appendix B: Survey Tables, Table 10.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

5.2.5 Key Risk Message Average Knowledge Scores

Table 23 presents the average knowledge score for each key risk message and an overall knowledge score for all key risk messages combined. The overall knowledge score of 89.1 (95% CI: 88.0 90.2) indicates a high percentage of respondents demonstrated understanding of the key risk messages. The average knowledge score for each of the key risk messages was greater than 86 for all key risk messages.

Table 23. Average Knowledge Scores - Completed Surveys

	Score [95% CI][1]
KRM #1	87.4 [85.8, 89.0]
KRM #2	86.3 [84.6, 88.0]
KRM #3	94.2 [93.2, 95.2]
KRM #4	89.6 [87.5, 91.7]
Overall Knowledge Score	89.1 [88.0, 90.2]

Source: Appendix B: Survey Tables, Table 11
[1] 95% CIs are constructed based on normal distribution function.

5.2.6 Other Survey Questions

5.2.6.1 Additional Questions about TIRF Medicines Safety

Table 24 summarizes the prescribers' responses to additional questions about the safe use of TIRF medicines beyond those associated with the key risk messages.

A high percentage of prescribers (96.9%) correctly indicated a family history of asthma is not a risk factor for opioid abuse.

Most prescribers (90.5%) correctly indicated that for a patient starting titration with a TIRF medicine, they must start with the lowest available dose, unless the product Full Prescribing Information provides specific guidance. When presented with the scenario of a patient who has started titration with the lowest dose of a TIRF medicine, and for whom the breakthrough pain has not been sufficiently relieved after 30 minutes, 70.7% of prescribers correctly responded that they should provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.

In addition, a majority of prescribers (79.9%) correctly indicated use of a TIRF medicine with a CYP3A4 inhibitor may require a dose adjustment, and that the patient needs to be carefully monitored for opioid toxicity to minimize the risk of fatal respiratory depression.

All prescribers (100.0%) understood that patients must be instructed never to share their TIRF medicine with anyone else, even if that person has the same symptoms; and nearly all prescribers surveyed (99.7%) understood that TIRF medicines contain fentanyl in an amount that could be fatal for children of all ages, for individuals for whom they were not prescribed, and for those who are not opioid tolerant.

Table 24. Responses to Additional Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Prescribers (N=294) n (%)
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8c: A family history of asthma	
Yes	4 (1.4)
No[1]	285 (96.9)
I don't know	5 (1.7)
Question 17: A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.	
An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.	19 (6.5)
The dose that the prescriber believes is appropriate based on their clinical experience.	5 (1.7)
The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.[1]	266 (90.5)
The median available dose.	2 (0.7)
I don't know.	2 (0.7)
Question 18: A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? Please pick the best option of the scenarios described.	
Take another (identical) dose of the TIRF medicine immediately.	66 (22.4)
Take a dose of an alternative rescue medicine.	14 (4.8)
Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.[1]	208 (70.7)
Double the dose and take immediately.	5 (1.7)
I don't know.	1 (0.3)
Question 19: A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.	
The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.	17 (5.8)
Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.[1]	235 (79.9)
There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.	1 (0.3)
The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.	8 (2.7)

Table 24. Responses to Additional Questions about the Safe Use of TIRF Medicines - Completed Surveys

Question	Prescribers (N=294) n (%)
I don't know.	33 (11.2)
Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.	
20a: TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.	
True[1]	293 (99.7)
False	0
I don't know	1 (0.3)
20d: Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.	
True[1]	294 (100.0)
False	0
I don't know	0

Source: Appendix B: Survey Tables, Table 3
[1] Correct response.

5.2.6.2 Prescriber Activities When Prescribing TIRF Medicines

Prescribers were asked about specific activities performed when prescribing TIRF medicines (Table 25).

More than half of prescribers indicated they always ask patients (or their caregivers) about the presence of children in the home (61.9%), always instruct patients (or their caregivers) not to share TIRF medicines with anyone else (80.3%), always counsel patients (or their caregivers) that accidental exposure by a child may be fatal (70.7%), always instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children (78.9%), and always instruct patients (or their caregivers) about proper disposal of TIRF medicines (67.0%). In addition, 44.2% of prescribers indicated they always give patients (or their caregivers) the Medication Guide for their TIRF medicine, whereas 44.6% indicated they give it only with the first prescription.

Similarly, over half of prescribers indicated they always talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed (75.9%), instruct the patient on how to use the TIRF medicine that was most recently prescribed (69.4%), and instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed (53.1%).

Table 25. Responses to Questions about the Activities when Prescribing TIRF Medicines - Completed Surveys

Question	Prescribers (N=294) n (%)
Question 14: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.	
14a: Ask patients (or their caregivers) about the presence of children in the home	
Always	182 (61.9)
Only with the first prescription	66 (22.4)
Sometimes	35 (11.9)
Never	10 (3.4)
I don't know	1 (0.3)
14b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	
Always	236 (80.3)
Only with the first prescription	43 (14.6)
Sometimes	14 (4.8)
Never	1 (0.3)
I don't know	0
14c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	
Always	208 (70.7)
Only with the first prescription	55 (18.7)
Sometimes	23 (7.8)
Never	8 (2.7)
I don't know	0
14d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	
Always	232 (78.9)
Only with the first prescription	44 (15.0)
Sometimes	13 (4.4)
Never	5 (1.7)
I don't know	0
14e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	
Always	197 (67.0)
Only with the first prescription	56 (19.0)
Sometimes	34 (11.6)

Table 25. Responses to Questions about the Activities when Prescribing TIRF Medicines - Completed Surveys

Question	Prescribers (N=294) n (%)
Never	7 (2.4)
I don't know	0
14f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine	
Always	130 (44.2)
Only with the first prescription	131 (44.6)
Sometimes	17 (5.8)
Never	15 (5.1)
I don't know	1 (0.3)
Question 32: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.	
32a: Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed.	
Always	223 (75.9)
Only with the first prescription	53 (18.0)
Sometimes	16 (5.4)
Never	0
I don't know	2 (0.7)
32b: Instruct the patient on how to use the TIRF medicine that was most recently prescribed.	
Always	204 (69.4)
Only with the first prescription	67 (22.8)
Sometimes	21 (7.1)
Never	0
I don't know	2 (0.7)
32c: Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed.	
Always	156 (53.1)
Only with the first prescription	102 (34.7)
Sometimes	22 (7.5)
Never	12 (4.1)
I don't know	2 (0.7)

Source: Appendix B: Survey Tables, Table 6

5.3 Spontaneous Reporting of Adverse Events, Product Complaints, or Medical Information Requests

Among all survey respondents (N 524, Table 1), there were 51 reports of a potential adverse event or product complaint associated with the use of TIRF medicines made within the survey free text field during the online survey. No reports were made during the telephone survey. Verbatim statements are provided in Appendix B, Listing 5.

6. DISCUSSION AND CONCLUSIONS

Discussion

Survey invitations (and reminders) were sent to a random sample of prescribers enrolled in the TIRF REMS Access program that had prescribed a TIRF medicine in the last 6 months, a revision to the survey recruitment strategy per FDA request. From the total of 524 respondents who accessed the survey, 313 prescribers met eligibility criteria, and of those who met eligibility criteria, 294 completed the survey.

There were no statistically significant differences observed in the demographics between the prescribers completing the survey compared with the general population of prescribers based on REMS switch provider data (N 3045; Table 5) . There were statistically significant differences observed in the demographics between the prescribers completing the survey compared with the general population of prescribers based on IMS data (N (b) (4) on most questions with the exception of geographic distribution of practice location for which demographics between groups were similar (Table 6). It is important to note the sample size of the general population of prescribers (N (b) (4)) affects the power of the test, and therefore, may mean that even small differences between groups resulted in significant p-values. A significant difference in gender, medical degree, and number of years practicing medicine were noted; however, the majority of responders in each group selected the same responses to these questions. In addition, conflicting results were seen for the average prescribing frequency, indicating potential reporting bias. For differences specifically related to specialty, it is difficult to determine whether these are true differences or if this is impacted by reporting bias. While the differences are statistically significant, these differences should not have a big impact on the primary objectives of the survey since a relevant uniform correlation between demographic characteristics and the knowledge of the key risk messages could not be detected. Therefore, despite these differences, the TRIG concludes that the survey sample of 294 prescribers is a valid representation of the general population of TIRF prescribers.

The overall knowledge score of 89.1 (95% CI: 88.0 90.2) for the survey indicates a high percentage of respondents demonstrated understanding of the key risk messages (Table 23). The average knowledge score for each of the key risk messages was greater than 86 for all key risk messages.

Of the 38 questions/items included as part of key risk messages, 28 questions/items had a correct response rate >80% and 10 questions/items had a correct response rate between 65%

and 80%. None of the questions/items had a correct response rate that fell below the desired level of understanding of 65%.

As previously discussed, the survey was updated prior to launch based on FDA feedback received on 21 July 2016. Nearly all prescribers, correctly responded that misuse, abuse, addiction, and overdose were risks associated with the use of TIRF medicines and TIRF medicines should only be taken by patients who are opioid tolerant (added Question 22 and 21). Over 90% of prescribers correctly responded that per the approved labeling, TIRF medicines are not indicated for acute or postoperative pain, headache or migraine pain, dental pain, but are indicated for breakthrough pain from cancer (revised Question 9). Fewer prescribers, but still the majority, correctly responded that chronic non-cancer pain was not an approved indication for TIRF medicines (revised Question 9). For the added Question 32 (*How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know),* most prescribers selected *always* or *only with the first prescription* for talking to the patient about risks and possible side effects and instructing the patient on how to use and how to store or keep for the TIRF medicine that was most recently prescribed.

The correct response rates from the 12-month KAB survey through the 60-month KAB survey are shown in Table 26. Knowledge and understanding of the key risk message questions has generally remained stable or improved over time. Correct response rates for Items 9a, 9b, 9c, and 9d were similar compared with the 48-month survey; however, Item 9e had a notably improved correct response rate once the question was revised for this survey wave as detailed below:

- Question 9 as presented in the 48-month survey: *In your practice, for which of the following indications do you prescribe TIRF medicines to opioid tolerant patients? Please answer Yes, No, or I don't know for each option*; Item 9e, *chronic non-cancer pain*, correct response "*No*"; correct response rate 64.8%.
- Question 9 as presented in the 60-month survey: *Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option*; Item 9e, *chronic non-cancer pain*, correct response "*No*"; correct response rate 78.2%

There were 54 prescribers (18.4%) who responded "*Yes*" to Item 9e, and these prescribers were presented with 2 additional questions as requested by FDA. Question 10 addressed the type of chronic pain conditions they prescribe a TIRF medicine to treat. The most frequently reported conditions were back pain (16.7%), chronic pain (14.8%), and cancer pain (11.1%). Question 11 addressed the reasons for selecting a TIRF medicine to treat these conditions. The most frequently reported reasons were efficacy (24.1%), "I do not treat non-cancer patients" (13.0%), fast onset (11.1%), and that other types of treatments have failed (11.1%).

Table 26 below includes key risk messages and questions/items within each key risk message as presented in the 60-month survey. It is important to note the question/item numbering, wording, and association with a specific key risk message may have changed across survey

waves based on FDA feedback or other decisions made by the TRIG. A limitation to looking at correct response rates over time is that survey questions may have been modified. The primary focus of this table is to show general trends over time with a specific focus on changes from the 48-month survey to the 60-month survey.

Table 26. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
Key Risk Message 1: TIRF Medicines Are Contraindicated in Opioid Non-Tolerant Patients						
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:					
5a	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer (*Correct Response True*)	7.9[2]	90.4 (86.5, 93.5)	90.0 (86.0, 93.2)	95.2 (92.1 - 97.3)	94.9 (91.7 - 97.1)
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before (*Correct Response False*)	88.7[2]	88.1 (83.9, 91.5)	87.0 (82.7, 90.6)	93.9 (90.6 - 96.3)	93.9 (90.5 - 96.3)
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy (*Correct Response False*)	15.6[2]	82.1 (77.3, 86.3)	86.3 (81.9, 90.0)	86.8 (82.5 - 90.3)	92.5 (88.9 - 95.3)
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose (*Correct Response True*)	87.4 (83.1, 90.9)	87.7 (83.5, 91.2)	86.7 (82.3, 90.3)	90.3 (86.5 - 93.4)	91.8 (88.1 - 94.7)
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products (*Correct Response True*)	95.7 95.7 (92.8, 97.7)	93.7 (90.3, 96.2)	95.7 (92.7, 97.7)	96.1 (93.3 - 98.0)	95.6 (92.6 - 97.6)

Table 26. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
7c	TIRF medicines may be used to treat opioid non-tolerant patients (*Correct Response False*)	82.5 82.5 (77.7, 86.6)	80.1 (75.2, 84.5)	82.0 (77.2, 86.2)	84.8 (80.4 - 88.6)	88.4 (84.2 - 91.9)
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine (*Correct Response True*)	83.1 83.1 (78.4, 87.2)	80.8 (75.9, 85.1)	84.0 (79.4, 88.0)	85.5 (81.1 - 89.2)	85.7 (81.2 - 89.5)
13	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:					
13a	8 mg oral hydromorphone/day (*Correct Response True*)	N/A[3]	68.52	70.32	72.9 (67.6 - 77.8)	71.8 (66.3 - 76.8)
13b	60 mg oral morphine/day (*Correct Response True*)	N/A[3]	89.12	92.32	94.5 (91.4 - 96.8)	95.6 (92.6 - 97.6)
13c	30 mg oral oxycodone/day (*Correct Response True*)	N/A[3]	76.22	78.02	78.7 (73.7 - 83.1)	82.0 (77.1 - 86.2)
13d	25 mcg transdermal fentanyl/hour (*Correct Response True*)	N/A[3]	80.82	83.72	85.5 (81.1 - 89.2)	89.1 (85.0 - 92.4)
13e	25 mg oral oxymorphone/day (*Correct Response True*)	N/A[3]	69.92	74.72	72.3 (66.9 - 77.2)	79.6 (74.5 - 84.0)
13f	An equianalgesic dose of another oral opioid (*Correct Response True*)	N/A[3]	65.92	59.02	67.7 (62.2 - 72.9)	65.6 (59.9 - 71.1)

Table 26. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
21	TIRF medicines should only be taken by patients who are opioid tolerant (*Correct Response True*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	96.6 (93.8 - 98.4)
Key Risk Message 2: TIRF Medicines Are Only Indicated for the Management of Breakthrough Pain in Adult Cancer Patients 18 Years of Age and Older (16 Years of Age and Older for Actiq® Brand and Generic Equivalents) Who Are Already Receiving and Who Are Tolerant to Around-the-Clock Opioid Therapy for Their Underlying, Persistent Cancer Pain						
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
6a	According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time (*Correct Response False*)	N/A[3]	60.6[2]	60.0[2]	69.0 (63.6 - 74.1)	77.2 (72.0 - 81.9)
6b	According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain (*Correct Response False*)	N/A[3]	64.9[2]	70.3[2]	72.9 (67.6 - 77.8)	78.2 (73.1 - 82.8)
9	Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.[1]					
9a	Acute or postoperative pain (*Correct Response No*)	86.4 (82.0, 90.1)	93.0 (89.6, 95.6)	87.3 (83.0, 90.9)	90.3 (86.5 - 93.4)	94.6 (91.3 - 96.9)
9b	Headache or migraine pain (*Correct Response No*)	86.8 86.8 (82.4, 90.4)	92.4 (88.8, 95.1)	89.7 (85.7, 92.9)	94.8 (91.8 - 97.0)	93.9 (90.5 - 96.3)
9c	Dental pain (*Correct Response* No)	96.0 (93.2, 97.9)	96.7 (94.0, 98.4)	97.3 (94.8, 98.8)	98.4 (96.3 - 99.5)	96.3 (93.4 - 98.1)

Table 26. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
9d	Breakthrough pain from cancer (*Correct Response Yes*)	95.4 (92.3, 97.4)	92.4 (88.8, 95.1)	96.0 (93.1, 97.9)	92.9 (89.5 - 95.5)	99.3 (97.6 - 99.9)
9e	Chronic non-cancer pain (*Correct Response No*)	54.3[2]	58.9 (53.2, 64.5)	62.0 (56.2, 67.5)	64.8 (59.2 - 70.2)	78.2 (73.1 - 82.8)
15	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine?					
15b	Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks (*Correct Response*)	54.3[2]	65.9[2]	66.3 (60.7, 71.7)	73.2 (67.9 - 78.1)	72.1 (66.6 - 77.2)
20	Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.					
20b	Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain (*Correct Response True*)	91.7[2]	92.1[2]	90.7[2]	93.9 (90.6 - 96.3)	96.3 (93.4 - 98.1)
20c	Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine (*Correct Response False*)	68.5[2]	57.9[2]	61.0[2]	72.9 (67.6 - 77.8)	76.5 (71.3 - 81.3)

Table 26. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
Key Risk Message 3: TIRF Medicines Contain Fentanyl, an Opioid Agonist and a Schedule II Controlled Substance, with Abuse Liability Similar to other Opioid Analgesics						
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines *(Correct Response True)*	99.7 (98.2, 100.0)	99.0 (97.1, 99.8)	99.7 (98.2, 100.0)	98.7 (96.7 - 99.6)	99.0 (97.0 - 99.8)
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.					
8a	A personal history of psychiatric illness (*Correct Response Yes*)	82.5 (77.7, 86.6)	82.8 (78.0, 86.9)	84.0 (79.4, 88.0)	84.5 (80.0 - 88.4)	86.1 (81.6 - 89.8)
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse (*Correct Response Yes*)	99.3 (97.6, 99.9)	99.0 (97.1, 99.8)	99.7 (98.2, 100.0)	98.7 (96.7 - 99.6)	100.0 (98.8 - 100.0)
12	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
12a	TIRF medicines can be abused in a manner similar to other opioid agonists (*Correct Response True*)	97.7 (95.3, 99.1)	96.4 (93.6, 98.2)	97.3 (94.8, 98.8)	94.2 (91.0 - 96.5)	95.9 (93.0 - 97.9)
22	Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.					
22a	Misuse (*Correct Response True*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	98.6 (96.6 - 99.6)
22b	Abuse (*Correct Response True*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	99.0 (97.0 - 99.8)

Table 26. Correct Response Rate Over Time

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22c	Addiction (*Correct Response True*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	99.0 (97.0 - 99.8)
22d	Overdose (*Correct Response True*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	99.3 (97.6 - 99.9)
22e	Hypothyroidism (*Correct Response False*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	78.9 (73.8 - 83.4)
22f	Infection (*Correct Response False*)	N/A[3]	N/A[3]	N/A[3]	N/A[3]	86.1 (81.6 - 89.8)
Key Risk Message 4: TIRF Medicines Are Not Interchangeable with Each Other, Regardless of Route of Administration						
12	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
12b	TIRF medicines are interchangeable with each other regardless of route of administration (*Correct Response False*)	95.7 (92.8, 97.7)	92.4 (88.8, 95.1)	93.0 (89.5, 95.6)	92.6 (89.1 - 95.2)	92.2 (88.5 - 95.0)
12c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption (*Correct Response True*)	94.7 (91.5, 96.9)	94.7 (91.5, 96.9)	96.7 (94.0, 98.4)	95.5 (92.5 - 97.5)	96.3 (93.4 - 98.1)
12d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis (*Correct Response True*)	90.4 (86.5, 93.5)	90.7 (86.9, 93.8)	90.7 (86.8, 93.7)	90.0 (86.1 - 93.1)	91.5 (87.7 - 94.4)

Table 26. Correct Response Rate Over Time

60-Month Survey Question Number	Questions as Presented in the 60-Month Survey	12-Month Survey Correct/Desired Response % (95% CI)	24-Month Survey Correct/Desired Response % (95% CI)	36-Month Survey Correct/Desired Response % (95% CI)	48-Month Survey Correct/Desired Response % (95% CI)	60-Month Survey Correct/Desired Response % (95% CI)
16	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed?					
16b	The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose (*Correct Response*).	75.5[2]	74.5 (69.2, 79.3)	74.3 (69.0, 79.2)	77.4 (72.4 - 82.0)	78.6 (73.4 - 83.1)

[1] Question was revised for the 60-month survey.

[2] 95% confidence interval is not provided since the item was not part of a key risk message during the reporting period.

[3] Question was not asked during the reporting period.

The analysis stratified by whether the Full Prescribing Information or Medication Guide were received and read (received and read versus did not receive or read) showed a trend of higher correct-response rates for respondents who received and read the materials in some questions/items linked to Key Risk Messages 1, 2, and 4. There was also a trend toward lower correct response rate for prescribers practicing medicine less than 3 years when stratified by time practicing medicine for one item linked to Key Risk Message 1. No trends were evident when the results were stratified by medical degree of respondents or number of times per month TIRF medicines were prescribed within the last 6 months. For sub-group analysis by modality used to complete the survey (internet versus telephone), and by those practicing in a closed healthcare system, sample sizes were too small to allow for meaningful interpretation.

Conclusions

In general, there is an overall trend over time toward maintenance or improvement in prescriber knowledge and understanding of the key risk messages (Table 26). The 60-month survey shows a high level (correct response rate greater than or equal to 65%) of prescriber understanding of key risk messages based on the REMS goals. However, the TRIG acknowledges that there is room for improvement around prescriber knowledge related to conditions for use of a TIRF medicine, TIRF medicine use when stopping their around-the-clock opioid pain medicine, conversion of TIRF medicines, and definition of opioid tolerant.

Appendix A Prescriber Survey Protocol Track Change Document: Comparison of 48-month Survey to 60-month Survey

PROTOCOL TITLE:	**Quantitative Testing of Prescriber Knowledge, Attitudes, and Behavior about Transmucosal Immediate Release Fentanyl (TIRF) Products Safety and Use Information**
SPONSOR:	**TIRF REMS Industry Group (TRIG)** **Actavis Laboratories FL, Inc.** **BioDelivery Sciences International, Inc.** ~~***(BDSI) (replaced Meda Pharmaceuticals on March 11, 2015)***~~**(BDSI)** **Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)** **Depomed, Inc.** ~~**Galena Biopharma, Inc.**~~ **Insys Therapeutics, Inc.** **Mallinckrodt Pharmaceuticals** **Mylan~~,~~ Inc.** **Par ~~Pharmaceutical~~Pharmaceuticals, Inc.** **Sentynl Therapeutics, Inc.**
VERSION:	~~**10**~~**13.0**
DATE:	~~**21AUG2015**~~**04AUG2016**
APPROVED:	~~**FINAL**~~**Final**

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1. LIST OF ABBREVIATIONS

BDSI	BioDelivery Sciences International, Inc.
CATI	Computer-Assisted Telephone Interviewing
CI	Confidence Interval
EDC	Electronic Data Capture
ETASU	Elements to Assure Safe Use
FDA	Food and Drug Administration
HIPAA	Health Insurance Portability and Accountability Act
ISI	Important Safety Information
KAB	Knowledge, Attitudes, and Behavior
PI	Prescribing Information
REMS	Risk Evaluation and Mitigation Strategy
SE PSP	Safety Event Project Specific Procedure
TIRF	Transmucosal Immediate Release Fentanyl
TIRF REMS	TIRF REMS Access ~~Program~~program
TRIG	TIRF REMS Industry Group
UBC	United BioSource Corporation
US	United States

2. BACKGROUND

Transmucosal Immediate Release Fentanyl (TIRF) medicines include the class of immediate-release opioid analgesics that are indicated only for the management of breakthrough pain in cancer patients 18 years of age or older (16 or older for Actiq® and equivalent generics) who are already receiving and tolerant to opioid therapy for their underlying persistent cancer pain. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands. The TIRF REMS Industry Group (TRIG) includes Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. ~~(BDSI) (replaced Meda Pharmaceuticals on March 11, 2015~~(BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; ~~Galena Biopharma, Inc.;~~ Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan Inc.; Par Pharmaceuticals, Inc.; and ~~Par Pharmaceutical~~Sentynl Therapeutics, Inc.

The Food and Drug Administration (FDA) has determined that a class-wide Risk Evaluation and Mitigation Strategy (REMS) is required to mitigate the ~~risk~~risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors with the use of TIRF medicines. The TIRF REMS Access ~~Program~~program (hereafter referred to as TIRF REMS) was approved by the FDA on December 28, 2011.

The TIRF REMS consists of a Medication Guide, Elements to Assure Safe Use (ETASU), an Implementation System, and a Timetable for Submission of Assessments of the REMS. The goals of the TIRF REMS are to mitigate the ~~risk~~risks of misuse, abuse, addiction, overdose, and serious complications due to medication errors by the following:

1. Prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients.
2. Preventing inappropriate conversion between TIRF medicines.
3. Preventing accidental exposure to children and others for whom it was not prescribed.
4. Educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines.

An important component of the TIRF REMS assessment is the conduct of quantitative evaluation surveys to assess prescribers' understanding and knowledge of the safe use and appropriate prescribing of TIRF medicines as described in the TIRF REMS educational materials, ~~enrollment form~~Prescriber Enrollment Form, and Prescribing Information (PI) of each product. This protocol will describe the administration of the surveys that will be conducted among prescribers who are enrolled in the TIRF REMS Access ~~Program~~program. Data from the surveys, together with other REMS evaluation metrics, will be used to determine whether changes need to be made to the REMS processes or educational materials to make them more effective in achieving the goals of the REMS.

The surveys will be implemented so that data will be available for inclusion in the REMS Assessment Reports that will be submitted to the FDA at 12 months after approval of the TIRF REMS and annually thereafter.

3. OBJECTIVES OF THE PRESCRIBER EVALUATION SURVEY

The evaluation survey will use a questionnaire to document the level of knowledge and assess the attitudes and behavior of prescribers around the following key information and risk messages communicated through the REMS:

1. TIRF medicines are contraindicated in opioid non-tolerant patients.
2. TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 or older for Actiq® and equivalent generics) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain.
3. TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.
4. TIRF medicines are not interchangeable with each other, regardless of route of administration.
5. Patients and their caregivers must be instructed that TIRF medicines contain a medicine in an amount that can be fatal in children, in individuals for whom it is not prescribed, and in those who are not opioid tolerant.

The survey will also collect data on behaviors, such as receipt and use of educational materials and compliance with REMS requirements.

4. METHODS

The survey was designed in collaboration between the TRIG and United BioSource Corporation (UBC) and will be administered by UBC.

4.1 Survey Design

This survey will be conducted among a sample of prescribers who are enrolled in the TIRF REMS Access ~~Program.~~program and have prescribed a TIRF medicine in the last 6 months. Respondents who participate in the previous wave of the TIRF survey will not be eligible to participate in subsequent survey waves.

The survey will be administered using the following modalities:

- Self-administered, online through a secure website
- Telephone surveys facilitated by a trained interviewer from the Survey Coordinating Center using a computer-assisted telephone interviewing (CATI) program

The survey will begin with screening questions to confirm respondent eligibility to participate in the survey. Completion of the entire survey is expected to take approximately 20 minutes.

The survey included in Appendix A is written to reflect wording for both methods of survey administration: Internet-based and telephone.

All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium for their time.

4.1.1 Qualitative Research on the Survey

The FDA ~~provided feedback to the TRIG on the Knowledge, Attitudes, and Behaviors (KAB) survey results for prescribers included in the 12-month REMS Assessment results. The FDA~~ requested that the TRIG investigate the causes for the low correct response rates ~~to specific questions in the survey by conducting~~reported in the 12-month REMS Assessment Report. Qualitative research was conducted in 2013 to determine the reasons for the poor performance on these questions, and to assess proposed revised wording to select questions. ~~Qualitative research was performed in 2013 prior to Wave 2 of the survey.~~ Findings were incorporated into the survey and results from the revised survey were included in the 24-month REMS Assessment Report~~,~~.

4.1.2 Questions and Statements on REMS Goals

The KAB questionnaire is made up of multiple-choice, close-ended statements or questions (the majority of which use true/false or yes/no dichotomous response options), and one open-ended question. These questions will evaluate current knowledge, attitudes, and behavior regarding the key risk messages noted in Section 3.

Questions ~~will be~~are presented in several formats:

- Statements or questions asking the respondent to indicate whether a statement or question is true or false, or if they do not know the answer (there is a similar set of statements and questions that use "yes" or "no" as potential response options);
- Statements or questions asking the respondent to choose from a defined list of possible statements or answers; and
- One question allowing for the respondent to list questions about the products or comments.

Questionnaires will be analyzed to determine prescriber understanding of each key risk message.

For statements or questions that use "true" or "yes" vs. "false" or "no" response options, the desired response for key risk messages is generally "true" or "yes" indicating knowledge of, or behavior in accordance with, the objectives of the REMS. However, some questions are formatted to have the respondent disagree with the statement as written by providing response options of "false" or "no" to avoid having the same affirmative answer for all desired responses.

REMS statements, corresponding questions, and desired responses covering the key risk messages are identified below and can be found in the complete survey questionnaire (Appendix A).

Key Risk Message 1: TIRF medicines are contraindicated in opioid non-tolerant patients.		
Question No.	**Question**	**~~Correct Answer~~Desired Response**
5	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	**TRUE**
5b	Who are not currently taking opioid therapy, but have taken opioid therapy before	**FALSE**
5c	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	**FALSE**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	**TRUE**
7b	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	**TRUE**
7c	TIRF medicines may be used to treat opioid non-tolerant patients.	**FALSE**
7d	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	**TRUE**
~~11~~13	Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:	
~~11a~~13a	8 mg oral hydromorphone/day	**TRUE**
~~11b~~13b	60 mg oral morphine/day	**TRUE**
~~11c~~13c	30 mg oral oxycodone/day	**TRUE**
~~11d~~13d	25 mcg transdermal fentanyl/hour	**TRUE**
~~11e~~13e	25 mg oral oxymorphone/day	**TRUE**
~~11f~~13f	An equianalgesic dose of another oral opioid	**TRUE**
21	TIRF medicines should only be taken by patients	**TRUE**

	who are opioid tolerant.	

Key Risk Message 2: TIRF medicines are only indicated for the management of breakthrough pain in adult cancer patients 18 years of age and older (16 years of age and older for Actiq® brand and generic equivalents) who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying, persistent cancer pain.		
Question No.	**Question**	**Desired ~~response~~Response**
6	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a	According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	**FALSE**
6b	According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	**FALSE**
9	~~In your practice~~Per the approved labeling for TIRF medicines, for which of the following ~~indications do you prescribe~~indication(s) are TIRF medicines ~~to opioid tolerant patients~~approved? Please answer Yes, No, or I don't know for each option.	
9a	Acute or postoperative pain	**NO**
9b	Headache or migraine pain	**NO**
9c	Dental pain	**NO**
9d	Breakthrough pain from cancer	**YES**
9e	Chronic non-cancer pain	**NO**
15	The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	**~~15b.~~ Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.**
20	Before initiating treatment with a TIRF medicine, prescribers must review the	

	Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.	
20b	Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	**TRUE**
20c	Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.	**FALSE**

Key Risk Message 3: TIRF medicines contain fentanyl, an opioid agonist and a Schedule II-controlled substance, with abuse liability similar to other opioid analgesics.		
Question No.	**Question**	**~~Correct Answer~~Desired Response**
7	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
8	Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a	A personal history of psychiatric illness	**YES**
8b	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**
12	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12a	TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**
22	Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.	
22a	Misuse	**TRUE**
22b	Abuse	**TRUE**
22c	Addiction	**TRUE**
22d	Overdose	**TRUE**
22e	Hypothyroidism	**FALSE**
22f	Infection	**FALSE**

Key Risk Message 4: TIRF medicines are not interchangeable with each other, regardless of route of administration.		
Question No.	**Question**	**Desired ~~response~~Response**
12	Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12b	TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
12c	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**
12d	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**
16	A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.	**~~16b.~~ The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.**

4.1.3 Additional Questions

The survey includes questions about the requirements of the TIRF REMS Access ~~Program~~program and receipt and understanding of the TIRF educational materials and the Patient-Prescriber Agreement Form. The following question about patient counseling behaviors will be asked ~~after the key risk message questions~~:

Question 14: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.
Ask patients (or their caregivers) about the presence of children in the home
Instruct patients (or their caregivers) not to share TIRF medicines with anyone else
Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal
Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure
Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines
Give patients (or their caregivers) the Medication Guide for their TIRF medicine

Demographic information will be collected at the end of the survey.

4.2 Participant Recruitment

A random sample of prescribers who are enrolled in the TIRF REMS Access ~~Program~~program will be invited to participate via an invitation letter. The text of the sample written invitation to prescribers can be found in Appendix B. If the required number of completed surveys is not achieved within the expected timeframe of approximately one to two weeks after the first mailing, reminder letters will be sent to non-responders from the original sample with subsequent fax, e-mail, or United States (US) Mail follow-up to maximize participation. ~~The distribution within the mailing to the second sample will be adjusted in accordance with the allocation in the original sample.~~ If these efforts do not result in the required number of completed surveys within two to three weeks, then a new sample of prescribers will be randomly selected.

All respondents who complete the survey and who provide their contact information will be mailed a $125 honorarium to thank them for their participation. Prescribers who practice in Vermont, Massachusetts, or Minnesota and complete the survey will not receive compensation. Participants will be informed that prescribers from these states are eligible to participate, but they will not receive compensation for their participation. The mailing will also include a Thank You Letter, a copy of the Important Safety Information (ISI), and a copy of the correct answers to key risk message questions.

4.2.1 Measures to Minimize Bias in the Sample

The sample of prescribers who are invited to participate will be a random sample of all enrolled prescribers. The sample of participating prescribers will be self-selected since respondents will voluntarily respond to the invitation to participate; however, the survey recruitment strategies are intended to recruit a heterogeneous sample of prescribers for participation.

Prescribers will be offered online or telephone options for completing the survey. Multiple modalities for survey data collection allow for wider survey access to a more heterogeneous population.

Respondents will be provided a unique code during the recruitment process and will be asked to provide the unique code to gain access to the online survey or when calling the Survey Coordinating Center. The code will be deactivated after use to minimize the possibility for fraud.

~~5. STUDY POPULATION~~

5. STUDY POPULATION

5.1 Sample Size

A sample of 300 healthcare providers who are enrolled in the TIRF REMS Access ~~Program~~program is proposed for each survey wave. The size of the sample was determined based on both practical and statistical considerations. ~~There is no target comprehension rate specified *a priori*.~~ A sample of 300 completed surveys will allow estimation of the comprehension rate for each risk message with a moderately high degree of precision. The table below shows the precision of the estimates for level of understanding using two-sided 95% confidence intervals (CIs) obtained with the sample size of 300 completed surveys. The noted CIs are used to indicate that for any survey-estimated rate of understanding, the true population rate of understanding is at least as high as the lower limit of the 95% CI and may be as high as the upper limit of the 95% CI.

Table 5.1: Precision of Estimated Rates of Understanding with a Sample Size of 300

Estimated Rate of Understanding	Estimated Confidence Interval	
5%	2.8%	8.1%
10%	6.8%	14.0%
15%	11.2%	19.6%
20%	15.6%	25.0%
25%	20.2%	30.3%
30%	24.9%	35.5%
35%	29.6%	40.7%
40%	34.4%	45.8%
45%	39.3%	50.8%
50%	44.2%	55.8%
55%	49.2%	60.7%
60%	54.2%	65.6%
65%	59.3%	70.4%
70%	64.5%	75.1%
75%	69.7%	79.8%
80%	75.0%	84.4%
85%	80.4%	88.8%
90%	86.0%	93.2%
95%	91.9%	97.2%

5.1.1 Inclusion Criteria

All prescribers who are enrolled in the TIRF REMS Access ~~Program~~program and have prescribed a TIRF medicine in the last 6 months are eligible to participate in this survey, with the exceptions noted below.

5.1.2 Exclusion Criteria

The following respondents are not eligible to participate in the surveys:

- Prescribers who have previously participated in the TIRF REMS KAB survey.
- Prescribers or their immediate family members who have ~~ever worked for~~ ever worked for Actavis Laboratories FL, Inc.; Anesta LLC; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd); Depomed, Inc.; Galena Biopharma, Inc.; Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan~~,~~ Inc.; Par ~~Pharmaceutical~~Pharmaceuticals, Inc.;

Teva Pharmaceuticals, Ltd.; Sentynl Therapeutics, Inc.; UBC; McKesson Specialty Care Solutions; RelayHealth; or the FDA.

~~6. SURVEY PROCESS~~

6. ~~THE SURVEY WILL BEGIN WITH SCREENING QUESTIONS TO CONFIRM RESPONDENT ELIGIBILITY TO PARTICIPATE IN THE SURVEY.~~ SURVEY PROCESS

~~Completion of the entire survey is expected to take approximately 20 minutes.~~

6.1 Screening and Survey Administration

The questionnaire will begin with a screening module with questions to confirm prescriber eligibility. Depending on the answers to the screening questions, survey participation could either be terminated or continued. If ineligible, the respondent is immediately notified with a "thank you" message that survey participation has ended. If eligible, the respondent is allowed to continue survey participation.

The data entry system used for both methods of survey administration has been validated and is secure for receiving and storing survey data. The system is 21 CFR Part 11 and Health Insurance Portability and Accountability Act (HIPAA) compliant. Prescriber-identifying information will be stored separately from survey data.

Completion of the entire survey is expected to take approximately 20 minutes.

6.1.1 Telephone

A trained interviewer from the Survey Coordinating Center will conduct the telephone interviews using a CATI program. The screening and main elements of the questionnaire will be administered sequentially during the same telephone call.

Telephone interviewing allows participation of prescribers who do not have Internet access. It will also be convenient for prescribers to participate since they can call in and be interviewed at their convenience during the specified time period when the Survey Coordinating Center is available.

6.1.2 Internet

An Internet-based survey system will also be used for conducting the KAB surveys. If the prescriber selects to participate in the survey online, he/she will be directed to a secured website to complete screening questions. An Internet survey will be convenient for respondents to participate since they can complete the questionnaire at any time during the survey period.

6.2 Measures to Minimize Bias in the Survey Process

A number of controls will be in place to ensure the survey is conducted in a controlled and professional manner and to minimize bias. For example, a unique code will be given to each

survey participant and the code will be inactivated after use to minimize fraud. Telephone interviewers are highly trained and use a standardized script to administer the survey.

All questions will be programmed to ensure that questions are asked in the appropriate sequence. Skip patterns will be clearly indicated. Respondents cannot go back to a question once the question has been answered and cannot skip ahead. All questions must be answered in order to complete the survey. Response options presented in a list will be randomized to minimize positional bias. Programming will be reviewed by quality control and simulated users (User Acceptance Testing) prior to implementing the survey.

7. ANALYSIS

Information obtained from the survey will be reported as descriptive statistics for the survey administration, study population, and the survey questions. The data from the sample population will be reported using frequency distributions of responses to all questions.

The following will be reported as part of this analysis:

- The number of invitations issued to prescribers
- The number of invitations returned as undeliverable
- The number of reminder letters
- The number of respondents screened for participation
- The number of respondents eligible for participation
- The number of respondents eligible for participation who complete the survey
- Representativeness of prescribers based on geography
- Description of survey participants, including:
  - Gender
  - Medical degree of respondent: MD, DO, NP, PA
  - Medical specialty
  - Years of professional experience
  - How many times per month TIRF medicines were prescribed by the respondent in the last 6 months
  - Geographic region of practice

Additional descriptive statistics may be reported as appropriate.

7.1.1 Analysis Population

The analysis population will be based on eligible prescribers who completed all questions presented to them in the survey ("completers").

7.1.2 Description of Primary Analyses

Primary analyses are done for all key risk messages using data from all completers. The primary analysis for a key risk message evaluates the rate for each correct response to each individual question/item defined by the key risk message. The specific correct response to each question/item is identified in the body of the risk message table.

7.1.3 Description of Secondary Analyses

Secondary analyses are done only for those key risk messages that contain multiple questions/items using data from all completers. The secondary analysis entails a frequency distribution of the number of respondents who got 0, 1, etc. correct responses across the total number of items for the given key risk message.

Mean knowledge scores will be computed for each key risk message; an overall knowledge score will be computed for each respondent.

Additional analyses may be performed as needed.

8. SAFETY EVENT REPORTING

The term '~~Safety Event~~'safety event' is defined as any information reported by a survey respondent that meets the criteria of an adverse event or product complaint. While it is not the intention of the survey to solicit the report of information that meets the criteria of a ~~Safety Event~~safety event, it is possible that a respondent may spontaneously report information that meets this criteria in free text fields of the survey (Internet-based administration) or while in conversation with the Survey Coordinating Center (telephone-based administration). The Internet-based questionnaires will be monitored for any comments recorded in the free text fields. If an event is mentioned to a Survey Coordinating Center Associate, the Associate will document the safety event and the respondent's contact information. Respondents will also be informed that a representative from the appropriate TIRF medicine manufacturer may contact them if there are questions about the survey. Information on all reports (Internet or telephone) that may constitute an adverse event or other safety event will be forwarded to the appropriate TIRF medicine manufacturer as described in the Safety Event Project Specific Procedure (SE PSP). Additional detail regarding processes for adverse event reporting will be specified in the SE PSP.

9. PRIVACY PROTECTION AND CONFIDENTIALITY

All data collected during the survey will be held confidential. The electronic data capture (EDC) system used for data collection encrypts all identifiable information, and respondent identifiers are stored separately from the survey responses.

Respondent names and addresses are collected in order to mail the $125 honorarium, a Thank You Letter, the correct responses to key risk messages, and the ISI after the survey is completed. Respondent contact information is also requested when necessary to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions in addition to instances where a safety event is reported and a TIRF medicine manufacturer must obtain follow-up information (see Section 8 above).

Respondents will be informed when they access the survey that they may be contacted if there are any questions about their survey responses. Respondents will be informed that their answers to the survey questions will not affect their ability to prescribe TIRF medicines.

Appendix A Prescriber Questionnaire

Survey Legend

[PROGRAMMER] is used to indicate directions to the programmer and is set in bold, red, uppercase letters between square brackets.

(INTERVIEWER) is used to indicate directions to the telephone interviewer and is set in bold, blue, text between parentheses. This text appears when content is to be administered by telephone only (for example, spontaneous adverse event reporting).

[ONLINE] indicates a question is worded specifically for administering the survey online.

[PHONE] indicates a question is worded specifically to be read by a telephone interviewer and differs from the online text.

[BEGIN SURVEY CONTENT] and **[END SURVEY CONTENT]** are used to indicate to the programmer the type of survey administration and the beginning and end of the survey or sections within the survey content, for example, **[BEGIN ADVERSE EVENT/PRODUCT COMPLAINT]** and **[END ADVERSE EVENT/PRODUCT COMPLAINT]**.

[TERMINATE] is displayed next to responses that should cause the survey to end. The following termination language will be programmed into the survey or read by the interviewer unless different language is specified with the question.

> *Thank you very much for your time today. Based on your answer, you are not eligible to take this survey. We appreciate your interest in the survey.*

[RANDOMIZE LIST] is inserted before questions to indicate to the programmer that the responses should be randomized. Responses such as "I don't know," "Prefer not to answer" or "None of the above" will always appear at the end of the randomized responses.

Response options for questions that allow multiple responses must be indicated with check boxes (□). At least one option must be selected for the question to be considered answered.

> If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option~~.~~, if applicable.

Response options for questions that allow only one response must be indicated with radio buttons (○).

> If any response option requires text to be collected and does not need another question label, show **[FREE TEXT]** after the response option, if applicable.

[FREE TEXT] indicates to the programmer that one line should be provided for data entry.

Survey Legend

[MULTILINE INPUT] indicates to the programmer that multiple lines should be provided for data entry (for example, two address lines).

[DROP-DOWN LIST INPUT WITH STATES TABLE] indicates to the programmer that the response should be a drop-down list containing the states and US territories in the table below.

Alabama	Georgia	Massachusetts	New York	Tennessee
Alaska	Guam	Michigan	North Carolina	Texas
American Samoa	Hawaii	Minnesota	North Dakota	US Virgin Islands
Arizona	Idaho	Mississippi	Northern Mariana Islands	Utah
Arkansas	Illinois	Missouri	Ohio	Vermont
California	Indiana	Montana	Oklahoma	Virginia
Colorado	Iowa	Nebraska	Oregon	Washington
Connecticut	Kansas	Nevada	Pennsylvania	West Virginia
Delaware	Kentucky	New Hampshire	Puerto Rico	Wisconsin
District of Columbia	Louisiana	New Jersey	Rhode Island	Wyoming
Florida	Maine	New Mexico	South Carolina	
	Maryland		South Dakota	

The following is used to categorize survey populations into standard geographic regions but it is not displayed in the survey.

Geographic Distribution (based on address) [1]: Northeast, Midwest, South, and West regions

Northeast Region

- New England Division - ME, NH, VT, MA, RI, CT
- Middle Atlantic Division - NY, NJ, PA

Midwest Region

- East North Central Division - OH, IN, IL, MI, WI
- West North Central Division - MN, IA, MO, ND, SD, NE, KS

South Region

Survey Legend

- South Atlantic Division - DE, MD, DC, VA, WV, NC, SC, GA, FL
- East South Central Division - KY, TN, AL, MS
- West South Central Division - AR, LA, OK, TX

West

- Mountain Division - MT, ID, WY, CO, NM, AZ, UT, NV
- Pacific Division WA, OR, CA, AK, HI

The following US territories are categorized as **Other**: Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa, and Guam.

[1] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT.

[BEGIN SURVEY CONTENT]

[BEGIN ONLINE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; ~~Galena Biopharma, Inc.;~~ Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan Inc.; Par Pharmaceuticals, Inc.; and ~~Par Pharmaceutical~~Sentynl Therapeutics, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

How We Use Your Information

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send ~~you~~ the honorarium to you after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

How We Protect Your Privacy

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to

allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

How to Learn More about This Survey

If you have questions about the survey, or problems with the survey, please contact the Survey Coordinating Center at 1-877-379-3297. Be sure to write down this telephone number; it will not be displayed again.

Taking the Survey

Once you have answered a question and moved on, you cannot go back and change your answers.

Thank you for your participation in this survey.

[END ONLINE PREAMBLE 1]

[BEGIN PHONE PREAMBLE 1]

Before you begin, we would like to share some important information about this survey. The manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines are conducting this survey, as required by the FDA, to assess prescribers' understanding of the safe use and prescribing of these medicines. These medicines are known as rapid onset opioids and referred to in this survey as "TIRF medicines." **(INTERVIEWER: Say "TIRF" then spell out T-I-R-F)** The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands. The manufacturers of these medicines include Actavis Laboratories FL, Inc.; BioDelivery Sciences International, Inc. (BDSI); Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.); Depomed, Inc.; ~~Galena Biopharma, Inc.;~~ Insys Therapeutics, Inc.; Mallinckrodt Pharmaceuticals; Mylan Inc.; Par Pharmaceuticals, Inc.; and ~~Par Pharmaceutical~~Sentynl Therapeutics, Inc. The survey will take approximately 20 minutes.

There are no known risks to you in taking this survey. You may refuse to take part or withdraw at any time. Your answers to the questions or your decision to take part in the survey will not affect your ability to prescribe TIRF medicines.

Now I would like to read some information about how your contact information will be used.

Your answers to the survey questions will be combined with answers given by other healthcare professionals taking the survey. All answers will be put together and reported in anonymous form to the manufacturers of TIRF medicines. Your name will not be used in any report. If you are eligible to take the survey, complete all the questions, and provide your contact information, you will receive a $125 honorarium for your time and participation. This compensation represents the fair value for your services in connection with completion of the survey. The amount of the compensation was not determined in any manner that takes into account the volume or value of any referrals or business otherwise generated by you.

Your name and address will be used to send ~~you~~ the honorarium to you after you complete the survey. Your personal information will also be used if we have questions about your survey or if we are required to use your information to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. ~~-~~Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Providing a telephone number is optional. Your telephone number will be used only if there are any questions about your survey responses.

Now I would like to tell you some information about how we protect your privacy.

We respect that the privacy of your personal information is important to you. You will not be contacted for marketing purposes based on your personal information or your answers to the survey. Neither the manufacturers of TIRF medicines nor their contractors will sell, transfer, or rent your information. Your answers will be kept strictly confidential. Your personal information will not be used in a manner inconsistent with this document. Your privacy will be protected; however, research survey records may be inspected by the FDA. Your choice to

allow manufacturers of TIRF medicines to use your information is entirely voluntary but necessary to take part in this survey.

Now I will tell you how you can learn more about this survey. Please have a pen or pencil ready to write down a telephone number you can call if you have any questions about the survey. If you have questions about the survey, please ask me at any time. If you have questions at a later time, please contact the Survey Coordinating Center at 1-877-379-3297. Please feel free to ask me to repeat any questions or statements as we go through the survey. Once you have answered a question and moved on, we cannot go back and change your answers. Thank you for your participation in this survey.

[END PHONE PREAMBLE 1]

[BEGIN INCLUSION/EXCLUSION QUESTIONS]

1. Your agreement to participate in this survey confirms mutual understanding in connection with completion of the survey and the fair market value of the payment to be rendered in connection with those services.

   Do you agree to participate in this survey?

   - Yes
   - No **[TERMINATE]**

2. Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.

   - Yes **[TERMINATE]**
   - No
   - I don't know **[TERMINATE]**

3. Are you enrolled in the TIRF REMS Access ~~Program~~program?

   - Yes
   - No **[TERMINATE]**
   - I don't know **[TERMINATE]**

4. Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.

- ☐ Actavis Laboratories FL, Inc. **[TERMINATE]**
- ☐ Anesta LLC **[TERMINATE]**
- ☐ BioDelivery Sciences International, Inc. (BDSI) **[TERMINATE]**
- ☐ Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.) **[TERMINATE]**
- ☐ Depomed, Inc. **[TERMINATE]**
- ☐ Galena Biopharma, Inc. **[TERMINATE]**
- ☐ Insys Therapeutics, Inc. **[TERMINATE]**
- ☐ Mallinckrodt Pharmaceuticals **[TERMINATE]**
- ☐ McKesson Specialty Care Solutions **[TERMINATE]**
- ☐ Mylan~~,~~ Inc. **[TERMINATE]**
- ☐ Par ~~Pharmaceutical~~Pharmaceuticals, Inc. **[TERMINATE]**
- ☐ RelayHealth **[TERMINATE]**
- ☐ Sentynl Therapeutics, Inc. **[TERMINATE]**
- ☐ Teva Pharmaceuticals, Ltd. **[TERMINATE]**
- ☐ United BioSource Corporation **[TERMINATE]**
- ☐ FDA **[TERMINATE]**
- ☐ None of these apply **[IF SELECTED IN ADDITION TO OTHER RESPONSES, TERMINATE]**
- ☐ I don't know **[TERMINATE]**
- ☐ Prefer not to answer **[TERMINATE]**

[END INCLUSION/EXCLUSION QUESTIONS]

5. Please select True, False, or I don't know for each of the following.

   According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
5a.	Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	○	○	○
5b.	Who are not currently taking opioid therapy, but have taken opioid therapy before	○	○	○
5c.	Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	○	○	○

6. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
6a.	According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	○	○	○
6b.	According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	○	○	○

7. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	True	False	I don't know
7a.	TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	○	○	○
7b.	Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	○	○	○
7c.	TIRF medicines may be used to treat opioid non-tolerant patients.	○	○	○
7d.	Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	○	○	○
7e.	It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	○	○	○

8. Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	Yes	No	I don't know
8a.	A personal history of psychiatric illness	○	○	○
8b.	A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	○	○	○
8c.	A family history of asthma	○	○	○

9. ~~In your practice~~Per the approved labeling for TIRF medicines, for which of the following ~~indications do you prescribe~~indication(s) are TIRF medicines ~~to opioid tolerant patients~~approved? Please answer Yes, No, or I don't know for each option.

	[RANDOMIZE LIST]	**Yes**	**No**	**I don't know**
9a.	Acute or postoperative pain	○	○	○
9b.	Headache or migraine pain	○	○	○
9c.	Dental pain	○	○	○
9d.	Breakthrough pain from cancer	○	○	○
9e.	Chronic non-cancer pain	○	○	○

[IF 9E YES, DISPLAY Q10 and Q11 ON SUBSEQUENT PAGES]

10. For what type(s) of chronic non-cancer pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?

[MULTILINE INPUT]

~~11.~~ ~~Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?~~

~~**[MULTILINE INPUT]**~~

11. Why do you select a TIRF medicine to treat these chronic non-cancer pain conditions in patients who are opioid tolerant?

[MULTILINE INPUT]

12. Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
12a.	TIRF medicines can be abused in a manner similar to other opioid agonists.	○	○	○
12b.	TIRF medicines are interchangeable with each other	○	○	○

	regardless of route of administration.			
12c.	The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	○	○	○
12d.	Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	○	○	○

13. Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

		True	False	I don't know
13a.	8 mg oral hydromorphone/day	○	○	○
13b	60 mg oral morphine/day	○	○	○
13c.	30 mg oral oxycodone/day	○	○	○
13d	25 mcg transdermal fentanyl/hour	○	○	○
13e.	25 mg oral oxymorphone/day	○	○	○
13f.	An equianalgesic dose of another oral opioid	○	○	○

14. How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.

	[RANDOMIZE LIST]	Always	Only with the first prescription	Sometimes	Never	I don't know
14a.	Ask patients (or their caregivers) about the presence of children in the home	○	○	○	○	○
14b.	Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	○	○	○	○	○
14c.	Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	○	○	○	○	○
14d.	Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	○	○	○	○	○
14e.	Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	○	○	○	○	○

14f. Give patients (or their caregivers) the Medication Guide for their TIRF medicine	○	○	○	○	○

15. The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.

[RANDOMIZE LIST WITH I DON'T KNOW ALWAYS AT THE END]

- ○ Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.
- ○ Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.
- ○ Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.
- ○ Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.
- ○ I don't know

16. A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.

[RANDOMIZE LIST WITH I DON'T KNOW ALWAYS AT THE END]

- ○ The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.
- ○ The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.
- ○ Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.
- ○ The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.

- I don't know.

17. A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.

[RANDOMIZE LIST WITH I DON'T KNOW ALWAYS AT THE END]

- An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.
- The dose that the prescriber believes is appropriate based on their clinical experience.
- The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.
- The median available dose.
- I don't know.

18. A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? Please pick the best option of the scenarios described.

[RANDOMIZE LIST WITH I DON'T KNOW ALWAYS AT THE END]

- Take another (identical) dose of the TIRF medicine immediately.
- Take a dose of an alternative rescue medicine.
- Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.
- Double the dose and take immediately.
- I don't know.

19. A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.

[RANDOMIZE LIST WITH I DON'T KNOW ALWAYS AT THE END]

- The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.
- Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use

may cause potentially fatal respiratory depression.

- ○ There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.
- ○ The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.
- ○ I don't know.

20. Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.

	[RANDOMIZE LIST]	**True**	**False**	**I don't know**
20a.	TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.	○	○	○
20b.	Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	○	○	○
20c.	Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.	○	○	○
20d.	Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.	○	○	○

21. Please answer True, False, or I don't know for the following statement about TIRF medicines:

TIRF medicines should only be taken by patients who are opioid tolerant.

- ○ True
- ○ False
- ○ I don't know

22. Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.

[RANDOMIZE LIST]	**True**	**False**	**I don't know**
22a. Misuse	○	○	○
22b. Abuse	○	○	○
22c. Addiction	○	○	○
22d. Overdose	○	○	○
22e. Hypothyroidism	○	○	○
22f. Infection	○	○	○

[BEGIN PREAMBLE 2 – DISPLAY ON SAME PAGE AS NEXT QUESTION]

The next set of questions is about the educational materials for TIRF medicines and the TIRF Patient-Prescriber Agreement. As a reminder, the TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys® and generic versions of any of these brands.

[END PREAMBLE 2]

~~21.~~23 Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

- Yes
- ~~No **[GO TO Q23]**~~
- ~~I don't know **[GO TO Q23]**~~
- No **[GO TO Q25]**
- I don't know **[GO TO Q25]**

~~22.~~24 Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe?

- Yes
- No
- I don't know

~~23.~~25 Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?

- Yes
- No **[GO TO Q27]**
- I don't know **[GO TO Q27]**

- ~~No **[GO TO Q25]**~~
- ~~I don't know **[GO TO Q25]**~~

~~24.~~26 Did you read the Medication Guide for the TIRF medicine(s) that you prescribe?

- o Yes
- o No
- o I don't know

~~25.~~27 Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?

- o Yes
- ~~o No **[GO TO Q27]**~~
- ~~o I don't know **[GO TO Q27]**~~
- o No **[GO TO Q29]**
- o I don't know **[GO TO Q29]**

[IF QUESTION ~~26~~27 YES, DISPLAY QUESTION 28 ON SAME PAGE]

~~26. What are your questions? **[MULTILINE INPUT]**~~

28. What are your questions?

[MULTILINE INPUT]

~~27.~~29 Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?

- o Yes
- o No **[GO TO ~~DEMOGRAPHICS PREAMBLE 1~~QUESTION 32]**
- o I don't know **[GO TO ~~DEMOGRAPHICS PREAMBLE 1~~QUESTION 32]**

~~28.~~30 Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her?

- o Yes
- o No
- o I don't know

~~29.~~31 Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?

- o Yes
- o No
- o I don't know

32. How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.

	[RANDOMIZE LIST]	**Always**	**Only with the first prescription**	**Sometimes**	**Never**	**I don't know**
32a.	Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed.	o	o	o	o	o
32b.	Instruct the patient on how to use the TIRF medicine that was most recently prescribed.	o	o	o	o	o
32c.	Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed.	o	o	o	o	o

[BEGIN DEMOGRAPHICS PREAMBLE 1 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

There are just a few more questions to help us combine your answers with other answers we have received.

[END DEMOGRAPHICS PREAMBLE 1]

~~30.~~33 On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?

- o None **[GO TO DEMOGRAPHICS PREAMBLE 2]**
- o 1 2 times per month
- o 3 5 times per month
- o More than 5 times per month
- o I don't remember

31.34 Please select the TIRF medicines that you have prescribed within the last 6 months. Please select all that apply.

- ☐ Abstral®
- ☐ Actiq® or generic Actiq®
- ☐ Fentora®
- ☐ Lazanda®
- ☐ Subsys®

[BEGIN DEMOGRAPHICS PREAMBLE 2 - DISPLAY ON SAME PAGE WITH NEXT QUESTION]

These last few questions are for demographic purposes.

[END DEMOGRAPHICS PREAMBLE 2]

~~32.~~35 What is your gender?

- o Male
- o Female
- o Prefer not to answer

~~33.~~36 What is your medical degree?

- o MD
- o DO
- o Nurse Practitioner
- o Physician Assistant
- o Prefer not to answer

~~34.~~37 In total, how many years have you been practicing medicine, since completing your education?

- o Less than 3 years
- o 3 5 years
- o 6 10 years
- o 11 15 years
- o More than 15 years
- o Prefer not to answer

~~35.~~38 Do you practice in a closed healthcare system, such as: (b) (4) VA, DoD, or NIH?

- o Yes
- o No

~~36.~~39 In which state do you practice?

[DROP-DOWN LIST INPUT WITH STATES TABLE WITH "Prefer not to answer" at END]

~~37.~~40 What is your medical specialty?

- o Oncology
- o Primary care
- o Pain management
- o Other (please specify): **[FREE TEXT]**
- o No designated specialty

[PHONE - BEGIN ADVERSE EVENT/PRODUCT COMPLAINT – KEEP ON ONE PAGE]

(INTERVIEWER: Please record if respondent spontaneously reported an adverse event or product complaint during the course of this interview.)

- o Yes
- o No **[GO TO CLOSING 1]**

Enter Safety Adverse Event Verbatim

[MULTILINE INPUT]

(INTERVIEWER: Indicate to the respondent that someone may call back to ask more questions about the adverse event or product complaint that was reported.)

[END ADVERSE EVENT/PRODUCT COMPLAINT]

[BEGIN CLOSING 1 – KEEP ON ONE PAGE]

We would like to send you a $125 honorarium within the next few weeks to thank you for your time, but we need your name and address to do so. If you do not provide your name and address you will not receive the honorarium for your time and participation in the survey. As a reminder, physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion.

Do you agree to give us your name and mailing address so we can send you the honorarium?

- ○ Yes
- ○ No **[GO TO CLOSING 2]**

FIRST NAME: **[FREE TEXT]**

LAST NAME: **[FREE TEXT]**

ADDRESS: **[MULTILINE INPUT]**

CITY: **[FREE TEXT]**

STATE: **[DROP-DOWN LIST INPUT WITH STATES TABLE]**

ZIP: **[MUST BE 5 NUMERIC CHARACTERS ONLY]**

[END CLOSING 1]

[BEGIN CLOSING 2 – KEEP ON ONE PAGE]

We would also like to ask for your telephone number. Providing your telephone number is optional and it will be used to contact you only if there are questions about your survey responses.

Do you want to provide your telephone number?

○ Yes

○ No **[GO TO CLOSING 3]**

Telephone: **[MUST BE 10-DIGIT NUMERIC-ONLY CHARACTERS]**

[END CLOSING 2]

[BEGIN CLOSING 3]

That ends the survey. Thank you again for your help.

[END CLOSING 3]

[END SURVEY CONTENT]

Appendix B ~~SAMPLE~~ Prescriber ~~Invitation Letter~~Recruitment Materials

INVITATION LETTER

[CURR_DATE]~~———~~

[PRESCRIBER~~-~~_FIRST_NAME]

~~[~~[PRESCRIBER_LAST NAME], [TITLE]
[PRESCRIBER_STREET_ADDR]

~~[~~
[PRESCRIBER_CITY], [PRESCRIBER_STATE] [PRESCRIBER_ZIP]

Dear [PRESCRIBER~~-~~_FULL_NAME~~],~~],

You were selected to receive this letter because you have enrolled in the TIRF REMS Access ~~Program~~program and have prescribed a TIRF medicine in the last 6 months. We are contacting you to invite you to participate in a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess prescribers' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.

The manufacturers of TIRF medicines ~~(collectively referred to as the "TIRF REMS Industry Group")~~ include Actavis Laboratories FL~~,~~ Inc.~~;~~., BioDelivery Sciences International, Inc.~~ (BDSI);~~., Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.~~);~~.), Depomed, Inc.~~; Galena Biopharma, Inc.;~~., Insys Therapeutics, Inc.~~;~~., Mallinckrodt Pharmaceuticals~~;~~, Mylan Inc., Par Pharmaceuticals, Inc., and ~~Par Pharmaceutical~~Sentynl Therapeutics, Inc.~~.~~., (collectively referred to as the "TIRF REMS Industry Group"). These manufacturers are looking for 300 prescribers to complete the survey. Eligible prescribers who complete the survey will be sent a $125 honorarium to thank them for their time. The survey will take 15-20 minutes.

You are not obligated to take part in this survey. If you are interested in participating and to find out if you are eligible:

- Go online* to www.TIRFREMSsurvey.com any time, or
- Call 1-877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to provide this code prior to starting the survey: **[CODE_ID]**.

Please note that you should take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

Your answers will be kept strictly confidential and will be combined with the answers from other prescribers who take this survey. Your name will not be used in the report of this survey and your contact information will only be used to send you a $125 honorarium for the time you took to complete the survey and, if required, to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. ~~Prescribers~~Physicians who practice in Vermont, Massachusetts, or Minnesota should be

aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

~~You are under no obligation to participate in this survey. If you are interested in participating, go to **www.TIRFREMSsurvey.com** anytime or call **1-877-379-3297,** 8AM to 8PM Eastern Time Monday through Friday. You will be asked to give this unique code prior to starting the survey: **[CODE_ID]**.~~

~~* We recommend that you take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.~~

~~Please have this letter with you at the time you take the survey.~~ ~~Thank you in advance for your help with this important effort.~~

Sincerely,

The TIRF REMS Survey Team

1-877-379-3297

www.TIRFREMSsurvey.com

REMINDER LETTER

[CURR_DATE]

[PRESCRIBER_FIRST_NAME] [PRESCRIBER_LAST NAME], [TITLE]
[PRESCRIBER_STREET_ADDR]
[PRESCRIBER_CITY], [PRESCRIBER_STATE] [PRESCRIBER_ZIP]

Dear [PRESCRIBER_FULL_NAME],

Recently you were sent a letter, inviting you to participate in a survey being conducted by the manufacturers of Transmucosal Immediate Release Fentanyl (TIRF) medicines, as required by the Food and Drug Administration (FDA). The purpose of the survey is to assess prescribers' understanding of the safe and appropriate use of these medicines. The TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.

The manufacturers of TIRF medicines include Actavis Laboratories FL Inc., BioDelivery Sciences International, Inc., Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.), Depomed, Inc., Insys Therapeutics, Inc., Mallinckrodt Pharmaceuticals, Mylan Inc., Par Pharmaceuticals, Inc., and Sentynl Therapeutics, Inc., (collectively referred to as the "TIRF REMS Industry Group"). These manufacturers are looking for 300 prescribers to complete the survey. Eligible prescribers who complete the survey will be sent a $125 honorarium to thank them for their time. The survey will take 15-20 minutes.

You are not obligated to take part in this survey. If you are interested in participating and to find out if you are eligible:

- Go online* to www.TIRFREMSsurvey.com any time, or
- Call 1-877-379-3297, 8 a.m. to 8 p.m. Eastern Time, Monday through Friday

Please have this letter with you at the time you take the survey. You will be asked to give this code prior to starting the survey: **[CODE_ID]**.

Please note that you should take the survey on a desktop or laptop computer. Taking the survey on mobile devices, such as smart phones, tablets, and e-notebooks, is not supported.

Your answers will be kept strictly confidential and will be combined with the answers from other prescribers who take this survey. Your name will not be used in the report of this survey and your contact information will only be used to send you a $125 honorarium for the time you took to complete the survey and, if required, to comply with a federal or state law or regulation, including without limitation, reporting payments made to physicians under the federal physician payment sunshine provisions. Physicians who practice in Vermont, Massachusetts, or Minnesota should be aware that they will not be permitted to receive payment for survey completion and may elect not to complete the survey.

Sincerely,

The TIRF REMS Survey Team

1-877-379-3297

www.TIRFREMSsurvey.com

THANK YOU LETTER – HONORARIUM PAYMENT

[CURR_DATE]

[PRESCRIBER_FIRST_NAME] [PRESCRIBER_LAST NAME], [TITLE]
[PRESCRIBER_STREET_ADDR]
[PRESCRIBER_CITY], [PRESCRIBER_STATE] [PRESCRIBER_ZIP]

Dear [PRESCRIBER_FULL_NAME],

On behalf of the TIRF REMS Industry Group, we want to thank you for taking part in the TIRF REMS Survey. To express our appreciation for your valuable time, enclosed is a gift card for $125.

Card Activation Instructions:

To prevent loss, the enclosed card is not activated. Prior to using your card, please call the TIRF REMS Coordinating Center at 1-877-379-3297 between 8:00 a.m. and 8:00 p.m. Eastern Time, Monday through Friday, to activate your card. Please have your card available when you make the call. Also, please read the enclosed Terms and Conditions document before using your gift card as well as the privacy policy that can be found at: http://www.ctpayer.com/downloads/privacy_policy.pdf.

Please note the enclosed card needs to be activated on or before: **xx xxx xxxx**

Additionally, for your information and to reinforce important safety messages about TIRF medicines, we have enclosed the following two documents:

1. A copy of the correct answers to the important survey questions about the TIRF REMS key risk message questions.
2. A copy of the Important Safety Information.

Additional information regarding TIRF REMS Access program can be found at www.TIRFREMSaccess.com.

Thank you for your time and consideration regarding this important safety information.

Sincerely,

The TIRF REMS Survey Team

1-877-379-3297

www.TIRFREMSsurvey.com

Enclosures: Gift Card and Terms and Conditions
Correct Answers to Important Survey Questions
TIRF Important Safety Information

THANK YOU LETTER – NO HONORARIUM PAYMENT

[CURR_DATE]

[PRESCRIBER_FIRST_NAME] [PRESCRIBER_LAST NAME], [TITLE]
[PRESCRIBER_STREET_ADDR]
[PRESCRIBER_CITY], [PRESCRIBER_STATE] [PRESCRIBER_ZIP]

Dear [PRESCRIBER_FULL_NAME],

On behalf of the TIRF REMS Industry Group, we want to thank you for taking part in the TIRF REMS Survey.

For your information and to reinforce important safety messages about TIRF medicines, we have enclosed two documents:

1. A copy of the correct answers to the important survey questions about the TIRF REMS key risk message questions.
2. A copy of the Important Safety Information.

Additional information regarding TIRF REMS Access program can be found at www.TIRFREMSaccess.com.

Thank you for your time and consideration regarding this important safety information.

Sincerely,

The TIRF REMS Survey Team
1-877-379-3297
www.TIRFREMSsurvey.com

Enclosures: Correct Answers to Important Survey Questions
TIRF Important Safety Information

Appendix C Correct Answer Document

Correct Responses to Select PRESCRIBER Survey Questions about Important Safety Messages for Transmucosal Immediate Release Fentanyl (TIRF) medicines (TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands)

Q: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:

STATEMENT	DESIRED RESPONSE
Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	TRUE
Who are not currently taking opioid therapy, but have taken opioid therapy before	FALSE
Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	FALSE

Q: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

STATEMENT	DESIRED RESPONSE
TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	TRUE
Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	TRUE
TIRF medicines may be used to treat opioid non-tolerant patients.	FALSE
Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	TRUE
According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	FALSE
According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a	FALSE

TIRF medicine for breakthrough pain.	

Q: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:

STATEMENT	DESIRED RESPONSE
8 mg oral hydromorphone/day	**TRUE**
60 mg oral morphine/day	**TRUE**
30 mg oral oxycodone/day	**TRUE**
25 mcg transdermal fentanyl/hour	**TRUE**
25 mg oral oxymorphone/day	**TRUE**
An equianalgesic dose of another oral opioid	**TRUE**

Q: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.

STATEMENT	DESIRED RESPONSE
Acute or postoperative pain	**NO**
Headache or migraine pain	**NO**
Dental pain	**NO**
Breakthrough pain from cancer	**YES**
Chronic non-cancer pain	**NO**

Q: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.

A: Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.

Q. Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.

STATEMENT	DESIRED RESPONSE
Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	**TRUE**
Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.	**FALSE**

Q: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.

STATEMENT	DESIRED RESPONSE
It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	**TRUE**
TIRF medicines can be abused in a manner similar to other opioid agonists.	**TRUE**
Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	**TRUE**
TIRF medicines are interchangeable with each other regardless of route of administration.	**FALSE**
The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	**TRUE**

Q: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.

STATEMENT	DESIRED RESPONSE
A personal history of psychiatric illness	**YES**
A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	**YES**

Q: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.

A: The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.

Q: Please answer True, False, or I don't know for the following statement about TIRF medicines:

STATEMENT	DESIRED RESPONSE
TIRF medicines should only be taken by patients who are opioid tolerant.	**TRUE**

Q: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.

STATEMENT	DESIRED RESPONSE
Misuse	**TRUE**
Abuse	**TRUE**
Addiction	**TRUE**
Overdose	**TRUE**
Hypothyroidism	**FALSE**
Infection	**FALSE**

If you have questions or are unclear about any of these responses, please refer to the Full Prescribing Information, the Important Safety Information, and the Medication Guide for TIRF medicines.

Appendix B Survey Tables

Listing 1.1 and Listing 2.1 includes individual responses to Question 10 (*For what type(s) of chronic pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?*), and Question 11 (*Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?*), respectively. Aggregate data for Question 10 is provided in Table 14 and aggregate data for Question 11 is provided in Table 15. The verbatim responses are provided unedited as submitted by the prescriber.

Table 1.1: Survey Administration Statistics	
Parameter, n (%)	
Number of invitations distributed	2848
Number of invitations returned as undeliverable	205
Number of reminder letters distributed	8405
All Respondents[1]	524 (19.8)
Eligible Respondents[2]	313 (59.7)
Completed survey[3]	294 (93.9)
Did not complete the survey[3]	19 (6.1)
Respondents not eligible[2], [4]	211 (40.3)

Source: Appendix B: Survey Tables, Table 1.1
[1] Number of unique respondents who accessed the survey. Percentage is based on the number of invitations distributed excluding the number of invitations returned as undeliverable.
[2] Percentage is based on the number of all respondents.
[3] Percentage is based on the number of eligible respondents.
[4] Number of respondents who did not meet eligibility criteria or did not complete eligibility questions.

Table 1.2: Survey Participant Eligibility Results - All Respondents	
Question	**Prescribers (N=524) n (%)**
Question 1: Do you agree to participate in this survey?	
Yes	501 (95.6)
No[1]	0
Discontinued	23 (4.4)
Question 2: Have you ever taken part in this survey about TIRF medicines before? TIRF medicines include Abstral®, Actiq®, Fentora®, Lazanda®, Subsys®, and generic versions of any of these brands.	
Yes[1]	70 (13.4)
No	339 (64.7)
I don't know[1]	90 (17.2)
Question not asked [2]	0
Discontinued	25 (4.8)
Question 3: Are you enrolled in the TIRF REMS Access program?	
Yes	323 (61.6)
No[1]	7 (1.3)
I don't know[1]	8 (1.5)
Question not asked [2]	160 (30.5)
Discontinued	26 (5.0)
Question 4: Have you or any of your immediate family members ever worked for any of the following companies or agencies? Please select all that apply.[3]	
Actavis Laboratories FL, Inc.[1]	0
Anesta LLC[1]	0
BioDelivery Services International, Inc. (BDSI)[1]	0
Cephalon, Inc. (a wholly-owned subsidiary of Teva Pharmaceutical Industries, Ltd.)[1]	3 (0.6)
Depomed, Inc.[1]	3 (0.6)
Galena Biopharma, Inc.[1]	1 (0.2)
Insys Therapeutics, Inc.[1]	6 (1.1)
Mallinckrodt Pharmaceuticals[1]	1 (0.2)
McKesson Specialty Care Solutions[1]	0
Mylan Inc.[1]	0

Table 1.2: Survey Participant Eligibility Results - All Respondents	
Question	**Prescribers (N=524) n (%)**
Par Pharmaceuticals, Inc.[1]	0
RelayHealth[1]	0
Sentynl Therapeutics, Inc.[1]	0
Teva Pharmaceuticals, Ltd.[1]	1 (0.2)
United BioSource Corporation[1]	0
FDA[1]	0
None of these apply[4]	313 (59.7)
I don't know[1]	0
Prefer not to answer[1]	2 (0.4)
Question not asked [2]	175 (33.4)
Discontinued	26 (5.0)

Source: Appendix B: Survey Tables, Table 1.2
Note: Respondents who discontinued the survey before completing all eligibility questions without being identified as ineligible in any of the previous questions are counted as discontinued. Once a respondent is counted as discontinued, they will count as discontinued in all subsequent eligibility questions.
[1] Ineligible to participate in the survey.
[2] Question not asked due to termination response from a previous question.
[3] More than one response can be selected, so percentages may not sum to 100%.
[4] Ineligible to participate in the survey if selected additionally to another response.

Table 1.3: Time to Complete Survey - Completed Surveys			
	Telephone	**Internet**	**Total[1]**
Summary Statistic (minutes)			
N	5	289	294
Mean (SD)	23.90 (2.565)	18.91 (10.867)	18.99 (10.797)
Minimum	21.0	5.6	5.6
Median	25.42	16.02	16.17
Maximum	26.4	91.2	91.2
Category, n			
0 to <5 Minutes	0	0	0
5 to <10 Minutes	0	31	31
10 to <15 Minutes	0	95	95
15 to <20 Minutes	0	74	74
20 to <25 Minutes	2	36	38
25 to <30 Minutes	3	22	25
30 Minutes or more	0	31	31

Source: Appendix B: Survey Tables, Table 1.3
[1] Number of eligible prescribers completing the survey.

Table 2: Description of Eligible Prescribers - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
Question 33: On average, how many times per month have you prescribed the TIRF medicines within the last 6 months?	
None	15 (5.1)
1 - 2 times per month	188 (63.9)
3 - 5 times per month	64 (21.8)
More than 5 times per month	21 (7.1)
I don't remember	6 (2.0)
Question 34: Please select the TIRF medicines that you have prescribed within the last 6 months. Please select all that apply.[1], [2]	
Abstral®	31 (11.1)
Actiq® or generic Actiq®	158 (56.6)
Fentora®	93 (33.3)
Lazanda®	32 (11.5)
Subsys®	150 (53.8)
N/A (Answered "None" to Question 33)	15
Question 35: What is your gender?	
Male	175 (59.5)
Female	114 (38.8)
Prefer not to answer	5 (1.7)
Question 36: What is your medical degree?	
MD	167 (56.8)
DO	26 (8.8)
Nurse Practitioner	53 (18.0)
Physician Assistant	46 (15.6)
Prefer not to answer	2 (0.7)
Question 37: In total, how many years have you been practicing medicine, since completing your education?	
Less than 3 years	26 (8.8)
3 - 5 years	49 (16.7)
6 - 10 years	42 (14.3)

Table 2: Description of Eligible Prescribers - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
11 - 15 years	43 (14.6)
More than 15 years	134 (45.6)
Prefer not to answer	0
Question 38: Do you practice in a closed healthcare system, such as: Kaiser, VA, DoD, or NIH?	
Yes	4 (1.4)
No	290 (98.6)
Geographic Distribution (based on Question 39 - In which state do you practice?)[3]	
Northeast	62 (21.1)
Midwest	48 (16.3)
South	90 (30.6)
West	93 (31.6)
Other	0
Prefer not to answer	1 (0.3)
Question 40: What is your medical specialty?	
Oncology	45 (15.3)
Primary care	29 (9.9)
Pain management	173 (58.8)
Other (please specify)[4]	46 (15.6)
No designated specialty	1 (0.3)

Source: Appendix B: Survey Tables, Table 2
[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[2] More than one response can be selected, so percentages may not sum to 100%
[3] U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.
[4] Verbatim text for the question about medical specialty is presented in Listing 4.

Table 2a: Comparison of Survey Respondents to General Population of Prescribers			
Question	**Prescribers Completing Survey (Self-Report) (N=294) n (%)**	**Prescribers of TIRF Medicines in the Past Six Months (IMS Data)[1] (N=(b) (4)) n (%)**	**p-value**
Average times per month TIRF medicines have been prescribed within the last 6 months[2]			
None	15 (5.1)	(b) (4)	
1 - 2 times per month	188 (63.9)		
3 - 5 times per month	64 (21.8)		
More than 5 times per month	21 (7.1)		<.0001
I don't remember	6 (2.0)		
TIRF medicines prescribed within the last 6 months[3]			
Abstral®	31 (11.1)		
Actiq® or generic Actiq®	158 (56.6)		
Fentora®	93 (33.3)		
Lazanda®	32 (11.5)		
Subsys®	150 (53.8)		
N/A (Answered "None" to Question 33)	15		
Gender[4]			
Male	175 (59.5)		
Female	114 (38.8)		0.0002
Prefer not to answer/Unknown	5 (1.7)		
Medical Degree[5]			
MD	167 (56.8)		
DO	26 (8.8)		
Nurse Practitioner	53 (18.0)		
Physician Assistant	46 (15.6)		
Others	*N/A*		<.0001
Prefer not to answer	2 (0.7)		
Number of Years Practicing Medicine[6]			
Less than 3 years	26 (8.8)		

Data Source: ADPQ, ADTQ, IMFPRE33, IMFPRE34, IMFPRE35, IMFPRE36, IMFPRE37, IMFPRE40, IMFPREG
Program: TDESCIMS.SAS

Table 2a: Comparison of Survey Respondents to General Population of Prescribers			
Question	**Prescribers Completing Survey (Self-Report) (N=294) n (%)**	**Prescribers of TIRF Medicines in the Past Six Months (IMS Data)[1] (N=(b) (4)) n (%)**	**p-value**
3 - 5 years	49 (16.7)	(b) (4)	
6 - 10 years	42 (14.3)		
11 - 15 years	43 (14.6)		
More than 15 years	134 (45.6)		<.0001
Prefer not to answer/Unknown	0		
Geographic Distribution of Practice Location[7]			
Northeast	62 (21.1)		
Midwest	48 (16.3)		
South	90 (30.6)		
West	93 (31.6)		
Other	0		0.4771
Prefer not to answer	1 (0.3)		
Medical Specialty[8]			
Oncology	28 (9.5)		
Primary care	24 (8.2)		
Pain management	108 (36.7)		
Other (please specify)	35 (11.9)		
No designated specialty[9]	0		

Data Source: ADPQ, ADTQ, IMFPRE33, IMFPRE34, IMFPRE35, IMFPRE36, IMFPRE37, IMFPRE40, IMFPREG
Program: TDESCIMS.SAS

Table 2a: Comparison of Survey Respondents to General Population of Prescribers			
Question	Prescribers Completing Survey (Self-Report) (N=294) n (%)	Prescribers of TIRF Medicines in the Past Six Months (IMS Data)[1] (N(b) (4)) n (%)	p-value
NP/PA	99 (33.7)	(b) (4)	<.0001

Source: Appendix B: Survey Tables, Table 2a
Note: P-values are calculated by a chi-square test excluding prefer not to answer, other, and comparable categories.The question regarding TIRF medicine prescriptions filled in the last 6 months directed respondents to "select all that apply"; therefore, p-values were not calculated for the responses to this question.
N/A = Not available.
[1] Based on data from IMS provided on 07Dec2016. Data covered period of 01Mar2016 to 02Sep2016.
[2] Based on Question 33.
[3] Based on Question 34.
[4] Based on Question 35.
[5] Based on Question 36.
[6] Based on Question 37.
[7] Based on Question 39; U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.
[8] Based on Question 36/40. "NP/PA" for the survey data is calculated as the total number of prescribers who responded "Nurse Practitioner" or "Physician Assistant" to Question 36. The other categories for the survey data are based on responses to Question 40, for prescribers who are not categorized as "NP/PA."
[9] IMS data includes Not Applicable, Other Specialty, and Unspecified.

Table 2b: Comparison of Survey Respondents to General Population of Prescribers (REMS Switch Provider Data)

Question	Prescribers Completing Survey (Self-Report) (N=294) n (%)	Prescribers Completing Survey (REMS Switch Provider Data) (N=294) n (%)	Prescribers of TIRF Medicines in the Past Six Months (REMS Switch Provider Data) (N=3045) n (%)	p-value
Average times per month TIRF medicines have been prescribed within the last 6 months[1]				
None	15 (5.1)	0	0	
1 - 2 times per month	188 (63.9)	163 (55.4)	1671 (54.9)	
3 - 5 times per month	64 (21.8)	98 (33.3)	951 (31.2)	
More than 5 times per month	21 (7.1)	33 (11.2)	423 (13.9)	0.4088
I don't remember	6 (2.0)	*N/A*	*N/A*	
TIRF medicines prescribed within the last 6 months[2]				
Abstral®	31 (11.1)	18 (6.1)	199 (6.5)	
Actiq® or generic Actiq®	158 (56.6)	166 (56.5)	1652 (54.3)	
Fentora®	93 (33.3)	74 (25.2)	824 (27.1)	
Lazanda®	32 (11.5)	30 (10.2)	273 (9.0)	
Subsys®	150 (53.8)	137 (46.6)	1406 (46.2)	
N/A (Answered "None" to Question 33)	15	*N/A*	*N/A*	
Geographic region[3]				
Northeast	62 (21.1)	59 (20.1)	581 (19.1)	
Midwest	48 (16.3)	48 (16.3)	466 (15.3)	
South	90 (30.6)	107 (36.4)	1116 (36.7)	
West	93 (31.6)	80 (27.2)	882 (29.0)	
Other	0	0	0	0.8942

Table 2b: Comparison of Survey Respondents to General Population of Prescribers (REMS Switch Provider Data)

Question	Prescribers Completing Survey (Self-Report) (N=294) n (%)	Prescribers Completing Survey (REMS Switch Provider Data) (N=294) n (%)	Prescribers of TIRF Medicines in the Past Six Months (REMS Switch Provider Data) (N=3045) n (%)	p-value
Prefer not to answer	1 (0.3)	*N/A*	*N/A*	

Source: Appendix B: Survey Tables, Table 2b
Note: Switch provider data was provided by McKession on September 6th, 2016. P-values are based on the REMS switch provider data comparing the survey completers vs. the prescribers of TIRF medicines in the last 6 months.
N/A = Not available.
[1] Based on Question 33.
[2] Based on Question 34.
[3] Based on Question 39; U.S. Census Bureau, last revised Friday, 27-Jul-2001 12:59:43 EDT., Geography Division. Northeast includes CT, MA, ME, NH, NJ, NY, PA, RI, and VT. Midwest includes IA, IL, IN, KS, MI, MN, MO, ND, NE, OH, SD, and WI. South includes AL, AR, DC, DE, FL, GA, KY, LA, MD, MS, NC, OK, SC, TN, TX, VA, and WV. West includes AK, AZ, CA, CO, HI, ID, MT, NM, NV, OR, UT, WA, and WY. Other includes Puerto Rico, Northern Mariana Islands, US Virgin Islands, American Samoa and Guam.

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	
True[1]	279 (94.9)
False	11 (3.7)
I don't know	4 (1.4)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before	
True	16 (5.4)
False[1]	276 (93.9)
I don't know	2 (0.7)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	
True	17 (5.8)
False[1]	272 (92.5)
I don't know	5 (1.7)
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	
True	52 (17.7)
False[1]	227 (77.2)
I don't know	15 (5.1)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	
True	54 (18.4)
False[1]	230 (78.2)
I don't know	10 (3.4)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	
True[1]	270 (91.8)
False	21 (7.1)
I don't know	3 (1.0)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	
True[1]	281 (95.6)
False	3 (1.0)
I don't know	10 (3.4)
7c: TIRF medicines may be used to treat opioid non-tolerant patients.	
True	27 (9.2)
False[1]	260 (88.4)
I don't know	7 (2.4)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	
True[1]	252 (85.7)
False	37 (12.6)
I don't know	5 (1.7)
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	
True[1]	291 (99.0)
False	3 (1.0)
I don't know	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a: A personal history of psychiatric illness	
Yes[1]	253 (86.1)
No	27 (9.2)
I don't know	14 (4.8)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
Yes[1]	294 (100.0)
No	0
I don't know	0
8c: A family history of asthma	
Yes	4 (1.4)
No[1]	285 (96.9)
I don't know	5 (1.7)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.	
9a: Acute or postoperative pain	
Yes	9 (3.1)
No[1]	278 (94.6)
I don't know	7 (2.4)
9b: Headache or migraine pain	
Yes	6 (2.0)
No[1]	276 (93.9)
I don't know	12 (4.1)
9c: Dental pain	
Yes	4 (1.4)
No[1]	283 (96.3)
I don't know	7 (2.4)
9d: Breakthrough pain from cancer	
Yes[1]	292 (99.3)
No	2 (0.7)
I don't know	0
9e: Chronic non-cancer pain	
Yes[2]	54 (18.4)
No[1]	230 (78.2)
I don't know	10 (3.4)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.	
True[1]	282 (95.9)
False	10 (3.4)
I don't know	2 (0.7)
12b: TIRF medicines are interchangeable with each other regardless of route of administration.	
True	15 (5.1)
False[1]	271 (92.2)
I don't know	8 (2.7)
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	
True[1]	283 (96.3)
False	5 (1.7)
I don't know	6 (2.0)
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	
True[1]	269 (91.5)
False	11 (3.7)
I don't know	14 (4.8)
Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:	
13a: 8 mg oral hydromorphone/day	
True[1]	211 (71.8)
False	69 (23.5)
I don't know	14 (4.8)
13b: 60 mg oral morphine/day	
True[1]	281 (95.6)
False	6 (2.0)
I don't know	7 (2.4)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
13c: 30 mg oral oxycodone/day	
True[1]	241 (82.0)
False	44 (15.0)
I don't know	9 (3.1)
13d: 25 mcg transdermal fentanyl/hour	
True[1]	262 (89.1)
False	21 (7.1)
I don't know	11 (3.7)
13e: 25 mg oral oxymorphone/day	
True[1]	234 (79.6)
False	33 (11.2)
I don't know	27 (9.2)
13f: An equianalgesic dose of another oral opioid	
True[1]	193 (65.6)
False	56 (19.0)
I don't know	45 (15.3)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	20 (6.8)
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.[1]	212 (72.1)
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	18 (6.1)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	27 (9.2)
I don't know	17 (5.8)

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
Question 16: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.	
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	5 (1.7)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[1]	231 (78.6)
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	25 (8.5)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	21 (7.1)
I don't know.	12 (4.1)
Question 17: A patient is starting titration with a TIRF medicine. What dose must they start with? Please select one option.	
An appropriate dose based on the dose of the opioid medicine used for underlying persistent cancer pain.	19 (6.5)
The dose that the prescriber believes is appropriate based on their clinical experience.	5 (1.7)
The lowest available dose, unless individual product Full Prescribing Information provides product-specific guidance.[1]	266 (90.5)
The median available dose.	2 (0.7)
I don't know.	2 (0.7)
Question 18: A prescriber has started titrating a patient with the lowest dose of a TIRF medicine. However, after 30 minutes the breakthrough pain has not been sufficiently relieved. What should they advise the patient to do? Please pick the best option of the scenarios described.	
Take another (identical) dose of the TIRF medicine immediately.	66 (22.4)
Take a dose of an alternative rescue medicine.	14 (4.8)
Provide guidance based on the product-specific Medication Guide because the instructions are not the same for all TIRF medicines.[1]	208 (70.7)
Double the dose and take immediately.	5 (1.7)
I don't know.	1 (0.3)
Question 19: A patient is taking a TIRF medicine and the doctor would like to prescribe erythromycin, a CYP3A4 inhibitor. Please pick the best option of the scenarios described.	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
The patient can't be prescribed erythromycin, because using it at the same time as a TIRF medicine could be fatal.	17 (5.8)
Use of a TIRF medicine with a CYP3A4 inhibitor may require a dosage adjustment; carefully monitor the patient for opioid toxicity, otherwise such use may cause potentially fatal respiratory depression.[1]	235 (79.9)
There is no possible drug interaction between CYP3A4 inhibitors and TIRF medicines.	1 (0.3)
The dose of the TIRF medicine must be reduced by one half if a CYP3A4 inhibitor is prescribed in the same patient.	8 (2.7)
I don't know.	33 (11.2)
Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.	
20a: TIRF medicines contain fentanyl in an amount that could be fatal to children of all ages, in individuals for whom they were not prescribed, and in those who are not opioid tolerant.	
True[1]	293 (99.7)
False	0
I don't know	1 (0.3)
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	
True[1]	283 (96.3)
False	8 (2.7)
I don't know	3 (1.0)
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.	
True	58 (19.7)
False[1]	225 (76.5)
I don't know	11 (3.7)
20d: Instruct patients to never share their TIRF medicine with anyone else, even if that person has the same symptoms.	
True[1]	294 (100.0)
False	0
I don't know	0

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
Question 21: Please answer True, False, or I don't know for the following statement about TIRF medicines:	
TIRF medicines should only be taken by patients who are opioid tolerant.	
True[1]	284 (96.6)
False	8 (2.7)
I don't know	2 (0.7)
Question 22: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.	
22a: Misuse	
True[1]	290 (98.6)
False	4 (1.4)
I don't know	0
22b: Abuse	
True[1]	291 (99.0)
False	2 (0.7)
I don't know	1 (0.3)
22c: Addiction	
True[1]	291 (99.0)
False	3 (1.0)
I don't know	0
22d: Overdose	
True[1]	292 (99.3)
False	2 (0.7)
I don't know	0
22e: Hypothyroidism	
True	20 (6.8)
False[1]	232 (78.9)
I don't know	42 (14.3)
22f: Infection	

Table 3: Responses to All Questions about the Safe Use of TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
True	23 (7.8)
False[1]	253 (86.1)
I don't know	18 (6.1)

Source: Appendix B: Survey Tables, Table 3
[1] Correct response.
[2] Verbatim text for the type of chronic non-cancer pain and reason for selecting TIRF medicines to treat chronic non-cancer pain is presented in Listing 1 and Listing 2, respectively.

Table 4: Responses to Questions about TIRF Educational Materials - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
Question 23: Did you receive or do you have access to the Full Prescribing Information for the TIRF medicine(s) that you prescribe?	
Yes	285 (96.9)
No	5 (1.7)
I don't know	4 (1.4)
Question 24: Did you read the Full Prescribing Information for the TIRF medicine(s) that you prescribe?[1]	
Yes	248 (87.0)
No	31 (10.9)
I don't know	6 (2.1)
N/A (Answered "No" or "I don't know" to Question 23)	9
Question 25: Did you receive or do you have access to the Medication Guide for the TIRF medicine(s) that you prescribe?	
Yes	282 (95.9)
No	4 (1.4)
I don't know	8 (2.7)
Question 26: Did you read the Medication Guide for the TIRF medicine(s) that you prescribe?[1]	
Yes	260 (92.2)
No	17 (6.0)
I don't know	5 (1.8)
N/A (Answered "No" or "I don't know" to Question 25)	12
Question 27: Did you or do you have any questions about the information in the Full Prescribing Information or Medication Guide?[2]	
Yes	8 (2.7)
No	264 (89.8)
I don't know	22 (7.5)

Source: Appendix B: Survey Tables, Table 4
[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.
[2] Verbatim text for questions about the Full Prescribing Information or Medication Guide is presented in Listing 3.

Table 5: Responses to Questions about the Patient-Prescriber Agreement Form - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
Question 29: Do you review the Patient-Prescriber Agreement Form with each of your patients for whom you prescribe TIRF medicines or their caregiver?	
Yes	278 (94.6)
No	10 (3.4)
I don't know	6 (2.0)
Question 30: Do you and the patient or their caregiver sign the Patient-Prescriber Agreement Form for TIRF medicines after you have reviewed it with him/her?[1]	
Yes	272 (97.8)
No	2 (0.7)
I don't know	4 (1.4)
N/A (Answered "No" or "I don't know" to Question 29)	16
Question 31: Do you give a copy of the Patient-Prescriber Agreement Form for TIRF medicines to the patient or their caregiver?[1]	
Yes	250 (89.9)
No	15 (5.4)
I don't know	13 (4.7)
N/A (Answered "No" or "I don't know" to Question 29)	16

Source: Appendix B: Survey Tables, Table 5
[1] Percentages are calculated based on the sample presented with this question because of skip logic in the survey.

Table 6: Responses to Questions about the Activities when Prescribing TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
Question 14: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.	
14a: Ask patients (or their caregivers) about the presence of children in the home	
Always	182 (61.9)
Only with the first prescription	66 (22.4)
Sometimes	35 (11.9)
Never	10 (3.4)
I don't know	1 (0.3)
14b: Instruct patients (or their caregivers) not to share TIRF medicines with anyone else	
Always	236 (80.3)
Only with the first prescription	43 (14.6)
Sometimes	14 (4.8)
Never	1 (0.3)
I don't know	0
14c: Counsel patients (or their caregivers) that accidental exposure to TIRF medicines by a child may be fatal	
Always	208 (70.7)
Only with the first prescription	55 (18.7)
Sometimes	23 (7.8)
Never	8 (2.7)
I don't know	0
14d: Instruct patients (or their caregivers) to keep TIRF medicines out of the reach of children to prevent accidental exposure	
Always	232 (78.9)
Only with the first prescription	44 (15.0)
Sometimes	13 (4.4)
Never	5 (1.7)
I don't know	0
14e: Instruct patients (or their caregivers) about proper disposal of any unused or partially used TIRF medicines	

Table 6: Responses to Questions about the Activities when Prescribing TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
Always	197 (67.0)
Only with the first prescription	56 (19.0)
Sometimes	34 (11.6)
Never	7 (2.4)
I don't know	0
14f: Give patients (or their caregivers) the Medication Guide for their TIRF medicine	
Always	130 (44.2)
Only with the first prescription	131 (44.6)
Sometimes	17 (5.8)
Never	15 (5.1)
I don't know	1 (0.3)
Question 32: How frequently do you perform the following activities when prescribing TIRF medicines? Please answer Always, Only with the first prescription, Sometimes, Never, or I don't know.	
32a: Talk to the patient about the risks and possible side effects of the TIRF medicine that was most recently prescribed.	
Always	223 (75.9)
Only with the first prescription	53 (18.0)
Sometimes	16 (5.4)
Never	0
I don't know	2 (0.7)
32b: Instruct the patient on how to use the TIRF medicine that was most recently prescribed.	
Always	204 (69.4)
Only with the first prescription	67 (22.8)
Sometimes	21 (7.1)
Never	0
I don't know	2 (0.7)
32c: Instruct the patient on how to store or keep the TIRF medicine that was most recently prescribed.	
Always	156 (53.1)
Only with the first prescription	102 (34.7)

Table 6: Responses to Questions about the Activities when Prescribing TIRF Medicines - Completed Surveys	
Question	**Prescribers (N=294) n (%)**
Sometimes	22 (7.5)
Never	12 (4.1)
I don't know	2 (0.7)

Source: Appendix B: Survey Tables, Table 6

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys	
Question	**Prescribers (N=294) n (%) [95% CI][1]**
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:	
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer	
True[2]	279 (94.9) [91.7 - 97.1]
False	11 (3.7)
I don't know	4 (1.4)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before	
True	16 (5.4)
False[2]	276 (93.9) [90.5 - 96.3]
I don't know	2 (0.7)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy	
True	17 (5.8)
False[2]	272 (92.5) [88.9 - 95.3]
I don't know	5 (1.7)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.	
True[2]	270 (91.8) [88.1 - 94.7]
False	21 (7.1)
I don't know	3 (1.0)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.	
True[2]	281 (95.6) [92.6 - 97.6]
False	3 (1.0)
I don't know	10 (3.4)
7c: TIRF medicines may be used to treat opioid non-tolerant patients.	
True	27 (9.2)
False[2]	260 (88.4) [84.2 - 91.9]

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys	
Question	**Prescribers (N=294) n (%) [95% CI][1]**
I don't know	7 (2.4)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.	
True[2]	252 (85.7) [81.2 - 89.5]
False	37 (12.6)
I don't know	5 (1.7)
Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:	
13a: 8 mg oral hydromorphone/day	
True[2]	211 (71.8) [66.3 - 76.8]
False	69 (23.5)
I don't know	14 (4.8)
13b: 60 mg oral morphine/day	
True[2]	281 (95.6) [92.6 - 97.6]
False	6 (2.0)
I don't know	7 (2.4)
13c: 30 mg oral oxycodone/day	
True[2]	241 (82.0) [77.1 - 86.2]
False	44 (15.0)
I don't know	9 (3.1)
13d: 25 mcg transdermal fentanyl/hour	
True[2]	262 (89.1) [85.0 - 92.4]
False	21 (7.1)
I don't know	11 (3.7)
13e: 25 mg oral oxymorphone/day	
True[2]	234 (79.6) [74.5 - 84.0]
False	33 (11.2)
I don't know	27 (9.2)

Table 7.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys	
Question	**Prescribers (N=294) n (%) [95% CI][1]**
13f: An equianalgesic dose of another oral opioid	
True[2]	193 (65.6) [59.9 - 71.1]
False	56 (19.0)
I don't know	45 (15.3)
Question 21: Please answer True, False, or I don't know for the following statement about TIRF medicines:	
TIRF medicines should only be taken by patients who are opioid tolerant.	
True[2]	284 (96.6) [93.8 - 98.4]
False	8 (2.7)
I don't know	2 (0.7)

Source: Appendix B: Survey Tables, Table 7.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.1: Responses to Questions Linked to Key Risk Message #1 by Reading Full Prescribing Information or Medication Guide - Completed Surveys

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer		
True[2]	255 (95.1) [91.8 - 97.4]	24 (92.3) [74.9 - 99.1]
False	10 (3.7)	1 (3.8)
I don't know	3 (1.1)	1 (3.8)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
True	15 (5.6)	1 (3.8)
False[2]	253 (94.4) [90.9 - 96.8]	23 (88.5) [69.8 - 97.6]
I don't know	0	2 (7.7)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	16 (6.0)	1 (3.8)
False[2]	249 (92.9) [89.2 - 95.7]	23 (88.5) [69.8 - 97.6]
I don't know	3 (1.1)	2 (7.7)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True[2]	248 (92.5) [88.7 - 95.4]	22 (84.6) [65.1 - 95.6]
False	18 (6.7)	3 (11.5)
I don't know	2 (0.7)	1 (3.8)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[2]	256 (95.5) [92.3 - 97.7]	25 (96.2) [80.4 - 99.9]
False	3 (1.1)	0
I don't know	9 (3.4)	1 (3.8)
7c: TIRF medicines may be used to treat opioid non-tolerant patients.		

Table 7.1.1: Responses to Questions Linked to Key Risk Message #1 by Reading Full Prescribing Information or Medication Guide - Completed Surveys		
	Reading Full Prescribing Information or Medication Guide	
Question	Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
True	24 (9.0)	3 (11.5)
False[2]	239 (89.2) [84.8 - 92.6]	21 (80.8) [60.6 - 93.4]
I don't know	5 (1.9)	2 (7.7)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True[2]	230 (85.8) [81.1 - 89.8]	22 (84.6) [65.1 - 95.6]
False	34 (12.7)	3 (11.5)
I don't know	4 (1.5)	1 (3.8)
Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
13a: 8 mg oral hydromorphone/day		
True[2]	200 (74.6) [69.0 - 79.7]	11 (42.3) [23.4 - 63.1]
False	57 (21.3)	12 (46.2)
I don't know	11 (4.1)	3 (11.5)
13b: 60 mg oral morphine/day		
True[2]	258 (96.3) [93.2 - 98.2]	23 (88.5) [69.8 - 97.6]
False	6 (2.2)	0
I don't know	4 (1.5)	3 (11.5)
13c: 30 mg oral oxycodone/day		
True[2]	226 (84.3) [79.4 - 88.5]	15 (57.7) [36.9 - 76.6]
False	36 (13.4)	8 (30.8)
I don't know	6 (2.2)	3 (11.5)
13d: 25 mcg transdermal fentanyl/hour		
True[2]	242 (90.3) [86.1 - 93.6]	20 (76.9) [56.4 - 91.0]
False	19 (7.1)	2 (7.7)
I don't know	7 (2.6)	4 (15.4)

Table 7.1.1: Responses to Questions Linked to Key Risk Message #1 by Reading Full Prescribing Information or Medication Guide - Completed Surveys		
	Reading Full Prescribing Information or Medication Guide	
Question	Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
13e: 25 mg oral oxymorphone/day		
True[2]	218 (81.3) [76.2 - 85.8]	16 (61.5) [40.6 - 79.8]
False	26 (9.7)	7 (26.9)
I don't know	24 (9.0)	3 (11.5)
13f: An equianalgesic dose of another oral opioid		
True[2]	178 (66.4) [60.4 - 72.0]	15 (57.7) [36.9 - 76.6]
False	52 (19.4)	4 (15.4)
I don't know	38 (14.2)	7 (26.9)
Question 21: Please answer True, False, or I don't know for the following statement about TIRF medicines:		
TIRF medicines should only be taken by patients who are opioid tolerant.		
True[2]	260 (97.0) [94.2 - 98.7]	24 (92.3) [74.9 - 99.1]
False	7 (2.6)	1 (3.8)
I don't know	1 (0.4)	1 (3.8)

Source: Appendix B: Survey Tables, Table 7.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.2: Responses to Questions Linked to Key Risk Message #1 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer				
True[2]	157 (94.0) [89.3 - 97.1]	24 (92.3) [74.9 - 99.1]	51 (96.2) [87.0 - 99.5]	45 (97.8) [88.5 - 99.9]
False	6 (3.6)	2 (7.7)	2 (3.8)	1 (2.2)
I don't know	4 (2.4)	0	0	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
True	10 (6.0)	3 (11.5)	2 (3.8)	1 (2.2)
False[2]	157 (94.0) [89.3 - 97.1]	23 (88.5) [69.8 - 97.6]	50 (94.3) [84.3 - 98.8]	44 (95.7) [85.2 - 99.5]
I don't know	0	0	1 (1.9)	1 (2.2)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
True	8 (4.8)	3 (11.5)	2 (3.8)	4 (8.7)
False[2]	156 (93.4) [88.5 - 96.7]	23 (88.5) [69.8 - 97.6]	50 (94.3) [84.3 - 98.8]	41 (89.1) [76.4 - 96.4]
I don't know	3 (1.8)	0	1 (1.9)	1 (2.2)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
True[2]	149 (89.2) [83.5 - 93.5]	24 (92.3) [74.9 - 99.1]	50 (94.3) [84.3 - 98.8]	45 (97.8) [88.5 - 99.9]
False	16 (9.6)	2 (7.7)	2 (3.8)	1 (2.2)

Table 7.1.2: Responses to Questions Linked to Key Risk Message #1 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
I don't know	2 (1.2)	0	1 (1.9)	0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True[2]	159 (95.2) [90.8 - 97.9]	25 (96.2) [80.4 - 99.9]	52 (98.1) [89.9 - 100.0]	43 (93.5) [82.1 - 98.6]
False	3 (1.8)	0	0	0
I don't know	5 (3.0)	1 (3.8)	1 (1.9)	3 (6.5)
7c: TIRF medicines may be used to treat opioid non-tolerant patients.				
True	19 (11.4)	2 (7.7)	3 (5.7)	3 (6.5)
False[2]	146 (87.4) [81.4 - 92.0]	24 (92.3) [74.9 - 99.1]	47 (88.7) [77.0 - 95.7]	41 (89.1) [76.4 - 96.4]
I don't know	2 (1.2)	0	3 (5.7)	2 (4.3)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True[2]	144 (86.2) [80.1 - 91.1]	24 (92.3) [74.9 - 99.1]	45 (84.9) [72.4 - 93.3]	37 (80.4) [66.1 - 90.6]
False	20 (12.0)	2 (7.7)	8 (15.1)	7 (15.2)
I don't know	3 (1.8)	0	0	2 (4.3)
Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:				
13a: 8 mg oral hydromorphone/day				
True[2]	122 (73.1) [65.7 - 79.6]	20 (76.9) [56.4 - 91.0]	37 (69.8) [55.7 - 81.7]	30 (65.2) [49.8 - 78.6]

Table 7.1.2: Responses to Questions Linked to Key Risk Message #1 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
False	36 (21.6)	6 (23.1)	13 (24.5)	14 (30.4)
I don't know	9 (5.4)	0	3 (5.7)	2 (4.3)
13b: 60 mg oral morphine/day				
True[2]	159 (95.2) [90.8 - 97.9]	26 (100.0) [86.8 - 100.0]	50 (94.3) [84.3 - 98.8]	44 (95.7) [85.2 - 99.5]
False	4 (2.4)	0	1 (1.9)	1 (2.2)
I don't know	4 (2.4)	0	2 (3.8)	1 (2.2)
13c: 30 mg oral oxycodone/day				
True[2]	135 (80.8) [74.0 - 86.5]	22 (84.6) [65.1 - 95.6]	50 (94.3) [84.3 - 98.8]	32 (69.6) [54.2 - 82.3]
False	26 (15.6)	3 (11.5)	2 (3.8)	13 (28.3)
I don't know	6 (3.6)	1 (3.8)	1 (1.9)	1 (2.2)
13d: 25 mcg transdermal fentanyl/hour				
True[2]	148 (88.6) [82.8 - 93.0]	22 (84.6) [65.1 - 95.6]	50 (94.3) [84.3 - 98.8]	40 (87.0) [73.7 - 95.1]
False	15 (9.0)	2 (7.7)	1 (1.9)	3 (6.5)
I don't know	4 (2.4)	2 (7.7)	2 (3.8)	3 (6.5)
13e: 25 mg oral oxymorphone/day				
True[2]	129 (77.2) [70.1 - 83.4]	21 (80.8) [60.6 - 93.4]	43 (81.1) [68.0 - 90.6]	39 (84.8) [71.1 - 93.7]
False	23 (13.8)	2 (7.7)	3 (5.7)	5 (10.9)
I don't know	15 (9.0)	3 (11.5)	7 (13.2)	2 (4.3)

Table 7.1.2: Responses to Questions Linked to Key Risk Message #1 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
13f: An equianalgesic dose of another oral opioid				
True[2]	113 (67.7) [60.0 - 74.7]	17 (65.4) [44.3 - 82.8]	35 (66.0) [51.7 - 78.5]	27 (58.7) [43.2 - 73.0]
False	29 (17.4)	8 (30.8)	6 (11.3)	13 (28.3)
I don't know	25 (15.0)	1 (3.8)	12 (22.6)	6 (13.0)
Question 21: Please answer True, False, or I don't know for the following statement about TIRF medicines:				
TIRF medicines should only be taken by patients who are opioid tolerant.				
True[2]	160 (95.8) [91.6 - 98.3]	26 (100.0) [86.8 - 100.0]	52 (98.1) [89.9 - 100.0]	44 (95.7) [85.2 - 99.5]
False	6 (3.6)	0	0	2 (4.3)
I don't know	1 (0.6)	0	1 (1.9)	0

Source: Appendix B: Survey Tables, Table 7.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.3: Responses to Questions Linked to Key Risk Message #1 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=289) n (%) [95% CI][1]	Telephone (N=5) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer		
True[2]	274 (94.8) [91.6 - 97.1]	5 (100.0) [47.8 - 100.0]
False	11 (3.8)	0
I don't know	4 (1.4)	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
True	15 (5.2)	1 (20.0)
False[2]	272 (94.1) [90.7 - 96.5]	4 (80.0) [28.4 - 99.5]
I don't know	2 (0.7)	0
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	16 (5.5)	1 (20.0)
False[2]	268 (92.7) [89.1 - 95.4]	4 (80.0) [28.4 - 99.5]
I don't know	5 (1.7)	0
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True[2]	265 (91.7) [87.9 - 94.6]	5 (100.0) [47.8 - 100.0]
False	21 (7.3)	0
I don't know	3 (1.0)	0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[2]	276 (95.5) [92.4 - 97.6]	5 (100.0) [47.8 - 100.0]
False	3 (1.0)	0
I don't know	10 (3.5)	0
7c: TIRF medicines may be used to treat opioid non-tolerant patients.		
True	27 (9.3)	0

Table 7.1.3: Responses to Questions Linked to Key Risk Message #1 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=289) n (%) [95% CI][1]	Telephone (N=5) n (%) [95% CI][1]
False[2]	255 (88.2) [83.9 - 91.7]	5 (100.0) [47.8 - 100.0]
I don't know	7 (2.4)	0
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True[2]	248 (85.8) [81.2 - 89.6]	4 (80.0) [28.4 - 99.5]
False	36 (12.5)	1 (20.0)
I don't know	5 (1.7)	0
Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
13a: 8 mg oral hydromorphone/day		
True[2]	206 (71.3) [65.7 - 76.4]	5 (100.0) [47.8 - 100.0]
False	69 (23.9)	0
I don't know	14 (4.8)	0
13b: 60 mg oral morphine/day		
True[2]	276 (95.5) [92.4 - 97.6]	5 (100.0) [47.8 - 100.0]
False	6 (2.1)	0
I don't know	7 (2.4)	0
13c: 30 mg oral oxycodone/day		
True[2]	236 (81.7) [76.7 - 86.0]	5 (100.0) [47.8 - 100.0]
False	44 (15.2)	0
I don't know	9 (3.1)	0
13d: 25 mcg transdermal fentanyl/hour		
True[2]	257 (88.9) [84.7 - 92.3]	5 (100.0) [47.8 - 100.0]
False	21 (7.3)	0
I don't know	11 (3.8)	0
13e: 25 mg oral oxymorphone/day		
True[2]	229 (79.2) [74.1 - 83.8]	5 (100.0) [47.8 - 100.0]

Table 7.1.3: Responses to Questions Linked to Key Risk Message #1 by Modality to Complete Survey - Completed Surveys

Question	Modality to Complete Survey	
	Internet (N=289) n (%) [95% CI][1]	Telephone (N=5) n (%) [95% CI][1]
False	33 (11.4)	0
I don't know	27 (9.3)	0
13f: An equianalgesic dose of another oral opioid		
True[2]	188 (65.1) [59.2 - 70.5]	5 (100.0) [47.8 - 100.0]
False	56 (19.4)	0
I don't know	45 (15.6)	0
Question 21: Please answer True, False, or I don't know for the following statement about TIRF medicines:		
TIRF medicines should only be taken by patients who are opioid tolerant.		
True[2]	279 (96.5) [93.7 - 98.3]	5 (100.0) [47.8 - 100.0]
False	8 (2.8)	0
I don't know	2 (0.7)	0

Source: Appendix B: Survey Tables, Table 7.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.4: Responses to Questions Linked to Key Risk Message #1 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:				
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer				
True[2]	24 (92.3) [74.9 - 99.1]	45 (91.8) [80.4 - 97.7]	79 (92.9) [85.3 - 97.4]	131 (97.8) [93.6 - 99.5]
False	2 (7.7)	3 (6.1)	4 (4.7)	2 (1.5)
I don't know	0	1 (2.0)	2 (2.4)	1 (0.7)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before				
True	1 (3.8)	0	4 (4.7)	11 (8.2)
False[2]	25 (96.2) [80.4 - 99.9]	49 (100.0) [92.7 - 100.0]	80 (94.1) [86.8 - 98.1]	122 (91.0) [84.9 - 95.3]
I don't know	0	0	1 (1.2)	1 (0.7)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy				
True	1 (3.8)	1 (2.0)	5 (5.9)	10 (7.5)
False[2]	25 (96.2) [80.4 - 99.9]	46 (93.9) [83.1 - 98.7]	79 (92.9) [85.3 - 97.4]	122 (91.0) [84.9 - 95.3]
I don't know	0	2 (4.1)	1 (1.2)	2 (1.5)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.				
True[2]	25 (96.2) [80.4 - 99.9]	45 (91.8) [80.4 - 97.7]	78 (91.8) [83.8 - 96.6]	122 (91.0) [84.9 - 95.3]
False	1 (3.8)	4 (8.2)	6 (7.1)	10 (7.5)

Table 7.1.4: Responses to Questions Linked to Key Risk Message #1 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
I don't know	0	0	1 (1.2)	2 (1.5)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.				
True[2]	26 (100.0) [86.8 - 100.0]	43 (87.8) [75.2 - 95.4]	82 (96.5) [90.0 - 99.3]	130 (97.0) [92.5 - 99.2]
False	0	0	1 (1.2)	2 (1.5)
I don't know	0	6 (12.2)	2 (2.4)	2 (1.5)
7c: TIRF medicines may be used to treat opioid non-tolerant patients.				
True	3 (11.5)	2 (4.1)	10 (11.8)	12 (9.0)
False[2]	22 (84.6) [65.1 - 95.6]	45 (91.8) [80.4 - 97.7]	73 (85.9) [76.6 - 92.5]	120 (89.6) [83.1 - 94.2]
I don't know	1 (3.8)	2 (4.1)	2 (2.4)	2 (1.5)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.				
True[2]	23 (88.5) [69.8 - 97.6]	38 (77.6) [63.4 - 88.2]	75 (88.2) [79.4 - 94.2]	116 (86.6) [79.6 - 91.8]
False	2 (7.7)	9 (18.4)	8 (9.4)	18 (13.4)
I don't know	1 (3.8)	2 (4.1)	2 (2.4)	0
Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:				
13a: 8 mg oral hydromorphone/day				
True[2]	14 (53.8) [33.4 - 73.4]	35 (71.4) [56.7 - 83.4]	57 (67.1) [56.0 - 76.9]	105 (78.4) [70.4 - 85.0]

Table 7.1.4: Responses to Questions Linked to Key Risk Message #1 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
False	8 (30.8)	13 (26.5)	22 (25.9)	26 (19.4)
I don't know	4 (15.4)	1 (2.0)	6 (7.1)	3 (2.2)
13b: 60 mg oral morphine/day				
True[2]	23 (88.5) [69.8 - 97.6]	48 (98.0) [89.1 - 99.9]	79 (92.9) [85.3 - 97.4]	131 (97.8) [93.6 - 99.5]
False	0	1 (2.0)	4 (4.7)	1 (0.7)
I don't know	3 (11.5)	0	2 (2.4)	2 (1.5)
13c: 30 mg oral oxycodone/day				
True[2]	17 (65.4) [44.3 - 82.8]	40 (81.6) [68.0 - 91.2]	69 (81.2) [71.2 - 88.8]	115 (85.8) [78.7 - 91.2]
False	6 (23.1)	8 (16.3)	13 (15.3)	17 (12.7)
I don't know	3 (11.5)	1 (2.0)	3 (3.5)	2 (1.5)
13d: 25 mcg transdermal fentanyl/hour				
True[2]	20 (76.9) [56.4 - 91.0]	43 (87.8) [75.2 - 95.4]	79 (92.9) [85.3 - 97.4]	120 (89.6) [83.1 - 94.2]
False	2 (7.7)	4 (8.2)	3 (3.5)	12 (9.0)
I don't know	4 (15.4)	2 (4.1)	3 (3.5)	2 (1.5)
13e: 25 mg oral oxymorphone/day				
True[2]	17 (65.4) [44.3 - 82.8]	39 (79.6) [65.7 - 89.8]	68 (80.0) [69.9 - 87.9]	110 (82.1) [74.5 - 88.2]
False	5 (19.2)	8 (16.3)	7 (8.2)	13 (9.7)
I don't know	4 (15.4)	2 (4.1)	10 (11.8)	11 (8.2)

Table 7.1.4: Responses to Questions Linked to Key Risk Message #1 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
13f: An equianalgesic dose of another oral opioid				
True[2]	12 (46.2) [26.6 - 66.6]	35 (71.4) [56.7 - 83.4]	53 (62.4) [51.2 - 72.6]	93 (69.4) [60.9 - 77.1]
False	6 (23.1)	5 (10.2)	20 (23.5)	25 (18.7)
I don't know	8 (30.8)	9 (18.4)	12 (14.1)	16 (11.9)
Question 21: Please answer True, False, or I don't know for the following statement about TIRF medicines:				
TIRF medicines should only be taken by patients who are opioid tolerant.				
True[2]	24 (92.3) [74.9 - 99.1]	46 (93.9) [83.1 - 98.7]	83 (97.6) [91.8 - 99.7]	131 (97.8) [93.6 - 99.5]
False	2 (7.7)	3 (6.1)	2 (2.4)	1 (0.7)
I don't know	0	0	0	2 (1.5)

Source: Appendix B: Survey Tables, Table 7.1.4
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.5: Responses to Questions Linked to Key Risk Message #1 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:					
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer					
True[2]	15 (100.0) [78.2 - 100.0]	177 (94.1) [89.8 - 97.0]	61 (95.3) [86.9 - 99.0]	20 (95.2) [76.2 - 99.9]	6 (100.0) [54.1 - 100.0]
False	0	9 (4.8)	1 (1.6)	1 (4.8)	0
I don't know	0	2 (1.1)	2 (3.1)	0	0
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before					
True	1 (6.7)	7 (3.7)	4 (6.3)	4 (19.0)	0
False[2]	14 (93.3) [68.1 - 99.8]	179 (95.2) [91.1 - 97.8]	60 (93.8) [84.8 - 98.3]	17 (81.0) [58.1 - 94.6]	6 (100.0) [54.1 - 100.0]
I don't know	0	2 (1.1)	0	0	0
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy					
True	4 (26.7)	5 (2.7)	5 (7.8)	2 (9.5)	1 (16.7)
False[2]	11 (73.3) [44.9 - 92.2]	179 (95.2) [91.1 - 97.8]	59 (92.2) [82.7 - 97.4]	18 (85.7) [63.7 - 97.0]	5 (83.3) [35.9 - 99.6]
I don't know	0	4 (2.1)	0	1 (4.8)	0
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.					
True[2]	12 (80.0) [51.9 - 95.7]	174 (92.6) [87.8 - 95.9]	61 (95.3) [86.9 - 99.0]	17 (81.0) [58.1 - 94.6]	6 (100.0) [54.1 - 100.0]

Table 7.1.5: Responses to Questions Linked to Key Risk Message #1 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
False	2 (13.3)	13 (6.9)	2 (3.1)	4 (19.0)	0
I don't know	1 (6.7)	1 (0.5)	1 (1.6)	0	0
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.					
True[2]	15 (100.0) [78.2 - 100.0]	180 (95.7) [91.8 - 98.1]	60 (93.8) [84.8 - 98.3]	21 (100.0) [83.9 - 100.0]	5 (83.3) [35.9 - 99.6]
False	0	0	3 (4.7)	0	0
I don't know	0	8 (4.3)	1 (1.6)	0	1 (16.7)
7c: TIRF medicines may be used to treat opioid non-tolerant patients.					
True	3 (20.0)	15 (8.0)	3 (4.7)	4 (19.0)	2 (33.3)
False[2]	12 (80.0) [51.9 - 95.7]	168 (89.4) [84.0 - 93.4]	60 (93.8) [84.8 - 98.3]	16 (76.2) [52.8 - 91.8]	4 (66.7) [22.3 - 95.7]
I don't know	0	5 (2.7)	1 (1.6)	1 (4.8)	0
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.					
True[2]	13 (86.7) [59.5 - 98.3]	162 (86.2) [80.4 - 90.8]	57 (89.1) [78.8 - 95.5]	14 (66.7) [43.0 - 85.4]	6 (100.0) [54.1 - 100.0]
False	2 (13.3)	22 (11.7)	6 (9.4)	7 (33.3)	0
I don't know	0	4 (2.1)	1 (1.6)	0	0
Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:					

Table 7.1.5: Responses to Questions Linked to Key Risk Message #1 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
13a: 8 mg oral hydromorphone/day					
True[2]	10 (66.7) [38.4 - 88.2]	135 (71.8) [64.8 - 78.1]	51 (79.7) [67.8 - 88.7]	13 (61.9) [38.4 - 81.9]	2 (33.3) [4.3 - 77.7]
False	4 (26.7)	44 (23.4)	11 (17.2)	7 (33.3)	3 (50.0)
I don't know	1 (6.7)	9 (4.8)	2 (3.1)	1 (4.8)	1 (16.7)
13b: 60 mg oral morphine/day					
True[2]	14 (93.3) [68.1 - 99.8]	180 (95.7) [91.8 - 98.1]	61 (95.3) [86.9 - 99.0]	21 (100.0) [83.9 - 100.0]	5 (83.3) [35.9 - 99.6]
False	0	5 (2.7)	1 (1.6)	0	0
I don't know	1 (6.7)	3 (1.6)	2 (3.1)	0	1 (16.7)
13c: 30 mg oral oxycodone/day					
True[2]	10 (66.7) [38.4 - 88.2]	153 (81.4) [75.1 - 86.7]	56 (87.5) [76.8 - 94.4]	19 (90.5) [69.6 - 98.8]	3 (50.0) [11.8 - 88.2]
False	4 (26.7)	29 (15.4)	7 (10.9)	2 (9.5)	2 (33.3)
I don't know	1 (6.7)	6 (3.2)	1 (1.6)	0	1 (16.7)
13d: 25 mcg transdermal fentanyl/hour					
True[2]	11 (73.3) [44.9 - 92.2]	171 (91.0) [85.9 - 94.6]	57 (89.1) [78.8 - 95.5]	19 (90.5) [69.6 - 98.8]	4 (66.7) [22.3 - 95.7]
False	3 (20.0)	11 (5.9)	5 (7.8)	1 (4.8)	1 (16.7)
I don't know	1 (6.7)	6 (3.2)	2 (3.1)	1 (4.8)	1 (16.7)

Table 7.1.5: Responses to Questions Linked to Key Risk Message #1 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
13e: 25 mg oral oxymorphone/day					
True[2]	12 (80.0) [51.9 - 95.7]	152 (80.9) [74.5 - 86.2]	51 (79.7) [67.8 - 88.7]	17 (81.0) [58.1 - 94.6]	2 (33.3) [4.3 - 77.7]
False	2 (13.3)	18 (9.6)	9 (14.1)	2 (9.5)	2 (33.3)
I don't know	1 (6.7)	18 (9.6)	4 (6.3)	2 (9.5)	2 (33.3)
13f: An equianalgesic dose of another oral opioid					
True[2]	7 (46.7) [21.3 - 73.4]	131 (69.7) [62.6 - 76.2]	38 (59.4) [46.4 - 71.5]	14 (66.7) [43.0 - 85.4]	3 (50.0) [11.8 - 88.2]
False	1 (6.7)	31 (16.5)	19 (29.7)	3 (14.3)	2 (33.3)
I don't know	7 (46.7)	26 (13.8)	7 (10.9)	4 (19.0)	1 (16.7)
Question 21: Please answer True, False, or I don't know for the following statement about TIRF medicines:					
TIRF medicines should only be taken by patients who are opioid tolerant.					
True[2]	14 (93.3) [68.1 - 99.8]	183 (97.3) [93.9 - 99.1]	61 (95.3) [86.9 - 99.0]	20 (95.2) [76.2 - 99.9]	6 (100.0) [54.1 - 100.0]
False	1 (6.7)	4 (2.1)	2 (3.1)	1 (4.8)	0
I don't know	0	1 (0.5)	1 (1.6)	0	0

Source: Appendix B: Survey Tables, Table 7.1.5
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.1.6: Responses to Questions Linked to Key Risk Message #1 by Practicing in a Closed Healthcare System - Completed Surveys		
	Practicing in a Closed Healthcare System	
Question	Yes (N=4) n (%) [95% CI][1]	No (N=290) n (%) [95% CI][1]
Question 5: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients with cancer who are considered opioid-tolerant are those:		
5a: Who are taking around-the-clock opioid therapy for underlying, persistent cancer pain for one week or longer		
True[2]	4 (100.0) [39.8 - 100.0]	275 (94.8) [91.6 - 97.1]
False	0	11 (3.8)
I don't know	0	4 (1.4)
5b: Who are not currently taking opioid therapy, but have taken opioid therapy before		
True	1 (25.0)	15 (5.2)
False[2]	3 (75.0) [19.4 - 99.4]	273 (94.1) [90.8 - 96.5]
I don't know	0	2 (0.7)
5c: Who have no known contraindications to the drug fentanyl, but are not currently taking around-the-clock opioid therapy		
True	0	17 (5.9)
False[2]	4 (100.0) [39.8 - 100.0]	268 (92.4) [88.7 - 95.2]
I don't know	0	5 (1.7)
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7a: TIRF medicines are contraindicated in opioid non-tolerant patients because life-threatening respiratory depression could occur at any dose.		
True[2]	4 (100.0) [39.8 - 100.0]	266 (91.7) [87.9 - 94.6]
False	0	21 (7.2)
I don't know	0	3 (1.0)
7b: Death has occurred in opioid non-tolerant patients treated with some fentanyl products.		
True[2]	4 (100.0) [39.8 - 100.0]	277 (95.5) [92.5 - 97.6]
False	0	3 (1.0)
I don't know	0	10 (3.4)
7c: TIRF medicines may be used to treat opioid non-tolerant patients.		
True	0	27 (9.3)

Table 7.1.6: Responses to Questions Linked to Key Risk Message #1 by Practicing in a Closed Healthcare System - Completed Surveys		
	Practicing in a Closed Healthcare System	
Question	Yes (N=4) n (%) [95% CI][1]	No (N=290) n (%) [95% CI][1]
False[2]	4 (100.0) [39.8 - 100.0]	256 (88.3) [84.0 - 91.7]
I don't know	0	7 (2.4)
7d: Prescribers starting a patient on a TIRF medicine must begin with titration from the lowest dose available for that specific product, even if the patient has previously taken another TIRF medicine.		
True[2]	4 (100.0) [39.8 - 100.0]	248 (85.5) [80.9 - 89.4]
False	0	37 (12.8)
I don't know	0	5 (1.7)
Question 13: Please select True, False, or I don't know for each of the following. According to the labeling for TIRF medicines, patients considered opioid-tolerant are those who are taking, for one week or longer, at least:		
13a: 8 mg oral hydromorphone/day		
True[2]	3 (75.0) [19.4 - 99.4]	208 (71.7) [66.2 - 76.8]
False	1 (25.0)	68 (23.4)
I don't know	0	14 (4.8)
13b: 60 mg oral morphine/day		
True[2]	4 (100.0) [39.8 - 100.0]	277 (95.5) [92.5 - 97.6]
False	0	6 (2.1)
I don't know	0	7 (2.4)
13c: 30 mg oral oxycodone/day		
True[2]	3 (75.0) [19.4 - 99.4]	238 (82.1) [77.2 - 86.3]
False	1 (25.0)	43 (14.8)
I don't know	0	9 (3.1)
13d: 25 mcg transdermal fentanyl/hour		
True[2]	4 (100.0) [39.8 - 100.0]	258 (89.0) [84.8 - 92.3]
False	0	21 (7.2)
I don't know	0	11 (3.8)
13e: 25 mg oral oxymorphone/day		
True[2]	4 (100.0) [39.8 - 100.0]	230 (79.3) [74.2 - 83.8]

Table 7.1.6: Responses to Questions Linked to Key Risk Message #1 by Practicing in a Closed Healthcare System - Completed Surveys		
	Practicing in a Closed Healthcare System	
Question	Yes (N=4) n (%) [95% CI][1]	No (N=290) n (%) [95% CI][1]
False	0	33 (11.4)
I don't know	0	27 (9.3)
13f: An equianalgesic dose of another oral opioid		
True[2]	3 (75.0) [19.4 - 99.4]	190 (65.5) [59.7 - 71.0]
False	1 (25.0)	55 (19.0)
I don't know	0	45 (15.5)
Question 21: Please answer True, False, or I don't know for the following statement about TIRF medicines:		
TIRF medicines should only be taken by patients who are opioid tolerant.		
True[2]	4 (100.0) [39.8 - 100.0]	280 (96.6) [93.8 - 98.3]
False	0	8 (2.8)
I don't know	0	2 (0.7)

Source: Appendix B: Survey Tables, Table 7.1.6
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 7.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #1 - Completed Surveys	
Correct Responses	**Prescribers (N=294) n (%)**
0 correct responses	0
1 correct response	0
2 correct responses	0
3 correct responses	1 (0.3)
4 correct responses	0
5 correct responses	1 (0.3)
6 correct responses	1 (0.3)
7 correct responses	4 (1.4)
8 correct responses	9 (3.1)
9 correct responses	16 (5.4)
10 correct responses	23 (7.8)
11 correct responses	28 (9.5)
12 correct responses	39 (13.3)
13 correct responses	76 (25.9)
14 correct responses	96 (32.7)

Source: Appendix B: Survey Tables, Table 7.2

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys	
Question	**Prescribers (N=294) n (%) [95% CI][1]**
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.	
True	52 (17.7)
False[2]	227 (77.2) [72.0 - 81.9]
I don't know	15 (5.1)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.	
True	54 (18.4)
False[2]	230 (78.2) [73.1 - 82.8]
I don't know	10 (3.4)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.	
9a: Acute or postoperative pain	
Yes	9 (3.1)
No[2]	278 (94.6) [91.3 - 96.9]
I don't know	7 (2.4)
9b: Headache or migraine pain	
Yes	6 (2.0)
No[2]	276 (93.9) [90.5 - 96.3]
I don't know	12 (4.1)
9c: Dental pain	
Yes	4 (1.4)
No[2]	283 (96.3) [93.4 - 98.1]
I don't know	7 (2.4)
9d: Breakthrough pain from cancer	
Yes[2]	292 (99.3) [97.6 - 99.9]
No	2 (0.7)

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys	
Question	**Prescribers (N=294) n (%) [95% CI][1]**
I don't know	0
9e: Chronic non-cancer pain	
Yes	54 (18.4)
No[2]	230 (78.2) [73.1 - 82.8]
I don't know	10 (3.4)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.	
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	20 (6.8)
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.[2]	212 (72.1) [66.6 - 77.2]
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	18 (6.1)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	27 (9.2)
I don't know	17 (5.8)
Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.	
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.	
True[2]	283 (96.3) [93.4 - 98.1]
False	8 (2.7)
I don't know	3 (1.0)
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.	
True	58 (19.7)
False[2]	225 (76.5) [71.3 - 81.3]

Table 8.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys	
Question	**Prescribers (N=294) n (%) [95% CI][1]**
I don't know	11 (3.7)

Source: Appendix B: Survey Tables, Table 8.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.1: Responses to Questions Linked to Key Risk Message #2 by Reading Full Prescribing Information or Medication Guide - Completed Surveys

Question	Reading Full Prescribing Information or Medication Guide: Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Reading Full Prescribing Information or Medication Guide: Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.		
True	47 (17.5)	5 (19.2)
False[2]	209 (78.0) [72.5 - 82.8]	18 (69.2) [48.2 - 85.7]
I don't know	12 (4.5)	3 (11.5)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.		
True	50 (18.7)	4 (15.4)
False[2]	209 (78.0) [72.5 - 82.8]	21 (80.8) [60.6 - 93.4]
I don't know	9 (3.4)	1 (3.8)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
Yes	5 (1.9)	4 (15.4)
No[2]	256 (95.5) [92.3 - 97.7]	22 (84.6) [65.1 - 95.6]
I don't know	7 (2.6)	0
9b: Headache or migraine pain		
Yes	6 (2.2)	0
No[2]	252 (94.0) [90.5 - 96.5]	24 (92.3) [74.9 - 99.1]
I don't know	10 (3.7)	2 (7.7)
9c: Dental pain		
Yes	4 (1.5)	0
No[2]	259 (96.6) [93.7 - 98.5]	24 (92.3) [74.9 - 99.1]
I don't know	5 (1.9)	2 (7.7)
9d: Breakthrough pain from cancer		
Yes[2]	267 (99.6) [97.9 - 100.0]	25 (96.2) [80.4 - 99.9]

Table 8.1.1: Responses to Questions Linked to Key Risk Message #2 by Reading Full Prescribing Information or Medication Guide - Completed Surveys		
	Reading Full Prescribing Information or Medication Guide	
Question	Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
No	1 (0.4)	1 (3.8)
I don't know	0	0
9e: Chronic non-cancer pain		
Yes	48 (17.9)	6 (23.1)
No[2]	210 (78.4) [72.9 - 83.1]	20 (76.9) [56.4 - 91.0]
I don't know	10 (3.7)	0
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.		
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	20 (7.5)	0
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.[2]	192 (71.6) [65.8 - 77.0]	20 (76.9) [56.4 - 91.0]
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	16 (6.0)	2 (7.7)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	24 (9.0)	3 (11.5)
I don't know	16 (6.0)	1 (3.8)
Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.		
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.		
True[2]	257 (95.9) [92.8 - 97.9]	26 (100.0) [86.8 - 100.0]

Table 8.1.1: Responses to Questions Linked to Key Risk Message #2 by Reading Full Prescribing Information or Medication Guide - Completed Surveys		
	Reading Full Prescribing Information or Medication Guide	
Question	Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
False	8 (3.0)	0
I don't know	3 (1.1)	0
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.		
True	51 (19.0)	7 (26.9)
False[2]	210 (78.4) [72.9 - 83.1]	15 (57.7) [36.9 - 76.6]
I don't know	7 (2.6)	4 (15.4)

Source: Appendix B: Survey Tables, Table 8.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.2: Responses to Questions Linked to Key Risk Message #2 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.				
True	30 (18.0)	6 (23.1)	9 (17.0)	6 (13.0)
False[2]	130 (77.8) [70.8 - 83.9]	20 (76.9) [56.4 - 91.0]	39 (73.6) [59.7 - 84.7]	38 (82.6) [68.6 - 92.2]
I don't know	7 (4.2)	0	5 (9.4)	2 (4.3)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.				
True	31 (18.6)	6 (23.1)	10 (18.9)	7 (15.2)
False[2]	132 (79.0) [72.1 - 84.9]	19 (73.1) [52.2 - 88.4]	39 (73.6) [59.7 - 84.7]	38 (82.6) [68.6 - 92.2]
I don't know	4 (2.4)	1 (3.8)	4 (7.5)	1 (2.2)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
Yes	4 (2.4)	2 (7.7)	1 (1.9)	2 (4.3)
No[2]	157 (94.0) [89.3 - 97.1]	24 (92.3) [74.9 - 99.1]	51 (96.2) [87.0 - 99.5]	44 (95.7) [85.2 - 99.5]
I don't know	6 (3.6)	0	1 (1.9)	0
9b: Headache or migraine pain				
Yes	4 (2.4)	2 (7.7)	0	0

Table 8.1.2: Responses to Questions Linked to Key Risk Message #2 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
No[2]	155 (92.8) [87.8 - 96.2]	24 (92.3) [74.9 - 99.1]	52 (98.1) [89.9 - 100.0]	43 (93.5) [82.1 - 98.6]
I don't know	8 (4.8)	0	1 (1.9)	3 (6.5)
9c: Dental pain				
Yes	2 (1.2)	2 (7.7)	0	0
No[2]	160 (95.8) [91.6 - 98.3]	24 (92.3) [74.9 - 99.1]	53 (100.0) [93.3 - 100.0]	44 (95.7) [85.2 - 99.5]
I don't know	5 (3.0)	0	0	2 (4.3)
9d: Breakthrough pain from cancer				
Yes[2]	167 (100.0) [97.8 - 100.0]	26 (100.0) [86.8 - 100.0]	52 (98.1) [89.9 - 100.0]	45 (97.8) [88.5 - 99.9]
No	0	0	1 (1.9)	1 (2.2)
I don't know	0	0	0	0
9e: Chronic non-cancer pain				
Yes	24 (14.4)	5 (19.2)	16 (30.2)	9 (19.6)
No[2]	136 (81.4) [74.7 - 87.0]	21 (80.8) [60.6 - 93.4]	35 (66.0) [51.7 - 78.5]	36 (78.3) [63.6 - 89.1]
I don't know	7 (4.2)	0	2 (3.8)	1 (2.2)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.				

Table 8.1.2: Responses to Questions Linked to Key Risk Message #2 by Medical Degree of Respondent - Completed Surveys

Question	Medical Degree of Respondent			
	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	7 (4.2)	1 (3.8)	7 (13.2)	5 (10.9)
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.[2]	128 (76.6) [69.5 - 82.8]	18 (69.2) [48.2 - 85.7]	34 (64.2) [49.8 - 76.9]	31 (67.4) [52.0 - 80.5]
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	11 (6.6)	2 (7.7)	2 (3.8)	2 (4.3)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	12 (7.2)	3 (11.5)	6 (11.3)	6 (13.0)

Table 8.1.2: Responses to Questions Linked to Key Risk Message #2 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
I don't know	9 (5.4)	2 (7.7)	4 (7.5)	2 (4.3)
Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.				
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.				
True[2]	162 (97.0) [93.2 - 99.0]	25 (96.2) [80.4 - 99.9]	49 (92.5) [81.8 - 97.9]	45 (97.8) [88.5 - 99.9]
False	4 (2.4)	0	3 (5.7)	1 (2.2)
I don't know	1 (0.6)	1 (3.8)	1 (1.9)	0
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.				
True	37 (22.2)	6 (23.1)	5 (9.4)	10 (21.7)
False[2]	126 (75.4) [68.2 - 81.8]	19 (73.1) [52.2 - 88.4]	46 (86.8) [74.7 - 94.5]	33 (71.7) [56.5 - 84.0]
I don't know	4 (2.4)	1 (3.8)	2 (3.8)	3 (6.5)

Source: Appendix B: Survey Tables, Table 8.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.3: Responses to Questions Linked to Key Risk Message #2 by Modality to Complete Survey - Completed Surveys

Question	Modality to Complete Survey	
	Internet (N=289) n (%) [95% CI][1]	Telephone (N=5) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.		
True	52 (18.0)	0
False[2]	222 (76.8) [71.5 - 81.6]	5 (100.0) [47.8 - 100.0]
I don't know	15 (5.2)	0
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.		
True	54 (18.7)	0
False[2]	225 (77.9) [72.6 - 82.5]	5 (100.0) [47.8 - 100.0]
I don't know	10 (3.5)	0
Question 9: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
Yes	9 (3.1)	0
No[2]	274 (94.8) [91.6 - 97.1]	4 (80.0) [28.4 - 99.5]
I don't know	6 (2.1)	1 (20.0)
9b: Headache or migraine pain		
Yes	6 (2.1)	0
No[2]	271 (93.8) [90.3 - 96.3]	5 (100.0) [47.8 - 100.0]
I don't know	12 (4.2)	0
9c: Dental pain		
Yes	4 (1.4)	0
No[2]	278 (96.2) [93.3 - 98.1]	5 (100.0) [47.8 - 100.0]
I don't know	7 (2.4)	0
9d: Breakthrough pain from cancer		
Yes[2]	287 (99.3) [97.5 - 99.9]	5 (100.0) [47.8 - 100.0]

Table 8.1.3: Responses to Questions Linked to Key Risk Message #2 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=289) n (%) [95% CI][1]	Telephone (N=5) n (%) [95% CI][1]
No	2 (0.7)	0
I don't know	0	0
9e: Chronic non-cancer pain		
Yes	54 (18.7)	0
No[2]	225 (77.9) [72.6 - 82.5]	5 (100.0) [47.8 - 100.0]
I don't know	10 (3.5)	0
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.		
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	20 (6.9)	0
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.[2]	209 (72.3) [66.8 - 77.4]	3 (60.0) [14.7 - 94.7]
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	18 (6.2)	0
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	26 (9.0)	1 (20.0)
I don't know	16 (5.5)	1 (20.0)
Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.		
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.		
True[2]	278 (96.2) [93.3 - 98.1]	5 (100.0) [47.8 - 100.0]
False	8 (2.8)	0

Table 8.1.3: Responses to Questions Linked to Key Risk Message #2 by Modality to Complete Survey - Completed Surveys

Question	Modality to Complete Survey	
	Internet (N=289) n (%) [95% CI][1]	Telephone (N=5) n (%) [95% CI][1]
I don't know	3 (1.0)	0
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.		
True	56 (19.4)	2 (40.0)
False[2]	222 (76.8) [71.5 - 81.6]	3 (60.0) [14.7 - 94.7]
I don't know	11 (3.8)	0

Source: Appendix B: Survey Tables, Table 8.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.4: Responses to Questions Linked to Key Risk Message #2 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.				
True	3 (11.5)	7 (14.3)	15 (17.6)	27 (20.1)
False[2]	21 (80.8) [60.6 - 93.4]	38 (77.6) [63.4 - 88.2]	63 (74.1) [63.5 - 83.0]	105 (78.4) [70.4 - 85.0]
I don't know	2 (7.7)	4 (8.2)	7 (8.2)	2 (1.5)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.				
True	5 (19.2)	4 (8.2)	15 (17.6)	30 (22.4)
False[2]	20 (76.9) [56.4 - 91.0]	43 (87.8) [75.2 - 95.4]	67 (78.8) [68.6 - 86.9]	100 (74.6) [66.4 - 81.7]
I don't know	1 (3.8)	2 (4.1)	3 (3.5)	4 (3.0)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.				
9a: Acute or postoperative pain				
Yes	3 (11.5)	0	0	6 (4.5)
No[2]	22 (84.6) [65.1 - 95.6]	47 (95.9) [86.0 - 99.5]	82 (96.5) [90.0 - 99.3]	127 (94.8) [89.5 - 97.9]
I don't know	1 (3.8)	2 (4.1)	3 (3.5)	1 (0.7)
9b: Headache or migraine pain				
Yes	0	0	0	6 (4.5)

Table 8.1.4: Responses to Questions Linked to Key Risk Message #2 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
No[2]	25 (96.2) [80.4 - 99.9]	48 (98.0) [89.1 - 99.9]	78 (91.8) [83.8 - 96.6]	125 (93.3) [87.6 - 96.9]
I don't know	1 (3.8)	1 (2.0)	7 (8.2)	3 (2.2)
9c: Dental pain				
Yes	0	0	0	4 (3.0)
No[2]	25 (96.2) [80.4 - 99.9]	48 (98.0) [89.1 - 99.9]	83 (97.6) [91.8 - 99.7]	127 (94.8) [89.5 - 97.9]
I don't know	1 (3.8)	1 (2.0)	2 (2.4)	3 (2.2)
9d: Breakthrough pain from cancer				
Yes[2]	26 (100.0) [86.8 - 100.0]	49 (100.0) [92.7 - 100.0]	85 (100.0) [95.8 - 100.0]	132 (98.5) [94.7 - 99.8]
No	0	0	0	2 (1.5)
I don't know	0	0	0	0
9e: Chronic non-cancer pain				
Yes	7 (26.9)	4 (8.2)	15 (17.6)	28 (20.9)
No[2]	19 (73.1) [52.2 - 88.4]	43 (87.8) [75.2 - 95.4]	64 (75.3) [64.7 - 84.0]	104 (77.6) [69.6 - 84.4]
I don't know	0	2 (4.1)	6 (7.1)	2 (1.5)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.				

Table 8.1.4: Responses to Questions Linked to Key Risk Message #2 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	4 (15.4)	3 (6.1)	7 (8.2)	6 (4.5)
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.[2]	15 (57.7) [36.9 - 76.6]	36 (73.5) [58.9 - 85.1]	63 (74.1) [63.5 - 83.0]	98 (73.1) [64.8 - 80.4]
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	2 (7.7)	4 (8.2)	3 (3.5)	9 (6.7)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	3 (11.5)	4 (8.2)	8 (9.4)	12 (9.0)

Table 8.1.4: Responses to Questions Linked to Key Risk Message #2 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
I don't know	2 (7.7)	2 (4.1)	4 (4.7)	9 (6.7)
Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.				
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.				
True[2]	25 (96.2) [80.4 - 99.9]	46 (93.9) [83.1 - 98.7]	80 (94.1) [86.8 - 98.1]	132 (98.5) [94.7 - 99.8]
False	1 (3.8)	1 (2.0)	4 (4.7)	2 (1.5)
I don't know	0	2 (4.1)	1 (1.2)	0
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.				
True	2 (7.7)	10 (20.4)	17 (20.0)	29 (21.6)
False[2]	21 (80.8) [60.6 - 93.4]	36 (73.5) [58.9 - 85.1]	64 (75.3) [64.7 - 84.0]	104 (77.6) [69.6 - 84.4]
I don't know	3 (11.5)	3 (6.1)	4 (4.7)	1 (0.7)

Source: Appendix B: Survey Tables, Table 8.1.4
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.5: Responses to Questions Linked to Key Risk Message #2 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.					
True	3 (20.0)	32 (17.0)	11 (17.2)	6 (28.6)	0
False[2]	9 (60.0) [32.3 - 83.7]	147 (78.2) [71.6 - 83.9]	53 (82.8) [71.3 - 91.1]	13 (61.9) [38.4 - 81.9]	5 (83.3) [35.9 - 99.6]
I don't know	3 (20.0)	9 (4.8)	0	2 (9.5)	1 (16.7)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.					
True	4 (26.7)	29 (15.4)	15 (23.4)	5 (23.8)	1 (16.7)
False[2]	10 (66.7) [38.4 - 88.2]	153 (81.4) [75.1 - 86.7]	46 (71.9) [59.2 - 82.4]	16 (76.2) [52.8 - 91.8]	5 (83.3) [35.9 - 99.6]
I don't know	1 (6.7)	6 (3.2)	3 (4.7)	0	0
Question 9: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.					
9a: Acute or postoperative pain					
Yes	0	5 (2.7)	0	3 (14.3)	1 (16.7)
No[2]	14 (93.3) [68.1 - 99.8]	178 (94.7) [90.4 - 97.4]	63 (98.4) [91.6 - 100.0]	18 (85.7) [63.7 - 97.0]	5 (83.3) [35.9 - 99.6]
I don't know	1 (6.7)	5 (2.7)	1 (1.6)	0	0
9b: Headache or migraine pain					

Table 8.1.5: Responses to Questions Linked to Key Risk Message #2 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
Yes	0	5 (2.7)	0	1 (4.8)	0
No[2]	14 (93.3) [68.1 - 99.8]	177 (94.1) [89.8 - 97.0]	63 (98.4) [91.6 - 100.0]	17 (81.0) [58.1 - 94.6]	5 (83.3) [35.9 - 99.6]
I don't know	1 (6.7)	6 (3.2)	1 (1.6)	3 (14.3)	1 (16.7)
9c: Dental pain					
Yes	0	2 (1.1)	1 (1.6)	1 (4.8)	0
No[2]	15 (100.0) [78.2 - 100.0]	182 (96.8) [93.2 - 98.8]	63 (98.4) [91.6 - 100.0]	18 (85.7) [63.7 - 97.0]	5 (83.3) [35.9 - 99.6]
I don't know	0	4 (2.1)	0	2 (9.5)	1 (16.7)
9d: Breakthrough pain from cancer					
Yes[2]	15 (100.0) [78.2 - 100.0]	187 (99.5) [97.1 - 100.0]	64 (100.0) [94.4 - 100.0]	20 (95.2) [76.2 - 99.9]	6 (100.0) [54.1 - 100.0]
No	0	1 (0.5)	0	1 (4.8)	0
I don't know	0	0	0	0	0
9e: Chronic non-cancer pain					
Yes	3 (20.0)	36 (19.1)	4 (6.3)	8 (38.1)	3 (50.0)
No[2]	12 (80.0) [51.9 - 95.7]	145 (77.1) [70.5 - 82.9]	58 (90.6) [80.7 - 96.5]	12 (57.1) [34.0 - 78.2]	3 (50.0) [11.8 - 88.2]
I don't know	0	7 (3.7)	2 (3.1)	1 (4.8)	0

Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.

Table 8.1.5: Responses to Questions Linked to Key Risk Message #2 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	1 (6.7)	15 (8.0)	3 (4.7)	1 (4.8)	0
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.[2]	11 (73.3) [44.9 - 92.2]	141 (75.0) [68.2 - 81.0]	47 (73.4) [60.9 - 83.7]	11 (52.4) [29.8 - 74.3]	2 (33.3) [4.3 - 77.7]
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	2 (13.3)	8 (4.3)	6 (9.4)	2 (9.5)	0

Table 8.1.5: Responses to Questions Linked to Key Risk Message #2 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	0	16 (8.5)	3 (4.7)	6 (28.6)	2 (33.3)
I don't know	1 (6.7)	8 (4.3)	5 (7.8)	1 (4.8)	2 (33.3)
Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.					
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.					
True[2]	14 (93.3) [68.1 - 99.8]	181 (96.3) [92.5 - 98.5]	62 (96.9) [89.2 - 99.6]	21 (100.0) [83.9 - 100.0]	5 (83.3) [35.9 - 99.6]
False	0	6 (3.2)	2 (3.1)	0	0
I don't know	1 (6.7)	1 (0.5)	0	0	1 (16.7)
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.					
True	3 (20.0)	33 (17.6)	12 (18.8)	8 (38.1)	2 (33.3)
False[2]	10 (66.7) [38.4 - 88.2]	148 (78.7) [72.2 - 84.3]	50 (78.1) [66.0 - 87.5]	13 (61.9) [38.4 - 81.9]	4 (66.7) [22.3 - 95.7]

Table 8.1.5: Responses to Questions Linked to Key Risk Message #2 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
I don't know	2 (13.3)	7 (3.7)	2 (3.1)	0	0

Source: Appendix B: Survey Tables, Table 8.1.5
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.1.6: Responses to Questions Linked to Key Risk Message #2 by Practicing in a Closed Healthcare System - Completed Surveys		
	Practicing in a Closed Healthcare System	
Question	Yes (N=4) n (%) [95% CI][1]	No (N=290) n (%) [95% CI][1]
Question 6: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
6a: According to the product labeling, a cancer patient may start a TIRF medicine and an around-the-clock opioid at the same time.		
True	1 (25.0)	51 (17.6)
False[2]	3 (75.0) [19.4 - 99.4]	224 (77.2) [72.0 - 81.9]
I don't know	0	15 (5.2)
6b: According to the product labeling, a cancer patient who has been on an around-the-clock opioid for 1 day may start taking a TIRF medicine for breakthrough pain.		
True	2 (50.0)	52 (17.9)
False[2]	2 (50.0) [6.8 - 93.2]	228 (78.6) [73.4 - 83.2]
I don't know	0	10 (3.4)
Question 9: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Please answer Yes, No, or I don't know for each option.		
9a: Acute or postoperative pain		
Yes	0	9 (3.1)
No[2]	4 (100.0) [39.8 - 100.0]	274 (94.5) [91.2 - 96.8]
I don't know	0	7 (2.4)
9b: Headache or migraine pain		
Yes	0	6 (2.1)
No[2]	4 (100.0) [39.8 - 100.0]	272 (93.8) [90.4 - 96.3]
I don't know	0	12 (4.1)
9c: Dental pain		
Yes	0	4 (1.4)
No[2]	4 (100.0) [39.8 - 100.0]	279 (96.2) [93.3 - 98.1]
I don't know	0	7 (2.4)
9d: Breakthrough pain from cancer		
Yes[2]	4 (100.0) [39.8 - 100.0]	288 (99.3) [97.5 - 99.9]

Table 8.1.6: Responses to Questions Linked to Key Risk Message #2 by Practicing in a Closed Healthcare System - Completed Surveys		
	Practicing in a Closed Healthcare System	
Question	Yes (N=4) n (%) [95% CI][1]	No (N=290) n (%) [95% CI][1]
No	0	2 (0.7)
I don't know	0	0
9e: Chronic non-cancer pain		
Yes	1 (25.0)	53 (18.3)
No[2]	3 (75.0) [19.4 - 99.4]	227 (78.3) [73.1 - 82.9]
I don't know	0	10 (3.4)
Question 15: The patients described are experiencing breakthrough pain. According to the labeling, a TIRF medicine is not appropriate for one of them. Which patient should not receive a TIRF medicine? Please select one option.		
Adult male with advanced lung cancer; underlying persistent cancer pain managed with 25 mcg/hour transdermal fentanyl patches for the past two months.	0	20 (6.9)
Adult female with localized breast cancer; just completed a mastectomy and reconstructive surgery; persistent cancer pain managed with 30 mg oral morphine daily for the past 6 weeks.[2]	3 (75.0) [19.4 - 99.4]	209 (72.1) [66.5 - 77.2]
Adult male patient with advanced prostate cancer who, over the last 2 weeks, has been prescribed 100 mg oral morphine daily for pain due to bone metastasis.	1 (25.0)	17 (5.9)
Adult female with advanced sarcoma who has been taking a daily dose of 12 mg oral hydromorphone for the last 3 weeks.	0	27 (9.3)
I don't know	0	17 (5.9)
Question 20: Before initiating treatment with a TIRF medicine, prescribers must review the Medication Guide with the patient. Please select True, False, or I don't know for each of the following counseling statements.		
20b: Inform patients that TIRF medicines must not be used for acute or postoperative pain, pain from injuries, headache/migraine, or any other short-term pain.		
True[2]	4 (100.0) [39.8 - 100.0]	279 (96.2) [93.3 - 98.1]
False	0	8 (2.8)

Table 8.1.6: Responses to Questions Linked to Key Risk Message #2 by Practicing in a Closed Healthcare System - Completed Surveys

Question	Practicing in a Closed Healthcare System	
	Yes (N=4) n (%) [95% CI][1]	No (N=290) n (%) [95% CI][1]
I don't know	0	3 (1.0)
20c: Instruct patients that they can continue to take their TIRF medicine, if they stop taking their around-the-clock opioid medicine.		
True	1 (25.0)	57 (19.7)
False[2]	3 (75.0) [19.4 - 99.4]	222 (76.6) [71.2 - 81.3]
I don't know	0	11 (3.8)

Source: Appendix B: Survey Tables, Table 8.1.6
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 8.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #2 - Completed Surveys	
Correct Responses	**Prescribers (N=294) n (%)**
0 correct responses	0
1 correct response	0
2 correct responses	2 (0.7)
3 correct responses	1 (0.3)
4 correct responses	3 (1.0)
5 correct responses	6 (2.0)
6 correct responses	11 (3.7)
7 correct responses	35 (11.9)
8 correct responses	46 (15.6)
9 correct responses	92 (31.3)
10 correct responses	98 (33.3)

Source: Appendix B: Survey Tables, Table 8.2

Table 9.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys	
Question	**Prescribers (N=294) n (%) [95% CI][1]**
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.	
True[2]	291 (99.0) [97.0 - 99.8]
False	3 (1.0)
I don't know	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.	
8a: A personal history of psychiatric illness	
Yes[2]	253 (86.1) [81.6 - 89.8]
No	27 (9.2)
I don't know	14 (4.8)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse	
Yes[2]	294 (100.0) [98.8 - 100.0]
No	0
I don't know	0
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.	
True[2]	282 (95.9) [93.0 - 97.9]
False	10 (3.4)
I don't know	2 (0.7)
Question 22: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.	
22a: Misuse	
True[2]	290 (98.6) [96.6 - 99.6]
False	4 (1.4)
I don't know	0
22b: Abuse	

Table 9.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys	
Question	**Prescribers (N=294) n (%) [95% CI][1]**
True[2]	291 (99.0) [97.0 - 99.8]
False	2 (0.7)
I don't know	1 (0.3)
22c: Addiction	
True[2]	291 (99.0) [97.0 - 99.8]
False	3 (1.0)
I don't know	0
22d: Overdose	
True[2]	292 (99.3) [97.6 - 99.9]
False	2 (0.7)
I don't know	0
22e: Hypothyroidism	
True	20 (6.8)
False[2]	232 (78.9) [73.8 - 83.4]
I don't know	42 (14.3)
22f: Infection	
True	23 (7.8)
False[2]	253 (86.1) [81.6 - 89.8]
I don't know	18 (6.1)

Source: Appendix B: Survey Tables, Table 9.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.1: Responses to Questions Linked to Key Risk Message #3 by Reading Full Prescribing Information or Medication Guide - Completed Surveys		
	Reading Full Prescribing Information or Medication Guide	
Question	Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True[2]	265 (98.9) [96.8 - 99.8]	26 (100.0) [86.8 - 100.0]
False	3 (1.1)	0
I don't know	0	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8a: A personal history of psychiatric illness		
Yes[2]	234 (87.3) [82.7 - 91.1]	19 (73.1) [52.2 - 88.4]
No	23 (8.6)	4 (15.4)
I don't know	11 (4.1)	3 (11.5)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes[2]	268 (100.0) [98.6 - 100.0]	26 (100.0) [86.8 - 100.0]
No	0	0
I don't know	0	0
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[2]	259 (96.6) [93.7 - 98.5]	23 (88.5) [69.8 - 97.6]
False	8 (3.0)	2 (7.7)
I don't know	1 (0.4)	1 (3.8)
Question 22: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.		
22a: Misuse		
True[2]	266 (99.3) [97.3 - 99.9]	24 (92.3) [74.9 - 99.1]
False	2 (0.7)	2 (7.7)

Table 9.1.1: Responses to Questions Linked to Key Risk Message #3 by Reading Full Prescribing Information or Medication Guide - Completed Surveys

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
I don't know	0	0
22b: Abuse		
True[2]	268 (100.0) [98.6 - 100.0]	23 (88.5) [69.8 - 97.6]
False	0	2 (7.7)
I don't know	0	1 (3.8)
22c: Addiction		
True[2]	267 (99.6) [97.9 - 100.0]	24 (92.3) [74.9 - 99.1]
False	1 (0.4)	2 (7.7)
I don't know	0	0
22d: Overdose		
True[2]	267 (99.6) [97.9 - 100.0]	25 (96.2) [80.4 - 99.9]
False	1 (0.4)	1 (3.8)
I don't know	0	0
22e: Hypothyroidism		
True	19 (7.1)	1 (3.8)
False[2]	213 (79.5) [74.1 - 84.1]	19 (73.1) [52.2 - 88.4]
I don't know	36 (13.4)	6 (23.1)
22f: Infection		
True	20 (7.5)	3 (11.5)
False[2]	233 (86.9) [82.3 - 90.7]	20 (76.9) [56.4 - 91.0]
I don't know	15 (5.6)	3 (11.5)

Source: Appendix B: Survey Tables, Table 9.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.2: Responses to Questions Linked to Key Risk Message #3 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True[2]	165 (98.8) [95.7 - 99.9]	26 (100.0) [86.8 - 100.0]	52 (98.1) [89.9 - 100.0]	46 (100.0) [92.3 - 100.0]
False	2 (1.2)	0	1 (1.9)	0
I don't know	0	0	0	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes[2]	145 (86.8) [80.7 - 91.6]	21 (80.8) [60.6 - 93.4]	44 (83.0) [70.2 - 91.9]	41 (89.1) [76.4 - 96.4]
No	14 (8.4)	4 (15.4)	7 (13.2)	2 (4.3)
I don't know	8 (4.8)	1 (3.8)	2 (3.8)	3 (6.5)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes[2]	167 (100.0) [97.8 - 100.0]	26 (100.0) [86.8 - 100.0]	53 (100.0) [93.3 - 100.0]	46 (100.0) [92.3 - 100.0]
No	0	0	0	0
I don't know	0	0	0	0
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True[2]	158 (94.6) [90.0 - 97.5]	26 (100.0) [86.8 - 100.0]	51 (96.2) [87.0 - 99.5]	45 (97.8) [88.5 - 99.9]
False	9 (5.4)	0	1 (1.9)	0

Table 9.1.2: Responses to Questions Linked to Key Risk Message #3 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
I don't know	0	0	1 (1.9)	1 (2.2)
Question 22: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.				
22a: Misuse				
True[2]	165 (98.8) [95.7 - 99.9]	25 (96.2) [80.4 - 99.9]	52 (98.1) [89.9 - 100.0]	46 (100.0) [92.3 - 100.0]
False	2 (1.2)	1 (3.8)	1 (1.9)	0
I don't know	0	0	0	0
22b: Abuse				
True[2]	166 (99.4) [96.7 - 100.0]	26 (100.0) [86.8 - 100.0]	51 (96.2) [87.0 - 99.5]	46 (100.0) [92.3 - 100.0]
False	1 (0.6)	0	1 (1.9)	0
I don't know	0	0	1 (1.9)	0
22c: Addiction				
True[2]	167 (100.0) [97.8 - 100.0]	26 (100.0) [86.8 - 100.0]	50 (94.3) [84.3 - 98.8]	46 (100.0) [92.3 - 100.0]
False	0	0	3 (5.7)	0
I don't know	0	0	0	0
22d: Overdose				
True[2]	167 (100.0) [97.8 - 100.0]	25 (96.2) [80.4 - 99.9]	52 (98.1) [89.9 - 100.0]	46 (100.0) [92.3 - 100.0]
False	0	1 (3.8)	1 (1.9)	0

Table 9.1.2: Responses to Questions Linked to Key Risk Message #3 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
I don't know	0	0	0	0
22e: Hypothyroidism				
True	9 (5.4)	4 (15.4)	6 (11.3)	1 (2.2)
False[2]	135 (80.8) [74.0 - 86.5]	18 (69.2) [48.2 - 85.7]	41 (77.4) [63.8 - 87.7]	36 (78.3) [63.6 - 89.1]
I don't know	23 (13.8)	4 (15.4)	6 (11.3)	9 (19.6)
22f: Infection				
True	10 (6.0)	3 (11.5)	6 (11.3)	4 (8.7)
False[2]	147 (88.0) [82.1 - 92.5]	21 (80.8) [60.6 - 93.4]	45 (84.9) [72.4 - 93.3]	38 (82.6) [68.6 - 92.2]
I don't know	10 (6.0)	2 (7.7)	2 (3.8)	4 (8.7)

Source: Appendix B: Survey Tables, Table 9.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.3: Responses to Questions Linked to Key Risk Message #3 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=289) n (%) [95% CI][1]	Telephone (N=5) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True[2]	286 (99.0) [97.0 - 99.8]	5 (100.0) [47.8 - 100.0]
False	3 (1.0)	0
I don't know	0	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8a: A personal history of psychiatric illness		
Yes[2]	248 (85.8) [81.2 - 89.6]	5 (100.0) [47.8 - 100.0]
No	27 (9.3)	0
I don't know	14 (4.8)	0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes[2]	289 (100.0) [98.7 - 100.0]	5 (100.0) [47.8 - 100.0]
No	0	0
I don't know	0	0
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[2]	277 (95.8) [92.9 - 97.8]	5 (100.0) [47.8 - 100.0]
False	10 (3.5)	0
I don't know	2 (0.7)	0
Question 22: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.		
22a: Misuse		
True[2]	285 (98.6) [96.5 - 99.6]	5 (100.0) [47.8 - 100.0]
False	4 (1.4)	0
I don't know	0	0

Table 9.1.3: Responses to Questions Linked to Key Risk Message #3 by Modality to Complete Survey - Completed Surveys

Question	Modality to Complete Survey	
	Internet (N=289) n (%) [95% CI][1]	Telephone (N=5) n (%) [95% CI][1]
22b: Abuse		
True[2]	286 (99.0) [97.0 - 99.8]	5 (100.0) [47.8 - 100.0]
False	2 (0.7)	0
I don't know	1 (0.3)	0
22c: Addiction		
True[2]	286 (99.0) [97.0 - 99.8]	5 (100.0) [47.8 - 100.0]
False	3 (1.0)	0
I don't know	0	0
22d: Overdose		
True[2]	287 (99.3) [97.5 - 99.9]	5 (100.0) [47.8 - 100.0]
False	2 (0.7)	0
I don't know	0	0
22e: Hypothyroidism		
True	20 (6.9)	0
False[2]	227 (78.5) [73.4 - 83.1]	5 (100.0) [47.8 - 100.0]
I don't know	42 (14.5)	0
22f: Infection		
True	23 (8.0)	0
False[2]	248 (85.8) [81.2 - 89.6]	5 (100.0) [47.8 - 100.0]
I don't know	18 (6.2)	0

Source: Appendix B: Survey Tables, Table 9.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.4: Responses to Questions Linked to Key Risk Message #3 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.				
True[2]	26 (100.0) [86.8 - 100.0]	49 (100.0) [92.7 - 100.0]	84 (98.8) [93.6 - 100.0]	132 (98.5) [94.7 - 99.8]
False	0	0	1 (1.2)	2 (1.5)
I don't know	0	0	0	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.				
8a: A personal history of psychiatric illness				
Yes[2]	21 (80.8) [60.6 - 93.4]	47 (95.9) [86.0 - 99.5]	77 (90.6) [82.3 - 95.8]	108 (80.6) [72.9 - 86.9]
No	4 (15.4)	1 (2.0)	1 (1.2)	21 (15.7)
I don't know	1 (3.8)	1 (2.0)	7 (8.2)	5 (3.7)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse				
Yes[2]	26 (100.0) [86.8 - 100.0]	49 (100.0) [92.7 - 100.0]	85 (100.0) [95.8 - 100.0]	134 (100.0) [97.3 - 100.0]
No	0	0	0	0
I don't know	0	0	0	0
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.				
True[2]	25 (96.2) [80.4 - 99.9]	47 (95.9) [86.0 - 99.5]	84 (98.8) [93.6 - 100.0]	126 (94.0) [88.6 - 97.4]
False	1 (3.8)	1 (2.0)	1 (1.2)	7 (5.2)

Table 9.1.4: Responses to Questions Linked to Key Risk Message #3 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
I don't know	0	1 (2.0)	0	1 (0.7)
Question 22: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.				
22a: Misuse				
True[2]	26 (100.0) [86.8 - 100.0]	47 (95.9) [86.0 - 99.5]	84 (98.8) [93.6 - 100.0]	133 (99.3) [95.9 - 100.0]
False	0	2 (4.1)	1 (1.2)	1 (0.7)
I don't know	0	0	0	0
22b: Abuse				
True[2]	26 (100.0) [86.8 - 100.0]	47 (95.9) [86.0 - 99.5]	85 (100.0) [95.8 - 100.0]	133 (99.3) [95.9 - 100.0]
False	0	2 (4.1)	0	0
I don't know	0	0	0	1 (0.7)
22c: Addiction				
True[2]	25 (96.2) [80.4 - 99.9]	48 (98.0) [89.1 - 99.9]	85 (100.0) [95.8 - 100.0]	133 (99.3) [95.9 - 100.0]
False	1 (3.8)	1 (2.0)	0	1 (0.7)
I don't know	0	0	0	0
22d: Overdose				
True[2]	26 (100.0) [86.8 - 100.0]	49 (100.0) [92.7 - 100.0]	84 (98.8) [93.6 - 100.0]	133 (99.3) [95.9 - 100.0]
False	0	0	1 (1.2)	1 (0.7)

Table 9.1.4: Responses to Questions Linked to Key Risk Message #3 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
I don't know	0	0	0	0
22e: Hypothyroidism				
True	3 (11.5)	3 (6.1)	5 (5.9)	9 (6.7)
False[2]	21 (80.8) [60.6 - 93.4]	36 (73.5) [58.9 - 85.1]	65 (76.5) [66.0 - 85.0]	110 (82.1) [74.5 - 88.2]
I don't know	2 (7.7)	10 (20.4)	15 (17.6)	15 (11.2)
22f: Infection				
True	2 (7.7)	4 (8.2)	7 (8.2)	10 (7.5)
False[2]	24 (92.3) [74.9 - 99.1]	41 (83.7) [70.3 - 92.7]	72 (84.7) [75.3 - 91.6]	116 (86.6) [79.6 - 91.8]
I don't know	0	4 (8.2)	6 (7.1)	8 (6.0)

Source: Appendix B: Survey Tables, Table 9.1.4
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.5: Responses to Questions Linked to Key Risk Message #3 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.					
True[2]	15 (100.0) [78.2 - 100.0]	187 (99.5) [97.1 - 100.0]	62 (96.9) [89.2 - 99.6]	21 (100.0) [83.9 - 100.0]	6 (100.0) [54.1 - 100.0]
False	0	1 (0.5)	2 (3.1)	0	0
I don't know	0	0	0	0	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.					
8a: A personal history of psychiatric illness					
Yes[2]	11 (73.3) [44.9 - 92.2]	158 (84.0) [78.0 - 89.0]	59 (92.2) [82.7 - 97.4]	19 (90.5) [69.6 - 98.8]	6 (100.0) [54.1 - 100.0]
No	4 (26.7)	16 (8.5)	5 (7.8)	2 (9.5)	0
I don't know	0	14 (7.4)	0	0	0
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse					
Yes[2]	15 (100.0) [78.2 - 100.0]	188 (100.0) [98.1 - 100.0]	64 (100.0) [94.4 - 100.0]	21 (100.0) [83.9 - 100.0]	6 (100.0) [54.1 - 100.0]
No	0	0	0	0	0
I don't know	0	0	0	0	0
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.					

Table 9.1.5: Responses to Questions Linked to Key Risk Message #3 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
True[2]	15 (100.0) [78.2 - 100.0]	179 (95.2) [91.1 - 97.8]	62 (96.9) [89.2 - 99.6]	21 (100.0) [83.9 - 100.0]	5 (83.3) [35.9 - 99.6]
False	0	7 (3.7)	2 (3.1)	0	1 (16.7)
I don't know	0	2 (1.1)	0	0	0
Question 22: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.					
22a: Misuse					
True[2]	15 (100.0) [78.2 - 100.0]	185 (98.4) [95.4 - 99.7]	63 (98.4) [91.6 - 100.0]	21 (100.0) [83.9 - 100.0]	6 (100.0) [54.1 - 100.0]
False	0	3 (1.6)	1 (1.6)	0	0
I don't know	0	0	0	0	0
22b: Abuse					
True[2]	15 (100.0) [78.2 - 100.0]	185 (98.4) [95.4 - 99.7]	64 (100.0) [94.4 - 100.0]	21 (100.0) [83.9 - 100.0]	6 (100.0) [54.1 - 100.0]
False	0	2 (1.1)	0	0	0
I don't know	0	1 (0.5)	0	0	0
22c: Addiction					
True[2]	15 (100.0) [78.2 - 100.0]	185 (98.4) [95.4 - 99.7]	64 (100.0) [94.4 - 100.0]	21 (100.0) [83.9 - 100.0]	6 (100.0) [54.1 - 100.0]
False	0	3 (1.6)	0	0	0
I don't know	0	0	0	0	0

Table 9.1.5: Responses to Questions Linked to Key Risk Message #3 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
22d: Overdose					
True[2]	15 (100.0) [78.2 - 100.0]	187 (99.5) [97.1 - 100.0]	63 (98.4) [91.6 - 100.0]	21 (100.0) [83.9 - 100.0]	6 (100.0) [54.1 - 100.0]
False	0	1 (0.5)	1 (1.6)	0	0
I don't know	0	0	0	0	0
22e: Hypothyroidism					
True	1 (6.7)	13 (6.9)	4 (6.3)	2 (9.5)	0
False[2]	9 (60.0) [32.3 - 83.7]	148 (78.7) [72.2 - 84.3]	54 (84.4) [73.1 - 92.2]	17 (81.0) [58.1 - 94.6]	4 (66.7) [22.3 - 95.7]
I don't know	5 (33.3)	27 (14.4)	6 (9.4)	2 (9.5)	2 (33.3)
22f: Infection					
True	1 (6.7)	15 (8.0)	3 (4.7)	4 (19.0)	0
False[2]	12 (80.0) [51.9 - 95.7]	159 (84.6) [78.6 - 89.4]	60 (93.8) [84.8 - 98.3]	17 (81.0) [58.1 - 94.6]	5 (83.3) [35.9 - 99.6]
I don't know	2 (13.3)	14 (7.4)	1 (1.6)	0	1 (16.7)

Source: Appendix B: Survey Tables, Table 9.1.5
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.1.6: Responses to Questions Linked to Key Risk Message #3 by Practicing in a Closed Healthcare System - Completed Surveys		
	Practicing in a Closed Healthcare System	
Question	Yes (N=4) n (%) [95% CI][1]	No (N=290) n (%) [95% CI][1]
Question 7: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
7e: It is important to monitor for signs of abuse and addiction in patients who take TIRF medicines.		
True[2]	4 (100.0) [39.8 - 100.0]	287 (99.0) [97.0 - 99.8]
False	0	3 (1.0)
I don't know	0	0
Question 8: Which of the following are risk factors for opioid abuse? Please answer Yes, No, or I don't know for each option.		
8a: A personal history of psychiatric illness		
Yes[2]	4 (100.0) [39.8 - 100.0]	249 (85.9) [81.3 - 89.7]
No	0	27 (9.3)
I don't know	0	14 (4.8)
8b: A personal history of past or current alcohol or drug abuse, or a family history of illicit drug use or alcohol abuse		
Yes[2]	4 (100.0) [39.8 - 100.0]	290 (100.0) [98.7 - 100.0]
No	0	0
I don't know	0	0
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
12a: TIRF medicines can be abused in a manner similar to other opioid agonists.		
True[2]	4 (100.0) [39.8 - 100.0]	278 (95.9) [92.9 - 97.8]
False	0	10 (3.4)
I don't know	0	2 (0.7)
Question 22: Which of the following risks are associated with the use of TIRF medicines? Please answer True, False, or I don't know for the following statements.		
22a: Misuse		
True[2]	4 (100.0) [39.8 - 100.0]	286 (98.6) [96.5 - 99.6]
False	0	4 (1.4)
I don't know	0	0

Table 9.1.6: Responses to Questions Linked to Key Risk Message #3 by Practicing in a Closed Healthcare System - Completed Surveys

Question	Practicing in a Closed Healthcare System	
	Yes (N=4) n (%) [95% CI][1]	No (N=290) n (%) [95% CI][1]
22b: Abuse		
True[2]	4 (100.0) [39.8 - 100.0]	287 (99.0) [97.0 - 99.8]
False	0	2 (0.7)
I don't know	0	1 (0.3)
22c: Addiction		
True[2]	4 (100.0) [39.8 - 100.0]	287 (99.0) [97.0 - 99.8]
False	0	3 (1.0)
I don't know	0	0
22d: Overdose		
True[2]	4 (100.0) [39.8 - 100.0]	288 (99.3) [97.5 - 99.9]
False	0	2 (0.7)
I don't know	0	0
22e: Hypothyroidism		
True	0	20 (6.9)
False[2]	4 (100.0) [39.8 - 100.0]	228 (78.6) [73.4 - 83.2]
I don't know	0	42 (14.5)
22f: Infection		
True	0	23 (7.9)
False[2]	3 (75.0) [19.4 - 99.4]	250 (86.2) [81.7 - 90.0]
I don't know	1 (25.0)	17 (5.9)

Source: Appendix B: Survey Tables, Table 9.1.6
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 9.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #3 - Completed Surveys

Correct Responses	Prescribers (N=294) n (%)
0 correct responses	0
1 correct response	0
2 correct responses	0
3 correct responses	0
4 correct responses	0
5 correct responses	1 (0.3)
6 correct responses	2 (0.7)
7 correct responses	7 (2.4)
8 correct responses	33 (11.2)
9 correct responses	71 (24.1)
10 correct responses	180 (61.2)

Source: Appendix B: Survey Tables, Table 9.2

Table 10.1: Primary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys	
Question	**Prescribers (N=294) n (%) [95% CI][1]**
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.	
12b: TIRF medicines are interchangeable with each other regardless of route of administration.	
True	15 (5.1)
False[2]	271 (92.2) [88.5 - 95.0]
I don't know	8 (2.7)
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.	
True[2]	283 (96.3) [93.4 - 98.1]
False	5 (1.7)
I don't know	6 (2.0)
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.	
True[2]	269 (91.5) [87.7 - 94.4]
False	11 (3.7)
I don't know	14 (4.8)
Question 16: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.	
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	5 (1.7)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	231 (78.6) [73.4 - 83.1]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	25 (8.5)
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	21 (7.1)
I don't know.	12 (4.1)

Source: Appendix B: Survey Tables, Table 10.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.1: Responses to Questions Linked to Key Risk Message #4 by Reading Full Prescribing Information or Medication Guide - Completed Surveys

Question	Reading Full Prescribing Information or Medication Guide: Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Reading Full Prescribing Information or Medication Guide: Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
12b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	12 (4.5)	3 (11.5)
False[2]	249 (92.9) [89.2 - 95.7]	22 (84.6) [65.1 - 95.6]
I don't know	7 (2.6)	1 (3.8)
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True[2]	259 (96.6) [93.7 - 98.5]	24 (92.3) [74.9 - 99.1]
False	4 (1.5)	1 (3.8)
I don't know	5 (1.9)	1 (3.8)
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2]	246 (91.8) [87.8 - 94.8]	23 (88.5) [69.8 - 97.6]
False	10 (3.7)	1 (3.8)
I don't know	12 (4.5)	2 (7.7)
Question 16: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.		
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	4 (1.5)	1 (3.8)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	217 (81.0) [75.8 - 85.5]	14 (53.8) [33.4 - 73.4]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	20 (7.5)	5 (19.2)

Table 10.1.1: Responses to Questions Linked to Key Risk Message #4 by Reading Full Prescribing Information or Medication Guide - Completed Surveys

Question	Reading Full Prescribing Information or Medication Guide	
	Received and read PI or Med Guide (N=268) n (%) [95% CI][1]	Did not receive or read PI or Med Guide (N=26) n (%) [95% CI][1]
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	18 (6.7)	3 (11.5)
I don't know.	9 (3.4)	3 (11.5)

Source: Appendix B: Survey Tables, Table 10.1.1
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.2: Responses to Questions Linked to Key Risk Message #4 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
12b: TIRF medicines are interchangeable with each other regardless of route of administration.				
True	9 (5.4)	2 (7.7)	3 (5.7)	1 (2.2)
False[2]	156 (93.4) [88.5 - 96.7]	24 (92.3) [74.9 - 99.1]	49 (92.5) [81.8 - 97.9]	40 (87.0) [73.7 - 95.1]
I don't know	2 (1.2)	0	1 (1.9)	5 (10.9)
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True[2]	163 (97.6) [94.0 - 99.3]	25 (96.2) [80.4 - 99.9]	51 (96.2) [87.0 - 99.5]	42 (91.3) [79.2 - 97.6]
False	2 (1.2)	0	2 (3.8)	1 (2.2)
I don't know	2 (1.2)	1 (3.8)	0	3 (6.5)
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True[2]	156 (93.4) [88.5 - 96.7]	24 (92.3) [74.9 - 99.1]	45 (84.9) [72.4 - 93.3]	42 (91.3) [79.2 - 97.6]
False	3 (1.8)	2 (7.7)	5 (9.4)	1 (2.2)
I don't know	8 (4.8)	0	3 (5.7)	3 (6.5)
Question 16: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.				

Table 10.1.2: Responses to Questions Linked to Key Risk Message #4 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	2 (1.2)	0	0	3 (6.5)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	135 (80.8) [74.0 - 86.5]	23 (88.5) [69.8 - 97.6]	39 (73.6) [59.7 - 84.7]	32 (69.6) [54.2 - 82.3]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	14 (8.4)	2 (7.7)	4 (7.5)	5 (10.9)

Table 10.1.2: Responses to Questions Linked to Key Risk Message #4 by Medical Degree of Respondent - Completed Surveys				
	Medical Degree of Respondent			
Question	MD (N=167) n (%) [95% CI][1]	DO (N=26) n (%) [95% CI][1]	Nurse Practitioner (N=53) n (%) [95% CI][1]	Physician Assistant (N=46) n (%) [95% CI][1]
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	11 (6.6)	1 (3.8)	6 (11.3)	3 (6.5)
I don't know.	5 (3.0)	0	4 (7.5)	3 (6.5)

Source: Appendix B: Survey Tables, Table 10.1.2
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.3: Responses to Questions Linked to Key Risk Message #4 by Modality to Complete Survey - Completed Surveys		
	Modality to Complete Survey	
Question	Internet (N=289) n (%) [95% CI][1]	Telephone (N=5) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
12b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	15 (5.2)	0
False[2]	266 (92.0) [88.3 - 94.9]	5 (100.0) [47.8 - 100.0]
I don't know	8 (2.8)	0
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True[2]	278 (96.2) [93.3 - 98.1]	5 (100.0) [47.8 - 100.0]
False	5 (1.7)	0
I don't know	6 (2.1)	0
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2]	264 (91.3) [87.5 - 94.3]	5 (100.0) [47.8 - 100.0]
False	11 (3.8)	0
I don't know	14 (4.8)	0
Question 16: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.		
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	5 (1.7)	0
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	226 (78.2) [73.0 - 82.8]	5 (100.0) [47.8 - 100.0]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	25 (8.7)	0

Table 10.1.3: Responses to Questions Linked to Key Risk Message #4 by Modality to Complete Survey - Completed Surveys

Question	Modality to Complete Survey	
	Internet (N=289) n (%) [95% CI][1]	Telephone (N=5) n (%) [95% CI][1]
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	21 (7.3)	0
I don't know.	12 (4.2)	0

Source: Appendix B: Survey Tables, Table 10.1.3
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.4: Responses to Questions Linked to Key Risk Message #4 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.				
12b: TIRF medicines are interchangeable with each other regardless of route of administration.				
True	2 (7.7)	0	6 (7.1)	7 (5.2)
False[2]	24 (92.3) [74.9 - 99.1]	45 (91.8) [80.4 - 97.7]	77 (90.6) [82.3 - 95.8]	125 (93.3) [87.6 - 96.9]
I don't know	0	4 (8.2)	2 (2.4)	2 (1.5)
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.				
True[2]	25 (96.2) [80.4 - 99.9]	47 (95.9) [86.0 - 99.5]	81 (95.3) [88.4 - 98.7]	130 (97.0) [92.5 - 99.2]
False	1 (3.8)	0	1 (1.2)	3 (2.2)
I don't know	0	2 (4.1)	3 (3.5)	1 (0.7)
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.				
True[2]	20 (76.9) [56.4 - 91.0]	43 (87.8) [75.2 - 95.4]	76 (89.4) [80.8 - 95.0]	130 (97.0) [92.5 - 99.2]
False	3 (11.5)	2 (4.1)	3 (3.5)	3 (2.2)
I don't know	3 (11.5)	4 (8.2)	6 (7.1)	1 (0.7)
Question 16: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.				

Table 10.1.4: Responses to Questions Linked to Key Risk Message #4 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	0	3 (6.1)	0	2 (1.5)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	18 (69.2) [48.2 - 85.7]	39 (79.6) [65.7 - 89.8]	66 (77.6) [67.3 - 86.0]	108 (80.6) [72.9 - 86.9]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	2 (7.7)	3 (6.1)	6 (7.1)	14 (10.4)

Table 10.1.4: Responses to Questions Linked to Key Risk Message #4 by Time Practicing Medicine - Completed Surveys				
	Time Practicing Medicine			
Question	Less than 3 years (N=26) n (%) [95% CI][1]	3 to 5 years (N=49) n (%) [95% CI][1]	6 to 15 years (N=85) n (%) [95% CI][1]	More than 15 years (N=134) n (%) [95% CI][1]
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	3 (11.5)	3 (6.1)	9 (10.6)	6 (4.5)
I don't know.	3 (11.5)	1 (2.0)	4 (4.7)	4 (3.0)

Source: Appendix B: Survey Tables, Table 10.1.4
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.5: Responses to Questions Linked to Key Risk Message #4 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.					
12b: TIRF medicines are interchangeable with each other regardless of route of administration.					
True	1 (6.7)	5 (2.7)	6 (9.4)	3 (14.3)	0
False[2]	14 (93.3) [68.1 - 99.8]	177 (94.1) [89.8 - 97.0]	57 (89.1) [78.8 - 95.5]	17 (81.0) [58.1 - 94.6]	6 (100.0) [54.1 - 100.0]
I don't know	0	6 (3.2)	1 (1.6)	1 (4.8)	0
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.					
True[2]	14 (93.3) [68.1 - 99.8]	181 (96.3) [92.5 - 98.5]	62 (96.9) [89.2 - 99.6]	20 (95.2) [76.2 - 99.9]	6 (100.0) [54.1 - 100.0]
False	1 (6.7)	3 (1.6)	1 (1.6)	0	0
I don't know	0	4 (2.1)	1 (1.6)	1 (4.8)	0
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.					
True[2]	13 (86.7) [59.5 - 98.3]	172 (91.5) [86.5 - 95.1]	60 (93.8) [84.8 - 98.3]	19 (90.5) [69.6 - 98.8]	5 (83.3) [35.9 - 99.6]
False	0	7 (3.7)	2 (3.1)	2 (9.5)	0
I don't know	2 (13.3)	9 (4.8)	2 (3.1)	0	1 (16.7)
Question 16: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.					

Table 10.1.5: Responses to Questions Linked to Key Risk Message #4 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	0	3 (1.6)	1 (1.6)	1 (4.8)	0
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	14 (93.3) [68.1 - 99.8]	145 (77.1) [70.5 - 82.9]	55 (85.9) [75.0 - 93.4]	15 (71.4) [47.8 - 88.7]	2 (33.3) [4.3 - 77.7]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	0	15 (8.0)	4 (6.3)	4 (19.0)	2 (33.3)

Table 10.1.5: Responses to Questions Linked to Key Risk Message #4 by Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months - Completed Surveys

Question	Number of Times Prescribing TIRF Medicines per Month Within the Last 6 Months				
	None (N=15) n (%) [95% CI][1]	1 - 2 times per month (N=188) n (%) [95% CI][1]	3 - 5 times per month (N=64) n (%) [95% CI][1]	More than 5 times per month (N=21) n (%) [95% CI][1]	I don't remember (N=6) n (%) [95% CI][1]
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	0	17 (9.0)	3 (4.7)	1 (4.8)	0
I don't know.	1 (6.7)	8 (4.3)	1 (1.6)	0	2 (33.3)

Source: Appendix B: Survey Tables, Table 10.1.5
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.1.6: Responses to Questions Linked to Key Risk Message #4 by Practicing in a Closed Healthcare System - Completed Surveys		
	Practicing in a Closed Healthcare System	
Question	Yes (N=4) n (%) [95% CI][1]	No (N=290) n (%) [95% CI][1]
Question 12: Please answer True, False, or I don't know for each statement based on the labeling for TIRF medicines.		
12b: TIRF medicines are interchangeable with each other regardless of route of administration.		
True	0	15 (5.2)
False[2]	4 (100.0) [39.8 - 100.0]	267 (92.1) [88.3 - 94.9]
I don't know	0	8 (2.8)
12c: The conversion of one TIRF medicine for another TIRF medicine may result in a fatal overdose because of differences in the pharmacokinetics of fentanyl absorption.		
True[2]	4 (100.0) [39.8 - 100.0]	279 (96.2) [93.3 - 98.1]
False	0	5 (1.7)
I don't know	0	6 (2.1)
12d: Dosing of TIRF medicines is not equivalent on a microgram-to-microgram basis.		
True[2]	4 (100.0) [39.8 - 100.0]	265 (91.4) [87.5 - 94.3]
False	0	11 (3.8)
I don't know	0	14 (4.8)
Question 16: A patient is already taking a TIRF medicine but wants to change their medicine. His/her doctor decides to prescribe a different TIRF medicine (that is not a bioequivalent generic version of a branded product) in its place. According to the labeling, how should the prescriber proceed? Please select one option.		
The prescriber can safely convert to the equivalent dosage of the new TIRF medicine as it has the same effect as other TIRF medicines.	1 (25.0)	4 (1.4)
The prescriber must not convert to another TIRF medicine on a microgram-per-microgram basis because these medicines have different absorption properties and this could result in a fentanyl overdose.[2]	3 (75.0) [19.4 - 99.4]	228 (78.6) [73.4 - 83.2]
Convert from the other TIRF medicine to the new TIRF medicine at half of the dose.	0	25 (8.6)

Table 10.1.6: Responses to Questions Linked to Key Risk Message #4 by Practicing in a Closed Healthcare System - Completed Surveys

Question	Practicing in a Closed Healthcare System	
	Yes (N=4) n (%) [95% CI][1]	No (N=290) n (%) [95% CI][1]
The prescriber should base the starting dose of the newly-prescribed TIRF medicine on the dose of the opioid medicine used for their underlying persistent cancer pain.	0	21 (7.2)
I don't know.	0	12 (4.1)

Source: Appendix B: Survey Tables, Table 10.1.6
[1] 95% exact two-sided confidence intervals are calculated using the Clopper-Pearson method.
[2] Correct response.

Table 10.2: Secondary Analysis of Responses to Questions Linked to Key Risk Message #4 - Completed Surveys

Correct Responses	Prescribers (N=294) n (%)
0 correct responses	2 (0.7)
1 correct response	3 (1.0)
2 correct responses	22 (7.5)
3 correct responses	61 (20.7)
4 correct responses	206 (70.1)

Source: Appendix B: Survey Tables, Table 10.2

Table 11: Average Knowledge Scores - Completed Surveys	
	Score [95% CI][1]
KRM #1	87.4 [85.8, 89.0]
KRM #2	86.3 [84.6, 88.0]
KRM #3	94.2 [93.2, 95.2]
KRM #4	89.6 [87.5, 91.7]
Overall Knowledge Score	89.1 [88.0, 90.2]

Source: Appendix B: Survey Tables, Table 11
[1] 95% CIs are constructed based on normal distribution function.

Table 12: Types of Chronic Pain Conditions Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain	
Question	**Prescribers (N=54)[1] n (%)**
Question 10: For what type(s) of chronic non-cancer pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?	
Total Number of Responses[2]	80
Back Pain	9 (16.7)
Chronic Pain	8 (14.8)
Cancer Pain	6 (11.1)
Not Applicable	6 (11.1)
Failed Back Syndrome	4 (7.4)
Arachnoiditis	2 (3.7)
Bone Pain	2 (3.7)
Breakthrough Pain	2 (3.7)
Degenerative Disc Disease	2 (3.7)
Failed Spine Surgery	2 (3.7)
Fibromyalgia	2 (3.7)
Neck Pain	2 (3.7)
Neuropathy	2 (3.7)
Orthopedic Pain	2 (3.7)
Post Laminectomy Syndrome	2 (3.7)
Reflex Sympathetic Distrophy	2 (3.7)
Spondylosis	2 (3.7)
AIDS	1 (1.9)
Arthritic Pain	1 (1.9)
Cannot be Categorized	1 (1.9)
Cervicalgia	1 (1.9)
Chronic Regional Pain Syndrome	1 (1.9)
Crohn's Disease	1 (1.9)
Dyspnea	1 (1.9)
Facial Pain	1 (1.9)

Table 12: Types of Chronic Pain Conditions Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain

Question	Prescribers (N=54)[1] n (%)
Failed Neck Syndrome	1 (1.9)
Headache	1 (1.9)
Intractable Pain	1 (1.9)
Knee Pain	1 (1.9)
Multiple Autoimmune Disease	1 (1.9)
Multiple Sclerosis	1 (1.9)
Neuralgia	1 (1.9)
Pancreatitis	1 (1.9)
Peripheral Neuropathic Pain	1 (1.9)
Phantom Limb Pain	1 (1.9)
Polyneuropathy	1 (1.9)
Rheumatoid Arthritis	1 (1.9)
Spinal Stenosis	1 (1.9)
Spine Pain	1 (1.9)
Torticollis	1 (1.9)

Source: Appendix B: Survey Tables, Table 12

[1] Number and percentages are based on the subset of completed surveys where prescribers responded "Yes" to prescribing TIRF medicines for chronic non-cancer pain (*Question 9e: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Chronic Non Cancer Pain "Yes"*) and were subsequently presented Question 10 and Question 11.

[2] Total number of responses may exceed the number of prescribers and percentages may not equal 100% as multiple responses were provided by some prescribers.

Table 13: Reasons for Selecting a TIRF Medicine Reported - Completed Surveys for Prescribers Who Prescribed TIRF Medicines for Chronic Non-Cancer Pain	
Question	**Prescribers (N=54)[1] n (%)**
Question 11: Why do you select a TIRF medicine to treat these chronic pain conditions in patients who are opioid tolerant?	
Total Number of Responses[2]	62
Efficacy	13 (24.1)
I Do Not Treat Non-Cancer Patients	7 (13.0)
Fast Onset	6 (11.1)
Other Treatments Have Failed	6 (11.1)
Not Applicable	5 (9.3)
Ease of Use	3 (5.6)
Exhausted Other Options	3 (5.6)
Lack of Tolerance of Other Options	3 (5.6)
Medication Was Initiated by Pain Specialist	3 (5.6)
No Reason Provided	3 (5.6)
Dosing Options	2 (3.7)
Patient Preference	2 (3.7)
Convenience	1 (1.9)
Insurance Issues	1 (1.9)
Long Lasting	1 (1.9)
Patient Lack of Tolerance of Other Options	1 (1.9)
Safety	1 (1.9)
Sustained Pain Relief	1 (1.9)

Source: Appendix B: Survey Tables, Table 13
[1] Number and percentages are based on the subset of completed surveys where prescribers responded "Yes" to prescribing TIRF medicines for chronic non-cancer pain (*Question 9e: Per the approved labeling for TIRF medicines, for which of the following indication(s) are TIRF medicines approved? Chronic Non Cancer Pain "Yes"*) and were subsequently presented Question 10 and Question 11.
[2] Total number of responses may exceed the number of prescribers and percentages may not equal 100% as multiple responses were provided by some prescribers.

Listing 1.1: Listing of Verbatim Responses to Question #10 (For what type(s) of chronic non-cancer pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?) - Completed Surveys

Survey Form ID	Verbatim Responses
0005-000001	NONE
0005-000007	Failed back surgery syndrome, torticollis, trigeminal neuralgia
0005-000011	I don't prescribe for chronic non cancer pain (outside of my scope of practice)
0005-000021	I have prescribed these only to patient with chronic pain syndromes whom I have inherited and have been on these medications for several years and are stable. I do not start TIRF medications now with patients with non cancer pain.
0005-000026	Chronic back pain and neck pain
0005-000034	i don't usually
0005-000040	Crohn's
0005-000046	bone pain from progressive osteosarcoma
0005-000050	post-laminectomy syndrome
0005-000055	Severe bone pain related to fractures related to bone metastasis (stage IV cancer)
0005-000063	chronic severe pain uncontrolled by other opiates, cancer pain uncontrolled by other opiates,
0005-000072	I do not. I only treat cancer patients.
0005-000083	FAILED BACK SYNDROME
0005-000085	arachnoiditis, chronic LBP, chronic cervialgia
0005-000107	Fibromyalgia, rheumatoid arthritis
0005-000111	Failed back and orthopedic pain
0005-000113	chronic pain syndrome. Sympathetic mediated syndrome. Phantom limb pain
0005-000119	Severe spinal stenosis in opioid-tolerant patient
0005-000125	failed spine surgery
0005-000127	Degenerative disc disease, polyneuropathy
0005-000128	axial spine pain, chronic daily headache with execerbation, Chronic regional pain syndrome.
0005-000139	I only see cancer pts and prescribe TIRF medications to cancer related pain
0005-000145	Patients already on a long acting opioid of sufficient dosing who require a breakthrough medication where other breakthrough medications do not work
0005-000210	Chronic knee pain due to joint degeneration, dyspnea for lung metastases
0005-000228	chronic, intractable pain, mostly back pain have used for patients with GI absorption issues

Listing 1.1: Listing of Verbatim Responses to Question #10 (For what type(s) of chronic non-cancer pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?) - Completed Surveys

Survey Form ID	Verbatim Responses
0005-000255	post laminectomy
0005-000687	Patients who are narcotic dependent with painful medical conditions, such as spinal tumors which are not canceror chronic orthopedic pain.
0005-000704	Chronic Pancreatitis
0005-000716	AIDS, one patient with multiple autoimmune diseases
0005-000753	chronic facial pain due to surgical complications
0005-000778	Severe back pain.
0005-000784	N/A. I work in the oncology setting. All the patients are oncology patients.
0005-000789	Multiple sclerosis
0005-000882	I personally dont presecribe for non cancer pain
0005-000989	I only prescribe to patients for cancer pain
0005-000996	N/A
0005-001005	Chronic pain not improved with alternative treatments.
0005-001042	severe neuropathy associated with HIV, chronic low back pain associated with disc disease, severe diffuse arthritic pain
0005-001044	Chronic Low back pain
0005-001053	None, only prescribe for cancer pain
0005-001081	RSD, Failed spine surgery, arachnoiditis, back pain due to degenerative discs and spondylosis
0005-001090	Failed surgical syndrome of back or neck
0005-001107	Im a cancer specialist and have not prescribe TIRF meds for noncancer pts. Based from a rep they used it for severe debilitating chronic back pain
0005-001121	lumbar and cervical spondylosis
0005-001135	post chemotherapy and radiation therapy neuropathy for patients with history of cancer
0005-001137	chronic back pain
0005-001205	Subsys. Lazanda, Fentanyl patch, Actiq, Abstral,
0005-001207	severe back or neck pain
0005-001210	A patient with chronic pain due to chronic, life-limiting illness for whom all other non-opioid pharmacologic and non-pharmacologic pain measures have been maximized for episodic breakthrough pain.
0005-001220	degenerative disc disease for which surgical intervention is not an option.

Listing 1.1: Listing of Verbatim Responses to Question #10 (For what type(s) of chronic non-cancer pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?) - Completed Surveys

Survey Form ID	Verbatim Responses
0005-001243	chronic pain which is severe in nature
0005-001250	fibromyalgia
0005-001322	Peripheral neuropathic pain
0005-001328	RSD

Note: Question 10 is only asked if Question 9e is answered "Yes".

Listing 1.2: Listing of Verbatim Responses to Question #10 (For what type(s) of chronic non-cancer pain conditions do you prescribe a TIRF medicine to opioid tolerant patients?) - Incomplete Surveys

Survey Form ID	Verbatim Responses
0005-001040	Chronic pancreatitis, chronic musculoskeletal conditions.
0005-001087	Severe, chronic abdominal pain
0005-001177	central pain syndrome
0005-001260	degenerative disc diseases of spine,stenosis, radiculopathy, herniated disc, spondylosis, spondylolysis, and all other chronic pain in the spine.

Note: Question 10 is only asked if Question 9e is answered "Yes".

Listing 2.1: Listing of Verbatim Responses to Question #11 (Why do you select a TIRF medicine to treat these chronic non-cancer pain conditions in patients who are opioid tolerant?) - Completed Surveys

Survey Form ID	Verbatim Responses
0005-000001	I DON'T
0005-000007	Quick onset, selective dosing
0005-000011	I don't see this type of patient. If I did, would best be used for transient elevations in pain, due to quicker onset of the drug.
0005-000021	I do not.
0005-000026	because they offer pain relief fast
0005-000034	i don't
0005-000040	do not tolerate other therapies
0005-000046	I am an oncologist, so I would not treat non-cancer patients
0005-000050	fast onset of relief for breakthrough pain
0005-000055	works well with pain management
0005-000063	long lasting, good control less breakthrough pain
0005-000072	not applicable
0005-000083	EFFICACY AND CONVENIENCE
0005-000085	ease of use
0005-000107	They work well for the pain
0005-000111	Better pain control
0005-000113	These medications are selected after failing other conservative treatments and initial low dose opioid therapy
0005-000119	Severe incident (movemnt-related) pain
0005-000125	for patients who are opioid tolerant but have problematic side effects with other opioid preparations.
0005-000127	Fentanyl is very effective in reducing pain
0005-000128	episodic nature of the pain
0005-000139	n/a
0005-000145	No other medication for breakthrough has been effective and I have maxed out long acting meds
0005-000210	Patient's previous use of this medication for these indications
0005-000228	fast acting controlled dosing
0005-000255	chronic pain condition

Listing 2.1: Listing of Verbatim Responses to Question #11 (Why do you select a TIRF medicine to treat these chronic non-cancer pain conditions in patients who are opioid tolerant?) - Completed Surveys

Survey Form ID	Verbatim Responses
0005-000687	It was started by anaesthesiologist or pain medicine specialist. I only continued what had been started elsewhere.
0005-000704	Because the GI population often cannot tolerate or absorb traditional oral opioid meds.
0005-000716	fast onset for severe pain
0005-000753	was chosen by patient's chronic pain doctor
0005-000778	Due to opioid tolerant.
0005-000784	na
0005-000789	patient preference or positive response with fentanyl patch who need short acting immediate relief for chronic intractable pain
0005-000882	I dont prescribe TIRF meds for non cancer pain pts
0005-000989	I select TIRF products for patients receiving Radiation therapy who are unable to swallow. Fentanyl patch
0005-000996	N/A
0005-001005	No improvement with conventional therapies.
0005-001042	sometimes these patients have exhausted other options; sometimes, insurance plans do not pay for other medications
0005-001044	Patients that other opioids are not effective
0005-001053	N/A
0005-001081	excellent control of their pain which helps improve daily function
0005-001090	Long history of tried and failed therapy with both LAO and SAO
0005-001107	I dont; i treat cancer patients
0005-001121	steady around-the -clock relief
0005-001135	when they are not candidates for morphine pump therapy.
0005-001137	for break through pain
0005-001205	For more effective and sustained pain relief
0005-001207	some patients need a stronger pain medicine
0005-001210	It is a measure enacted in a patient and family with no risk factors for opioid abuse, in a setting where all other measures at ameliorating severe, episodic pain have been trailed and maximized without adequate control. I have only one patient who is on a TIRF medication and she has an incurable, life-limiting, painful medical condition.
0005-001220	safety and ease of administration

Listing 2.1: Listing of Verbatim Responses to Question #11 (Why do you select a TIRF medicine to treat these chronic non-cancer pain conditions in patients who are opioid tolerant?) - Completed Surveys

Survey Form ID	Verbatim Responses
0005-001243	Short acting opiate with rapid onset of action
0005-001250	best effects
0005-001322	Very effective and ease of use
0005-001328	It was started by a pain specialist. I have merely continued it.

Note: Question 11 is only asked if Question 9e is answered "Yes".

Listing 2.2: Listing of Verbatim Responses to Question #11 (Why do you select a TIRF medicine to treat these chronic non-cancer pain conditions in patients who are opioid tolerant?) - Incomplete Surveys

Survey Form ID	Verbatim Responses
0005-001040	If other analgesic medications are not effective.
0005-001087	Breakthrough and cannot use other options
0005-001177	different molecule to treat pain
0005-001260	tolerance to certain short acting narcotics.

Note: Question 11 is only asked if Question 9e is answered "Yes".

Listing 3: Listing of Verbatim Responses to Question #28 (Questions about the Medication Guide) - Completed Surveys	
Survey Form ID	**Verbatim Responses**
0005-000079	Is Fentora absolutely contraindicated for opioid tolerant, NON-cancer pain. I know it is labeled for opioid tolerant cancer pain, but is it ABSOLUTELY contraindicated in all chronic, opiod tolerant NON cancer pain patients?
0005-000113	Information on prescribing guidelines and max dosages
0005-000154	best uses for failure of first dose for BTP
0005-000160	if they can be safely taken with certain antidepressants such as gebapentin,lamictal,duloxetine
0005-000821	I do not remember what is in it.
0005-000859	How can I access the information online?
0005-001042	I had questions prior to initiating prescriptions for the patients. I consulted with the filling pharmacist and discussed my questions with him. I do not have specific questions at this time.
0005-001323	What if you have a patient that has been using TIRF medications for years, the patient was 1st prescribed back when it was used for chronic pain patients. Patient is opiod tolerant no complications and has been taking it for over 20 years? do you stop writing the rx for those patients.

Listing 4: Listing of Verbatim Responses to Question #40 (What is your medical specialty?) - Completed Surveys	
Survey Form ID	**Verbatim Responses**
0005-000004	Radiation Oncology
0005-000013	palliative care
0005-000025	Palliative Medicine
0005-000040	gastroenterology
0005-000046	pediatric hematology/oncology
0005-000064	Neurology
0005-000080	hosppice and palliative
0005-000087	UROLOGY
0005-000091	Palliative Medicine
0005-000094	Palliative Medicine
0005-000096	palliative care
0005-000105	Physical Medicine and Pain Medicine
0005-000106	rehab medicine pmr
0005-000119	Palliative Medicine
0005-000140	Palliative Care
0005-000153	palliative care
0005-000154	anesthesia
0005-000168	Palliative Care
0005-000210	Palliative Care
0005-000233	PM&R
0005-000261	Palliative Care
0005-000553	Palliative Medicine
0005-000569	Palliative Medicine
0005-000692	Palliative Medicine
0005-000704	Palliative Care
0005-000707	Palliative Medicine
0005-000730	Palliative Medicine
0005-000734	pain and palliative
0005-000750	PMR/Pain

Listing 4: Listing of Verbatim Responses to Question #40 (What is your medical specialty?) - Completed Surveys	
Survey Form ID	**Verbatim Responses**
0005-000769	Radiation Oncology
0005-000818	Palliative Care
0005-000880	Neurology
0005-001061	PM&R
0005-001084	palliative medicine
0005-001137	infectious disease
0005-001180	internal medicine. hospice, palliative care
0005-001194	radiation oncology
0005-001205	Physical Medicine and Rehabilitation
0005-001206	Hospice and Palliative Care
0005-001209	psychiatry
0005-001210	Pediatric Palliative Care
0005-001222	physical medicine and rehabilitation
0005-001243	physical medicine and rehabilitation
0005-001344	PMR
0005-001345	urology
0005-001351	HOSPICE AND PALLIATIVE CARE WITH PAIN MANAGEMENT

Listing 5: Listing of Adverse Events and/or Product Complaints Reported by Modality	
Verbatim Text	**Modality of Report**
AIDS, one patient with multiple autoimmune diseases	Internet
arachnoiditis, chronic LBP, chronic cervialgia depomed follow up: A phone attempt was performed today (10-Oct-2016) to obtain follow-up for this case. Due to insufficient patient information, the physician was unable to determine the patient or provide any new information. Since she has no recollection of a patient experiencing these events with fentanyl, she believes one of her colleagues may have reported this case. At this time, no new information is available. (bold items not in EDC)	Internet
axial spine pain, chronic daily headache with execerbation, Chronic regional pain syndrome.	Internet
Because the GI population often cannot tolerate or absorb traditional oral opioid meds. Chronic Pancreatitis	Internet
best uses for failure of first dose for BTP	Internet
bone pain from progressive osteosarcoma	Internet
Breakthrough and cannot use other options and Severe, chronic abdominal pain	Internet
central pain syndrome; different molecule to treat pain	Internet
chronic back pain and for break throgh pain	Internet
Chronic back pain and neck pain	Internet
chronic facial pain due to surgical complications. was chosen by patient's chronic pain doctor	Internet
Chronic knee pain due to joint degeneration, dyspnea for lung metastases	Internet
chronic pain syndrome. Sympathetic mediated syndrome. Phantom limb pain	Internet
chronic pain which is severe in nature and Short acting opiate with rapid onset of action	Internet
Chronic pancreatitis, chronic musculoskeletal conditions. If other analgesic medications are not effective.	Internet
chronic severe pain uncontrolled by other opiates, cancer pain uncontrolled by other opiates,	Internet
chronic, intractable pain, mostly back pain have used for patients with GI absorption issues	Internet
Crohn's	Internet
degenerative disc disease for which surgical intervention is not an option.	Internet
Degenerative disc disease, polyneuropathy	Internet
degenerative disc diseases of spine,stenosis, radiculopathy, herniated disc, spondylosis, spondylolysis, and all other chronic pain in the spine. tolerance to certain short acting narcotics.	Internet
Failed back and orthopedic pain	Internet

Listing 5: Listing of Adverse Events and/or Product Complaints Reported by Modality	
Verbatim Text	**Modality of Report**
Failed back surgery syndrome, torticollis, trigeminal neuralgia	Internet
FAILED BACK SYNDROME	Internet
failed spine surgery	Internet
Fibromyalgia, rheumatoid arthritis	Internet
For more effective and sustained pain relief	Internet
How can I access the information online?	Internet
I have prescribed these only to patient with chronic pain syndromes whom I have inherited and have been on these medications for several years and are stable. I do not start TIRF medications now with patients with non cancer pain.	Internet
if they can be safely taken with certain antidepressants such as gebapentin,lamictal,duloxetine	Internet
Information on prescribing guidelines and max dosages	Internet
Is Fentora absolutely contraindicated for opioid tolerant, NON-cancer pain. I know it is labeled for opioid tolerant cancer pain, but is it ABSOLUTELY contraindicated in all chronic, opiod tolerant NON cancer pain patients?	Internet
It is a measure enacted in a patient and family with no risk factors for opioid abuse, in a setting where all other measures at ameliorating severe, episodic pain have been trailed and maximized without adequate control. I have only one patient who is on a TIRF medication and she has an incurable, life-limiting, painful medical condition. A patient with chronic pain due to chronic, life-limiting illness for whom all other non-opioid pharmacologic and non-pharmacologic pain measures have been maximized for episodic breakthrough pain.	Internet
Long history of tried and failed therapy with both LAO and SAO and Failed surgical syndrome of back or neck	Internet
lumbar and cervical spondylosis and steady around-the -clock relief	Internet
Multiple Sclerosis, patient preference or positive response with fentanyl patch who need short acting immediate relief for chronic intractable pain	Internet
No improvement with conventional therapies. Chronic pain not improved with alternative treatments.	Internet
Patients that other opioids are not effective. Chronic Low back pain.	Internet
Patients who are narcotic dependent with painful medical conditions, such as spinal tumors which are not canceror chronic orthopedic pain.	Internet
Peripheral neuropathic pain and very effective and ease to use	Internet
post chemotherapy and radiation therapy neuropathy for patients with history of cancer and when they are not candidates for morphine pump therapy.	Internet
post-laminectomy chronic pain condition	Internet

Listing 5: Listing of Adverse Events and/or Product Complaints Reported by Modality	
Verbatim Text	**Modality of Report**
post-laminectomy syndrome	Internet
RSD	Internet
RSD, Failed spine surgery, arachnoiditis, back pain due to degenerative discs and spondylosis	Internet
severe back or neck pain	Internet
severe back pain, due to opioid tolerant	Internet
Severe bone pain related to fractures related to bone metastasis (stage IV cancer)	Internet
Severe spinal stenosis in opioid-tolerant patient	Internet
sometimes these patients have exhausted other options; sometimes, insurance plans do not pay for other medications. severe neuropathy associated with HIV, chronic low back pain associated with disc disease, severe diffuse arthritic pain	Internet
What if you have a patient that has been using TIRF medications for years, the patient was 1st prescribed back when it was used for chronic pain patients. Patient is opiod tolerant no complications and has been taking it for over 20 years? do you stop writing the rx for those patients.	Internet