Title:	Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Program Twenty-Four Month FDA Assessment Report
Document Number:	Version 1
Product Name:	All Extended-Release (ER) and Long-Acting (LA) Opioid Analgesic Products
Companies:	REMS Program Companies (RPC)
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LIST OF ABBREVIATIONS

AAFP	American Academy of Family Physicians
AANP	American Association of Nurse Practitioners
ACASI	Audio Computer-assisted Self Interviewing
ACCME®	Accreditation Council for Continuing Medical Education
AE	Adverse Event
AMA	American Medical Association
ANCC	American Nurses Credentialing Center
ANSI	American National Standards Institute
AOA	American Osteopathic Association
ASI-MV	Addiction Severity Index- Multimedia Version
CAI	Computer-assisted Interviewing
CAPI	Computer-assisted Personal Interviewing
CBHSQ	Center for Behavioral Health Statistics and Quality
CCCE	Conjoint Committee for Continuing Education
CE	Continuing Education
CEO	Chief Executive Officer
CHAT	Comprehensive Health Assessment for Teens
CI	Confidence Interval
CMSS	Council of Medical Specialty Societies
CO*RE	Collaborative for REMS Education
DDRP	Dear DEA-Registered Prescriber
DEA	Drug Enforcement Administration
DPOLB	Dear Professional Organization/Licensing Board
ED	Emergency Department
EMR	Electronic Medical Records
ER	Extended-Release
ETASU	Elements to Assure Safe Use
FAQs	Frequently Asked Questions
FDA	Food and Drug Administration
FDCA	Food, Drug and Cosmetic Act
GMS	Grant Management System
HCP	Healthcare Professional

HCPCS	Healthcare Common Procedure Coding System
HIRD	HealthCore Integrated Research Database℠
ICD	International Classification of Diseases
IR	Immediate-Release
IVRS	Interactive Voice Response System
KP	Kaiser Permanente
KPNC	Kaiser Permanente Northern California
KPNW	Kaiser Permanente Northwest
KAS	Knowledge Assessment Score
LA	Long-Acting
LRx	Longitudinal Prescription
LTE	Long-term Evaluation
MECCS	Medical Education Communication Companies
MEMS	Medical Education and Metrics Standards
MTF	Monitoring the Future
NAVIPPRO®	National Addictions Vigilance Intervention and Prevention Program
NDA/ANDA	New Drug Application/Abbreviated New Drug Application
NIDA	National Institute on Drug Abuse
NPA™	National Prescription Audit™
NSAID	Non-steroidal Anti-inflammatory Drug
NSDUH	National Survey on Drug Use and Health
OOP	Opioid Overdose and Poisoning
OR	Odds Ratio
PCD	Patient Counseling Document
PCP	Primary Care Provider
PIE	Provider Information Exchange
PMR	Post-Marketing Requirement
RADARS®	Researched Abuse, Diversion and Addiction-Related Surveillance
REMS	Risk Evaluation and Mitigation Strategy
RFA	Request for Applications
RFP	Request for Proposal
RPC	REMS Program Companies
SAMHSA	Substance Abuse and Mental Health Services Administration

SD	Standard Deviation
TD	Trans Dermal
US	United States
USPS	United States Postal Service

1. EXECUTIVE SUMMARY

The Food and Drug Administration (FDA) has determined that a Risk Evaluation and Mitigation Strategy (REMS) is necessary for all Extended-Release and Long-Acting (ER/LA) opioid analgesic drug products to ensure that their benefits outweigh their risks. The goal of the ER/LA Opioid Analgesics REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications.

This Twenty-Four Month FDA Assessment Report is the third report since approval of the ER/LA Opioid Analgesics REMS on July 9, 2012. It includes information on all 8 Assessment Elements as delineated in the ER/LA Opioid Analgesic REMS Supporting Document:

- Assessment Element 1: Prescribers who have successfully completed REMS-compliant training
- Assessment Element 2: Independent audits of Continuing Medical Education/Continuing Education (CE) activities
- Assessment Element 3b: Long-term Evaluation Grants
- Assessment Element 4: Evaluation of Patients' understanding of the serious risks of ER/LA opioid analgesics
- Assessment Element 5: Surveillance monitoring for misuse, abuse, overdose, addiction, and death associated with ER/LA opioids, as well as resulting interventions
- Assessment Element 6: Evaluation of drug utilization patterns for ER/LA Opioids and comparator drug groups
- Assessment Element 7: Evaluation of changes in prescribing pattern behavior of ER/LA opioid prescribers
- Assessment Element 8: Monitoring patterns of prescribing to identify changes in access to ER/LA opioid analgesics

All operational requirements to date of the REMS have been implemented. This report also includes status updates on the new Interactive Voice Response System (IVRS) call center, distribution of the Dear DEA Registered Prescriber (DDRP) Letter 3, and ordering and distribution of the Patient Counseling Document (PCD).

The key accomplishments in the past 12 months include:

- Advancing the REMS Program Companies (RPC) partnership with the CE community; the development and implementation of an independent audit process for RPC-supported CE;
- Completion and analysis of a patient survey to assess patient knowledge of the risks and safe use of ER/LA opioid analgesic products;
- Initiation of in-depth surveillance monitoring for opioid misuse, abuse, overdose, and death;
- Analysis of drug utilization patterns and prescriber behaviors prior to and following implementation of the REMS;

- Monitoring of prescribing patterns to identify potential changes in access to ER/LA opioid analgesics;
- Launch of an IVRS call center allowing all stakeholders around-the-clock access to the program's Frequently Asked Questions (FAQs).

The impact of the REMS was assessed by changes over time for ER/LA opioids compared to comparator drug groups. Changes from before the REMS to after the REMS were assessed for Assessment Element 5, 6, and 7. A one-year transition period was used because the REMS was approved on July 9, 2012, certain elements of the REMS were implemented within 30 to 60 days after REMS approval (DDRP Letters sent to prescribers with Medication Guides and PCDs, website, call center), the first REMS-compliant CE course became available by March 1, 2013 in an online format, and it took several months for several CE-courses in both online and live educational sessions to become available.
Therefore three time periods were established for REMS assessment. RPC has used the terms Pre-REMS, REMS Launch, and Continuing Active for the 2-year pre-period, the 1-year transition period, and the 6-month post-period, respectively. In subsequent assessment reports, the post-period will be longer than 6 months. Although consistent timeframes were used for all reports for Elements 5, 6, and 7 each vendor used slightly different terminology to the 3 periods in their section of the report as shown in (Figure 6). When possible, text within this report the RPC terms consistently. A brief summary of the 8 Assessment Elements is provided below.

Assessment Element 1: Prescribers who have Successfully Completed REMS-Compliant Training

The data cut-off for entering and processing data from individual CE providers in the Medbiquitous database established for this REMS Assessment report was February 28, 2014. By this date, a total of 20,345 prescribers of ER/LA opioid analgesics have completed the RPC-supported, REMS-compliant training, 19,039 of whom completed a REMS-compliant CE training in the past-year reporting period of May 11, 2013 to February 28, 2014. During the past-year reporting period, 262 RPC-supported, REMS-compliant education activities began and were active.

The RPC continues to identify accredited providers to enable achievement of the REMS goals.

The RPC is aware that many more than 20,345 HCPs completed a REMS-compliant CE training course. For example, in addition to the 10,530 of the ER/LA opioid analgesic prescribers who completed a REMS-compliant CE training via the CO*RE curriculum, a further approximately 16,000 individuals completed a REMS-compliant CE training offered by CO*RE but did not meet all of the criteria that FDA has used to define the target population of prescribers for the ER/LA opioid REMS and therefore were not counted towards prescribers completed to date. The majority of the non-counting completers did not meet the qualifying criterion of having written an ER/LA prescription within the year prior to training. However, some of these completers may make important contributions to appropriate and safe use of opioids, such as nurses who care for patients taking opioids, nurses who counsel patients on instructions for use and safe use of medications in doctors' offices, pharmacists who dispense ER/LA opioids to patients, or prescribers who take a REMS-compliant CE training prior to starting to prescribe

ER/LA opioids. Consequently, while not includable in the metrics for Assessment Element 1, these HCPs may play important roles in disseminating information to patients using ER/LA opioids and providing feedback to ER/LA opioid prescribers about safe prescribing."

Assessment Element 2: Independent Audits of Continuing Education (CE) Activities

Independent audits have been conducted by 5 nationally recognized Accrediting Bodies on at least 10% of the RPC-supported, REMS-compliant CE activities during this reporting period. Of the 27 total audit reports received, 22 (82.8 %) met all criteria for REMS-compliant CE as defined in the REMS Supporting Document and the FDA Blueprint. The Accreditation Council for Continuing Medical Education (ACCME) noted observations for 10 of the 13 activities they audited. One of the activities did not meet expectations with respect to scope of evaluation; however, ACCME noted that this could not yet be assessed because the activity was still underway at the time of the audit. ACCME noted that the remaining five activities did not meet expectations with respect to the ACCME Standards for Commercial Support with respect to obtaining and prominently displaying financial relationships of faculty and/or staff involved in the activity. RPC has reviewed the documentation for the 5 ACCME audit reports that are referenced above and views these as important for compliance with Standards for Commercial Support but not impacting the fidelity of the educational content following the FDA Blueprint. The RPC is following up with each provider to ensure appropriate remediation.

Assessment Element 3b: Long-term Evaluation Grants

The results of the Long-term Evaluation (LTE) will be included in the Thirty-Six Month FDA Assessment Report. Refer to Section 5 for an update on the progress toward this goal.

Assessment Element 4: Evaluation of Patients' Understanding of the Serious Risks of ER/LA Opioid Analgesics

A patient survey was conducted to assess 1) patients' understanding of the serious risks of ER/LA opioid analgesics, 2) receipt and comprehension of the Medication Guide and PCD, 3) perceived access and satisfaction of access to pain medication, and 4) patient-reported frequency of appropriate prescriber behaviors, including appropriate screening and counseling about ER/LA opioids. Over 400 adults who filled at least one prescription for ER/LA opioid analgesics between December 1, 2012 and November 30, 2013 were randomly selected from a commercial health insurance plan and completed the survey. This timeframe represents an evaluation after the first DDRP Letter with Medication Guide and reference to the PCD were distributed to all prescribers who were registered with DEA to write Schedule 2 and 3 medicines, but slightly before or shortly after availability of the first REMS-compliant CE training course. Patients' level of understanding of the serious risks of ER/LA opioid analgesics was generally high: for questions about the safe use and appropriate storage of ER/LA opioid analgesics, the average correct response rate was 85.6% among individuals using ER/LA opioids, and only 8% of respondents had an average score below the pre-specified threshold for "low" knowledge of 70%. Receipt and comprehension of the Medication Guide was high too: 94% of patients reported receiving the ER/LA Medication Guide, 97% reported reading it, and 98% reported understanding it. Note that some patients reported reading and understanding the Medication Guide even though they had not reported receiving the Medication Guide. However, use of the PCD was lower: only about half of the respondents reported that their healthcare providers used the PCD for discussion or discussed safe discontinuation and disposal of ER/LA opioids at the time of prescribing.

Assessment Element 5: Surveillance Monitoring for Misuse, Abuse, Overdose, Addiction, and Death Associated with ER/LA Opioids, as well as Resulting Interventions

Surveillance monitoring was conducted using multiple surveillance systems to identify the impact of the REMS on opioid misuse, abuse, overdose, and death. Specifically, the Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System Poison Center Program and Treatment Center Program and Inflexxion's National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®) Addiction Severity Index-Multimedia Version (ASI-MV) and CHAT Systems were used to assess the impact of the REMS. The RADARS System provides post-marketing surveillance of prescription medication abuse, misuse, and diversion to pharmaceutical companies, regulatory agencies and policy-making organizations. The NAVIPPRO System ASI-MV and CHAT Systems provides real-time, product-specific surveillance information from a network of several hundred substance abuse treatment centers around the US in order to monitor emerging trends in substance abuse from adults and adolescents, respectively.

Results from the RADARS System Poison Center Program indicate a marked improvement in outcomes for ER/LA Opioids, including decreases in abuse exposures, misuse, as well as calls for major medical outcomes, hospitalizations, and deaths in the six months of the active period compared to the two year pre-implementation period. These include:

(b) (4)

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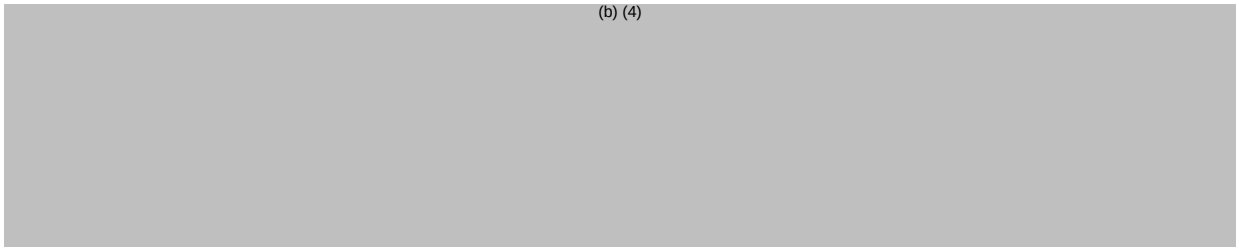
Surveillance monitoring of abuse in substance abuse treatment center programs using the NAVIPPRO ASI-MV System and the RADARS System substance abuse treatment program showed positive results overall, albeit with one exception, in the six months of the active period compared to the two year pre-implementation period.

(b) (4)

- 

(b) (4)

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An analysis of surveillance and signal monitoring was also conducted through an evaluation of the most recent National Survey on Drug Use and Health (NSDUH) and Monitoring the Future (MTF) annual reports. Due to the release dates of these reports, the majority of data from these sources only covered 2012. However limited 2013 data was available from MTF.

(b) (4)

Further, as a preliminary step in the evaluation of REMS-related changes in emergency room visits associated with opioid overdose or poisoning events, a study was performed to validate the International Classification of Diseases (ICD) 9 codes for identification of overdose or poisoning events by verifying the codes against medical records. Results from this study showed that ICD-9 codes for opioid-related poisoning had a positive predictive value of 70.8% to detect opioid overdose/poisoning events. An RFP for vendors to use these ICD-9 codes to assess the impact of the REMS on emergency room visits associated with opioid overdose or poisoning events has been distributed to relevant organizations. Information obtained through the post-marketing requirement (PMR) 2065-3 to validate opioid overdose events will be applied as appropriate to the future surveillance monitoring study of emergency department (ED) visits for opioid overdose and poisoning events.

Assessment Element 6: Evaluation of Drug Utilization Patterns

Assessment of drug utilization showed changes that are consistent with the desired outcomes of the REMS. These include:

- (b) (4)

Assessment Element 7: Evaluation of Changes in Prescriber Behavior

Metrics of appropriate prescribing behaviors showed a reduction in prescriptions of ER/LA opioid analgesics to non-opioid tolerant patients that are indicated only for opioid tolerant patients.

- (b) (4)

Assessment Element 8: Monitoring Patterns of Prescribing to Identify Changes in Access to ER/LA Opioid Analgesics

Surveys of prescribers and patients were used to identify changes in and the perception of changes in ER/LA opioid analgesic access. Prescriber survey results showed that a large number of prescribers indicated that they feel the current level of access is about right (N = 350, 57.9%) while 87 (14.4%) felt it is too difficult and 106 (17.5%) felt access is too easy.

In a sample of commercially-insured ER/LA opioid analgesic users, the majority of respondents reported satisfaction with their access to ER/LA opioid analgesic prescriptions, their ability to obtain medication from a pharmacy, and their general access to ER/LA opioid analgesic medication. Thus, there is no indication that the REMS is having a negative impact on access to ER/LA opioid analgesics as reported by patients and prescribers.

Drug utilization data was used to compare changes in prescribing of prescribers from specialties whose prescribing is hypothesized to be relatively unaffected by the REMS (such as oncologists and hospice providers) versus those for whom the REMS could have greater impact on prescribing (eg, dentists). Reductions were largest in those specialties that were hypothesized to be more affected by the REMS than other specialties. (b) (4)

[redacted]

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Overall Assessment of the Impact of the ER/LA Opioid Analgesic REMS

The REMS assessments included in this report show substantial improvements in patient knowledge of the risks and safe use messages related to ER/LA opioid analgesics, rates of misuse, abuse, and major medical outcomes including death, and prescribing behaviors, all while preserving access to valuable pain therapies. Since many interventions occurred during the time period of the REMS, these effects cannot be attributed specifically to the REMS. However, the REMS was implemented as part of the President's 2011 Prescription Drug Abuse Prevention Plan (http://www.whitehouse.gov/sites/default/files/ondcp/issues-content/prescription-drugs/rx_abuse_plan.pdf [last accessed June 27,2014]) to decrease opioid abuse and misuse that encompassed many of the interventions. As part of the President's plan, the REMS has made a positive impact on its intended goals. The RPC will continue to implement the REMS to build upon the positive initial impact seen to date.

2. BACKGROUND

In April 2011, in accordance with section 505-1 of the Federal Food Drug and Cosmetic Act, the FDA determined that a REMS was necessary for all ER/LA opioid analgesic drug products to ensure that their benefits outweigh their risks, especially with regard to specific adverse outcomes. The goal of the ER/LA Opioid Analgesics REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of particular interest include addiction, unintentional overdose, and death. In the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS

programs, the FDA determined that a single shared system should be used to implement this REMS.

The New Drug Application/Abbreviated New Drug Application (NDA/ANDA) holders of the following branded and generic drug products are required to participate in the ER/LA Opioid Analgesics REMS: extended-release and long-acting, oral-dosage formulations containing hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and tapentadol; transdermal delivery systems containing fentanyl or buprenorphine; and methadone formulations that are indicated for use as analgesics. The REMS was approved by FDA on July 9, 2012 (http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm).

The elements of the REMS include Medication Guides, Elements to Assure Safe Use (ETASU) and a Timetable for Submission of Assessments. Under the REMS, the NDA/ANDA holders must do the following:

- Ensure that training is available to prescribers who prescribe the ER/LA opioid analgesics
- Provide to prescribers information that the prescriber can use to educate patients about the risks of ER/LA opioid analgesics and their safe use, storage, and disposal
- Inform prescribers of the existence of the ER/LA Opioid Analgesics REMS and the need to successfully complete the necessary training

Training will be considered "REMS-compliant training" under this REMS if:

- Training provided by (CE) Providers is offered by an accredited Provider to licensed prescribers,
- It includes all elements of the FDA Blueprint for Prescriber Education for ER/LA Opioid analgesics ("FDA Blueprint"),
- It includes a post-course knowledge assessment of all of the sections of the FDA Blueprint, and
- It is subject to independent audit to confirm that conditions of the REMS training have been met.

As part of the REMS, performance goals were established for availability of the REMS-compliant training. These goals are:

- Not later than March 1, 2013, the first REMS-compliant training will be made available.
- Within two years from the time the first REMS-compliant training becomes available, 80,000 prescribers (based on 25% of the 320,000 active prescribers in 2011) will have been trained.
- Within three years from the time the first REMS-compliant training becomes available, 160,000 prescribers (based on 50% of the 320,000 active prescribers in 2011) will have been trained.
- Within four years from the time the first REMS-compliant training becomes available, 192,000 prescribers (based on 60% of the 320,000 active prescribers in 2011) will have been trained.

The REMS includes a plan to inform prescribers and potential prescribers identified via the Drug Enforcement Administration (DEA) registration database about the REMS and the need to complete the necessary training. The primary communication methods to disseminate this

information include DDRP Letters and DPOLB Letters. Performance goals established for these communications are:

- DDRP Letter 1 will be sent not later than 60 days after the initial approval of this REMS
- DDRP Letter 2 will be sent not later than 30 days before the first prescriber REMS-compliant training required by the REMS is offered by Providers
- At least annually from the date of initial approval of the REMS, the DEA Registration Database will be reviewed and DDRP Letter 3 will be sent to all newly DEA-registered prescribers who are registered to prescribe Schedule II and III drugs
- DPOLB Letter 1 will be sent not later than 60 days after REMS approval
- DPOLB Letter 2 will be sent not later than 30 days before the first prescriber REMS-compliant training is available

Educational materials must be developed for prescribers to use in educating their patients. The REMS includes the PCD on ER/LA opioid analgesics and Medication Guides. These materials must be accessible to prescribers; the RPC has developed an ER/LA Opioid Analgesics REMS website and based on FDA feedback received following the twelve-month FDA Assessment Report, the RPC transitioned from a centralized Call Center to an IVRS on March 19, 2014. Additional details provided in Section 11.3. A critical aspect of the REMS is assessment of the effectiveness of the program in meeting its goals. The FDA has indicated eight key areas for assessment as well as evaluation of the functional components of the REMS implementation. These elements are shown in the table below.

Table 1: FDA-REQUIRED REMS ASSESSMENTS

FDA REQUIREMENTS
Evaluation of Functional Components **Dates when the following were initiated:** • REMS Website • Dear DEA-Registered Prescriber Letter • Dear Professional Organizations, Licensing Boards, and Medical Societies Letter • Call Center (Modified March 19, 2014 to IVRS)
Assessment Element 1: Assessment of how many prescribers of ER/LA opioids have successfully completed the training. Specify performance goals for number of prescribers trained by time.
Assessment Element 2: Independent audit of the quality of the content of the educational materials used by the CE Providers to provide the education. The audit should evaluate the quality of the content against the content approved by the FDA as part of the REMS, as well as against the ACCME®'s and other accrediting bodies' standards for commercial support.
Assessment Element 3a: Prescriber survey Evaluation of Healthcare Professional (HCP) awareness and understanding of the serious risks associated with these products (e.g., through surveys of HCPs) and specification of measures that would be taken to increase awareness if surveys of HCPs indicate that HCP awareness is not adequate.
Assessment Element 3b: Long-term evaluation grants
Assessment Element 4: Patient survey Evaluation of patients' understanding of the serious risks of these products.

Table 1: FDA-REQUIRED REMS ASSESSMENTS

FDA REQUIREMENTS
Assessment Element 5: Surveillance monitoring for misuse, abuse, overdose, addiction, death and any intervention to be taken resulting from signals of these metrics, including information for different risk groups (e.g., teens, chronic abusers) and different settings (e.g., emergency rooms, addiction treatment centers, poison control call centers). As much as possible, the information should be drug-specific.
Assessment Element 6: Evaluation of drug utilization patterns (IMS data)
Assessment Element 7: Evaluation of changes in prescribing behavior Evaluation of changes in prescribing behavior of prescribers, e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills.
Assessment Element 8: Monitoring patterns of prescribing to identify changes in access to ER/LA opioid analgesics

REMS assessments have been submitted to the FDA at six months and twelve months since REMS approval, this is the Twenty-Four Month FDA Assessment Report and reports will be submitted annually hereafter. This report covers the time period from May 11, 2013 through May 9, 2014. This report includes an evaluation of the REMS Functional Components cited in Table 1 and describes the progress that has been made toward addressing the eight key assessments. To ensure inclusion of as much data as possible, while allowing for the necessary time to process data supporting each assessment, the reporting periods for assessments in this report vary. Below is a summary of the reporting periods by assessment.

Table 2: TWENTY-FOUR MONTH ASSESSMENT ELEMENTS DATA PERIODS

TWENTY-FOUR MONTH ASSESSMENT ELEMENTS		DATA PERIOD
Functional Components Assessment- Call Center Metrics		March 19, 2014 – May 8, 2014
Functional Components Assessment- Patient Counseling Document		May 11, 2013 – May 9, 2014
Assessment Element 1 Prescribers successfully completing training		May 11, 2013 – February 28, 2014
Assessment Element 2 Independent audit of CE activities		First Quarter 2013 – ongoing
Assessment Element 4 Evaluation of patient understanding (i.e., Patient Survey)		April 15, 2014 – May 7, 2014
Assessment Element 5	Component 2 & 3	Third Quarter 2010 – Fourth Quarter 2013

Table 2: TWENTY-FOUR MONTH ASSESSMENT ELEMENTS DATA PERIODS

TWENTY-FOUR MONTH ASSESSMENT ELEMENTS		DATA PERIOD
Surveillance monitoring for misuse, abuse, overdose, addiction, death and intervention taken	Component 4	July 2010 – December 2013
	Component 6	2012 NSDUH Annual Report 2012 MTF Overview, Volume I-II 2013 MTF Overview
Assessment Element 6 Evaluation of drug utilization patterns (IMS data, claims data)		July 2010 – December 2013
Assessment Element 7 Evaluation of changes in prescribing behavior		July 2010 – December 2013
Assessment Element 8 Changes in access to ER/LA Opioid Analgesics	Changes in access based on impact of REMS	July 2010 – December 2013
	Patient Perception on ER/LA Opioid Analgesic Access	April 15, 2014 – May 7, 2014
	Prescriber Perception on ER/LA Opioid Analgesic Access	February 8, 2013 – April 17, 2013

3. REMS ASSESSMENT RESULTS

3.1. Assessment Element 1 – Prescribers Who Have Successfully Completed Training

The assessment of the extent to which the training is effective in meeting the performance goals of the ER/LA Opioid Analgesics REMS is a key component of the overall REMS evaluation. This assessment began following the implementation of REMS-compliant CE activities on February 28, 2013. To assess the reach of the CE, the RPC established and implemented a plan to measure the number of ER/LA opioid analgesic prescribers who successfully completed the training. Since the launch of the first RPC-supported REMS-compliant CE activity on February 28, 2013,

- 20,345 ER/LA opioid analgesic prescribers have completed REMS-compliant training

- Of these, 19,198 ER/LA opioid analgesic prescribers completed REMS-compliant training during this reporting period (May 11, 2013 – February 28, 2014)

The following is an overview of the assessment strategy employed to evaluate REMS-compliant CE education supported by the RPC. In order to accurately collect, aggregate, and evaluate data in time for this Twenty-Four Month FDA Assessment Report the cutoff date for CE data was established as February 28, 2014[1].

3.1.1. Assessment Overview

The ER/LA Opioid Analgesics REMS represents the first time that accredited CE has been utilized to fulfill a REMS training requirement. As detailed in the Twelve-Month FDA Assessment Report, a multitude of systems and processes needed to be developed in order for accredited CE programs to offer REMS training. Further, implementation must be coordinated with the National CE Accrediting Bodies, CE Provider Organizations, and other key REMS stakeholders to enable provision of REMS-compliant CE. Data collection, aggregation, reporting, and independent audit processes became fully operational during this reporting period and serve as the basis for the data/information contained within this report.

3.1.2. REMS Continuing Education Stakeholders

Since the approval of the REMS on July 9, 2012, the RPC has continuously partnered with National Accrediting Bodies, Accredited CE Providers, and other key CE stakeholder organizations. Details regarding these CE stakeholders are outlined in Table 3.

[1] The data cut-off used for CE data contained in this report is February 28, 2014 to ensure inclusion of as much data as possible but allow for the needed time for transmission, aggregation and analysis of the data prior to incorporation into the report. This approach was discussed and agreed upon at the Conjoint Committee for Continuing Education Meeting on February 24, 2014 with FDA in attendance.

Table 3: OVERVIEW OF RPC-SUPPORTED, REMS-COMPLIANT CONTINUING EDUCATION STAKEHOLDER ORGANIZATIONS AND THEIR ROLES

CE STAKEHOLDER	OVERVIEW
Conjoint Committee on Continuing Education (CCCE)	• 20 + national organizations spanning the spectrum of medical/clinical education and practice; the Committee's focus is on identifying ways for CE to help improve performance of the United States (US) healthcare system. • Provide leadership, as well as integral input, feedback, and assistance in successfully operationalizing REMS CE • During 2014, formally expanded CCCE member organizations to include non-physician groups in recognition of the essential role of these healthcare professionals in caring for people with pain and adhering to safe prescribing practices for opioid analgesics. • Charged with implementing the Council for Medical Specialty Societies (CMSS) strategic focus referred to above • Organized and conducted the February 24, 2014 CCCE REMS meeting. Multiple REMS Work Groups were established and are currently prioritizing strategies to advance achievement of the REMS CE goals. Meeting participants included FDA, National CE Accrediting Bodies, 2 RPC-supported CE Providers, as well as representatives from the CMSS, MedBiquitous, an independent REMS/Public Health expert, and RPC.
Council of Medical Specialty Societies	• Consortium of 39 medical specialty organizations working to improve US healthcare through policy, accreditation, and broad-reaching medical education initiatives. • Key stakeholder representing > 700,000 physician members. • Strategic focus established in 2014: to address the public health crisis by emphasizing the importance of ER/LA opioid analgesics prescribers' voluntary participation in REMS-compliant CE • Actively engaged in fostering effective REMS communication and collaboration among regulatory agencies, policy makers, the CE community, and industry. • Executive Vice-President and Chief Executive Officer (CEO) of CMSS also serves as the Convener for the CCCE • Council members participate in CCCE REMS meetings and workgroups
MedBiquitous Consortium	• Develops and updates nationally recognized American National Standards Institute (ANSI)-accredited information technology standards for healthcare education and quality improvement. • Creator/owner of the Medical Education and Metrics Standards (MEMS) that underlay a uniform system of CE data collection, aggregation, and reporting. • Convener of the MedBiquitous Working Group comprised of representatives from National CE Accrediting Bodies, REMS CE Providers, Professional Organizations, FDA, RPC and the REMS CE Data Aggregation Vendor. • REMS deliverables to date have included: development of use cases; development/release of MedBiquitous Specifications V1.52; development/release of Implementation Guidelines for REMS CE Data Exchange V 0.67
National CE Accrediting Bodies	• Interface with CE Providers and RPC to ensure that REMS-compliant CE activities are conducted in accordance with established standards for commercially-supported accredited CE.

Table 3: OVERVIEW OF RPC-SUPPORTED, REMS-COMPLIANT CONTINUING EDUCATION STAKEHOLDER ORGANIZATIONS AND THEIR ROLES

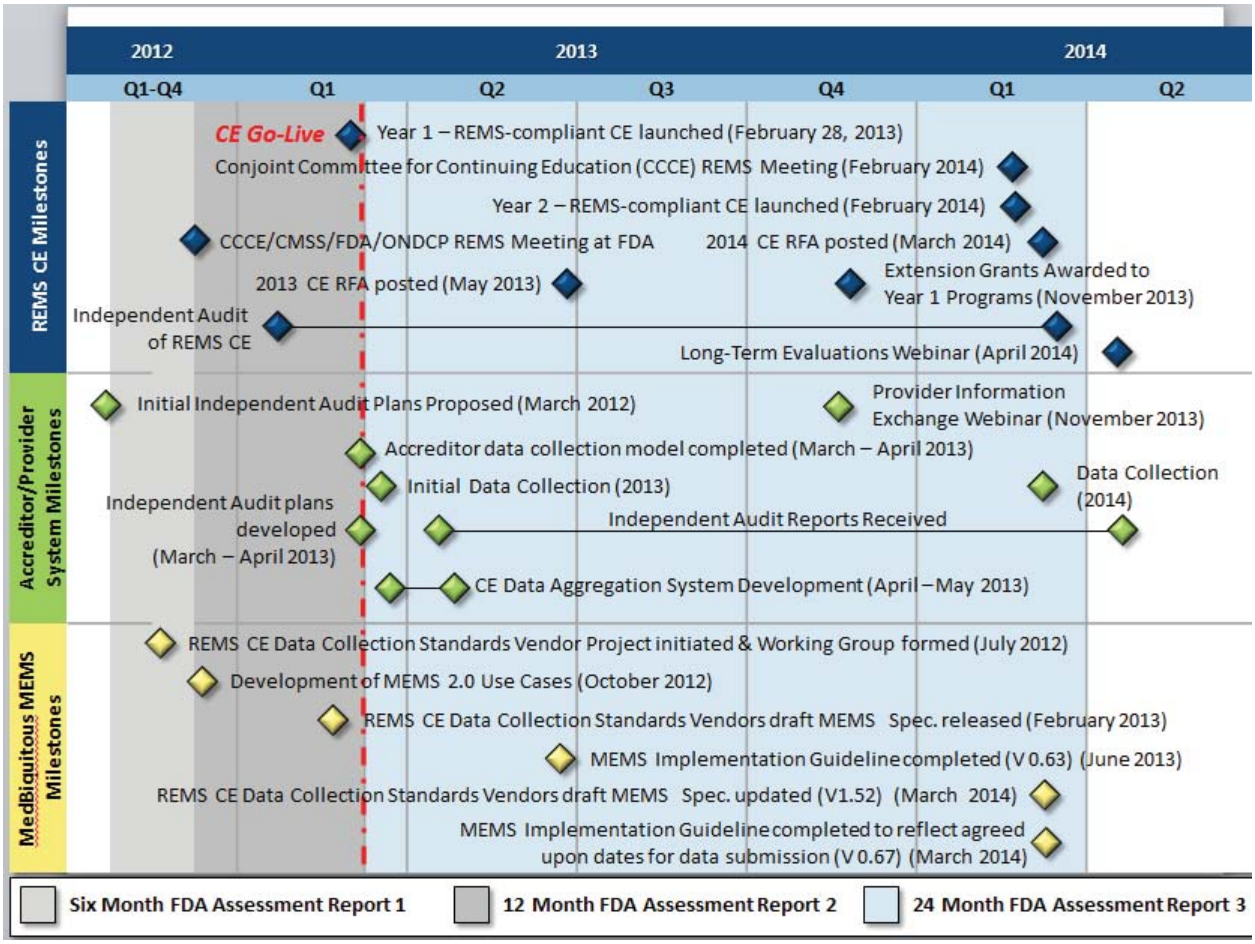
CE STAKEHOLDER	OVERVIEW
	• Act as independent auditors of REMS-compliant CE activities to ensure independent audit requirements described in the REMS are met and documented. • Serve as primary data collectors for REMS-compliant CE data; collect data from CE Providers and report it to the CE Data Aggregation Vendor contracted by RPC. • Participate in the MedBiquitous Working Group to ensure that the MEMS 2.0 specifications that will serve as the basis for uniform REMS CE data reporting are appropriate/ feasible from the Accrediting Body's standpoint. • Participate in Conjoint Committee for Continuing Education REMS meetings and REMS Workgroups. • Support CE Providers through provision of REMS informational resources and guidance regarding REMS-related questions (e.g., http://www.accme.org/sites/default/files/660_20131030_REMS_Fact_Sheet.pdf , last accessed June 4, 2014)
National CE Provider Organizations	• Represent various groups of CE Providers that may execute REMS-compliant CE, including RPC-supported activities. • Represent accredited Providers on the MedBiquitous Working Group to ensure the MEMS 2.0 Specifications that will serve as the basis for uniform REMS CE data reporting are appropriate/ feasible from the CE Provider's standpoint. • Participate in CCCE REMS meetings and CCCE REMS Workgroups. • Provide input/feedback on operational aspects of REMS CE to RPC via multiple webinars. • Assist in broadly communicating REMS information to groups of CE Providers and in surveying CE Providers to obtain input/feedback.
National Professional Societies	• Important stakeholders who have participated in both FDA and RPC REMS planning discussions to provide clinical and patient safety-related input/feedback. • Assist in raising REMS awareness and disseminating information about REMS CE through well-established communication networks with their constituents. • Participate in independent and collaborative initiatives to engage their members in completing REMS-compliant CE. • Participate in Conjoint Committee for Continuing Education REMS meetings and CCCE REMS Workgroups.

3.1.3. REMS Continuing Education Development Work Streams

As described earlier, multiple systems and processes have been established to provide the infrastructure for REMS CE data collection, reporting, aggregation and auditing. A graphic illustration of the RPC's major CE-development-related milestones can be seen in Figure 1 broken down by three work streams:

- REMS CE
- Accreditor/Provider Systems
- MedBiquitous MEMS

Figure 1: RPC Major Continuing Education-Related Milestones



3.1.3.1. REMS CE Work Stream

The availability of REMS CE was substantially expanded and awareness-raising efforts were intensified since the Twelve-Month FDA Assessment Report.

The Year 2 Request for Application (RFA) was issued in May 2013. Seven broad-based programs were approved and funded, significantly expanding the number and scope of CE activities available to train HCPs on the FDA Blueprint. In addition, 3 extension grants provided supplemental resources to ongoing programs funded in the Year 1 RFA cycle. This portfolio of CE activities was funded by the RPC to optimize ER/LA opioid analgesic completer ratios by supporting a collection of CE activities that:

- leverage the established partnerships, momentum and best practices of experienced REMS CE Providers through provision of extension grants
- integrate new programs geared towards key target audiences
- couple individual learning with institutional/organizational change opportunities to increase potential reach/impact

The second year of REMS-compliant CE was launched on schedule in February 2014. Details of these CE activities can be found in Section 3.1.6.1.

In addition to expanding the availability of CE activities, RPC advanced collaborative efforts with the CE Community to raise awareness of REMS CE and actively engage ER/LA opioid analgesic prescribers in completing REMS-compliant CE. On February 24, 2014, the CCCE convened a meeting in Chicago with all key stakeholders involved in the REMS CE effort, including the FDA. The primary objective of the meeting was to identify ways to increase the REMS CE completion rates. The meeting involved twenty national clinical/educational organizations, including all Accrediting Bodies involved in the REMS CE and the CMSS. Also in attendance were Doris Auth, PharmD, representing FDA; the Deputy Director of MedBiquitous; two RPC-supported REMS CE Providers; REMS/public health expert, Elaine Morrato, DrPH; and RPC CE Sub-team leadership.

During the meeting, experienced REMS CE Providers shared best practices and challenges encountered to date. The group then focused on identifying opportunities for increasing the number of ER/LA opioid analgesic prescribers completing voluntary REMS-compliant CE. Outcomes of the meeting included:

- A draft strategies and interventions document (Appendix A)
- Establishment of workgroups to evaluate, prioritize and address the proposed strategies and interventions
- Agreement to continue discussions between FDA and RPC CE Sub-team to assure communication and coordination of efforts (RPC will continue to provide updates on these collaborative efforts to FDA.)

Additional REMS-CE accomplishments during the reporting period May 11, 2013 – February 28, 2014 include:

- Completion of independent audit report cycle and receipt of documentation from Accreditors stating that 82.8% of activities audited met all criteria for REMS-compliant CE as defined in the REMS Supporting Document and the FDA Blueprint
- Development and posting of the 2014 CE RFA and evaluation of grant applications submitted by CE Providers
    - Provision of a provider information webinar to foster interest and respond to questions concerning the 2014 RFA
- Planning and execution of a Provider/Outcomes Organization webinar focused on the upcoming Long-term Evaluations

3.1.3.2. Accreditor/Provider Systems Work Stream

Since the Twelve-Month FDA Assessment Report, Accreditor and Provider system improvements include:

- Refinement and implementation of processes/systems necessary to perform REMS-required independent audits of at least 10% of RPC-supported CE program activities
- Evolution of Accreditor and Provider systems to collect, aggregate and analyze data
- Relationship building among RPC-supported grantees that included a successful Provider Information Exchange (PIE) webinar in November 2013 and May 2014

3.1.3.3. MedBiquitous MEMS Work Stream

Since the Twelve-Month FDA Assessment Report, the MedBiquitous Working Group has accomplished the following components of the MEMs Work Stream:

- Completed Version 0.63 MEMS Implementation Guideline (June 2013)
- Updated REMS CE Data Collection Standards Vendors draft MEMS Specifications (Version 1.52 March 2014)
- Completed Version 0.67 MEMS Implementation Guideline to reflect agreed upon dates for data submission (March 2014)

Following the submission of this Twenty-Four-Month FDA Assessment Report, the MedBiquitous Working Group is planning to hold a debrief session to determine whether any modifications are needed to the draft MEMS Implementation Guideline and Specifications. Subsequently, the specification will be submitted to the MedBiquitous Standards Committee for review, comment and final disposition. The working draft of the specifications is posted at http://www.medbiq.org/working_groups/metrics/MedicalEducationMetricsSpecifications.pdf (last accessed June 9, 2014).

3.1.4. Data Collection Processes

The CE Data Aggregation Vendor collected the ER/LA opioid analgesic prescriber completer data from CE Providers via Accrediting Bodies for this Assessment Report. These data focus on the number of ER/LA opioid analgesic prescribers who successfully completed REMS-compliant CE activities through the end of the CE data collection period (February 28, 2014).

3.1.5. Requirements for Assessment

The requirements of Assessment Element 1 include reporting the number of prescribers who have taken the REMS-compliant CE training and providing an aggregate-level description of the completers. Performance goals for the number of prescribers completing training include: number completed within 2 years, 3 years, and 4 years.

A summary of the RPC-supported REMS-compliant training activities available through this reporting period are presented below.

3.1.6. Data Collection and Analysis Method for Prescriber Education

CE data from all RPC-supported, REMS-compliant CE activities were aggregated into one single database in order to generate summary tables and graphs for inclusion in this report.

Each independent CE Provider transmitted required information associated with their RPC-supported, REMS-compliant CE activities to the appropriate National Accrediting Bodies. These Accrediting Bodies then compiled completer data from all RPC-supported CE providers and delivered these data to the CE Data Aggregation Vendor.

3.1.6.1. Dates of Availability of REMS-Compliant Training

A description of all REMS-compliant CE activities available May 11, 2013 to February 28, 2014, by Grantee, is provided in Table 4.

There are 6 additional RPC-supported, CE Providers that have either not accrued ER/LA opioid analgesic prescriber completers before February 28, 2014 or have not yet launched their activities.

Table 4: RPC-SUPPORTED REMS-COMPLIANT CONTINUING EDUCATION ACTIVITIES AVAILABLE DURING THE REPORTING PERIOD (MAY 11, 2013 – FEBRUARY 28, 2014)

GRANTEE[1]	PROGRAM START DATE	PROGRAM FORMAT(S)	NUMBER OF ACTIVITIES
Trustees of Boston University	February 28, 2013	Live training and Internet-based	35
CO*RE (Collaborative for REMS Education)	March 13, 2013	Live training and Internet-based	171
Association for Hospital Medical Education	August 29, 2013	Live training and Internet-based	49
American College of Physicians/Pri-Med	June 7, 2013	Live training and Internet-based	5
Utah Medical Association Foundation	January 1, 2014	Internet-based	1
University of Washington School of Medicine	February 2, 2014	Internet-based	1
TOTAL			262

[1] The table is organized by start date of the activities; if there were multiple activities, the start date reflects date of first activity.

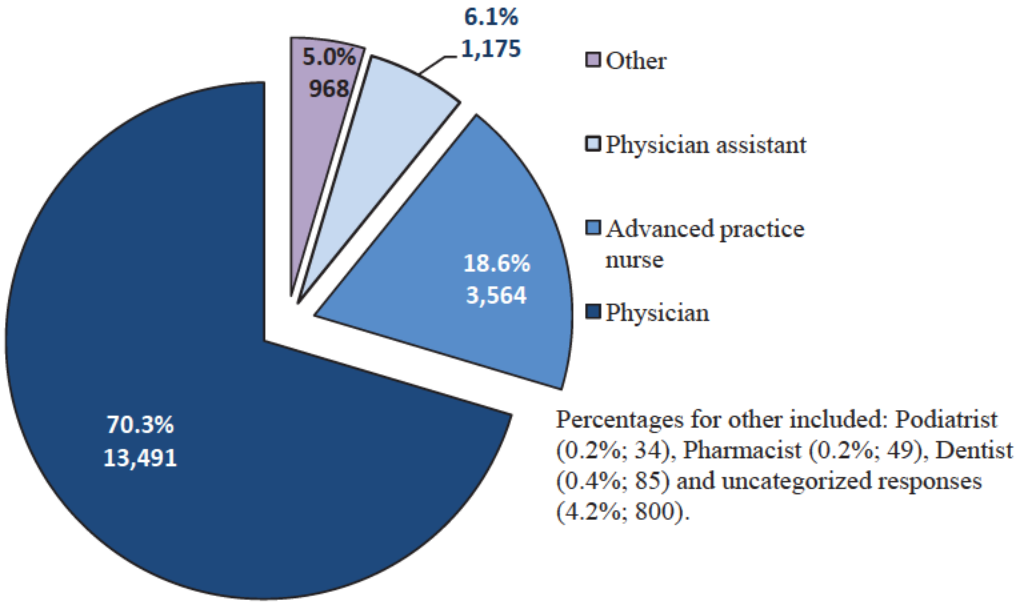
3.1.6.2. ER/LA Opioid Analgesic Prescribers Completing REMS-Compliant Training

As of the data cut-off, 20,345 prescribers have completed the RPC-supported REMS-compliant training. During this reporting period (through February 28, 2014) a total of 19,198 prescribers completed the training. Further the RPC has noted many health care professionals electing to complete the training but are excluded from the prescriber criteria, as they may not be DEA-Licensed or may not have written an ER/LA opioid analgesic prescription in the last twelve months. CO*RE noted that 62% of the CO*RE curriculum completers did not count towards the 20,345 who have completed the training to date. Two hundred and sixty two RPC-supported, REMS-compliant education activities were launched between May 11, 2013 and February 28, 2014. The activities were accredited by at least 1 of 8 National Accrediting Bodies. Most of the activities were presented as live training; some were internet-based. Data on the number of ER/LA opioid analgesic prescribers completing the training were collected. Per the MEMS Implementation Guidelines, "Prescribers" are defined as "clinicians who are registered with the DEA to prescribe Schedule II and/or III controlled substances and have written at least one ER/LA opioid analgesic prescription in the past year." Completion of an activity is defined as "Prescribers that have completed all components of an educational activity and met the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation." The majority of the ER/LA opioid analgesic prescribers who completed the training in this reporting period were physicians, with a large preponderance of primary care physicians.

3.1.6.2.1. Characteristics of ER/LA Opioid Analgesic Prescribers Completing Training

A break-down of training by profession of the ER/LA opioid analgesic prescribers is provided below. The majority of prescribers who completed the CE training were physicians.

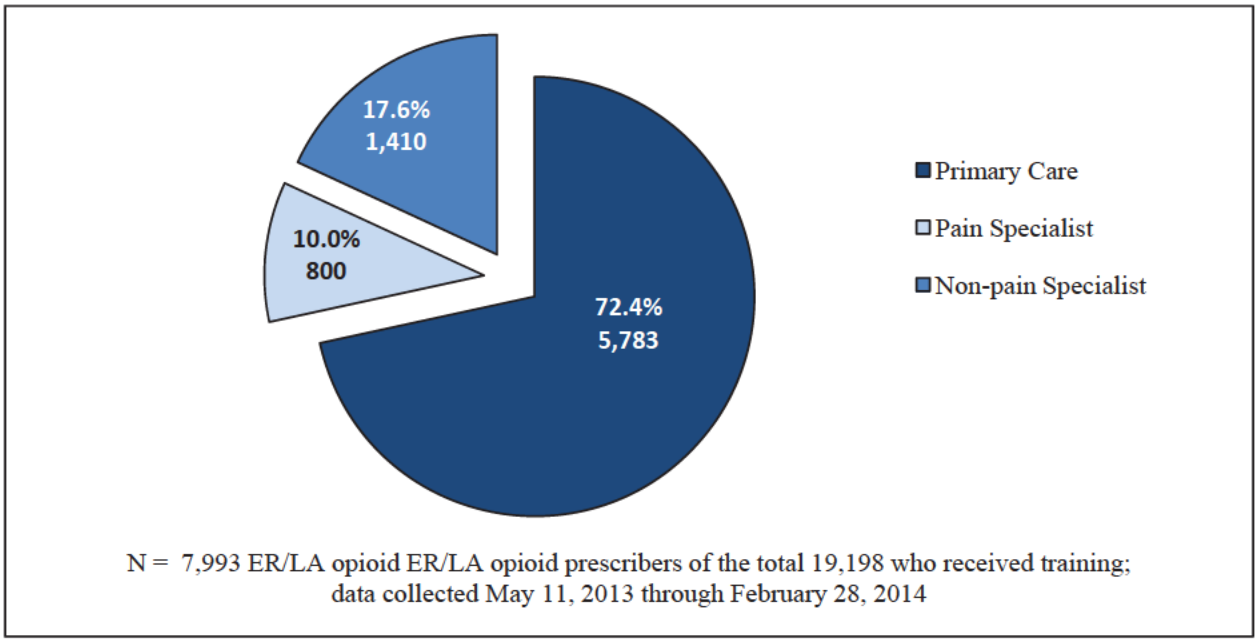
Figure 2: RPC-Supported, REMS-Compliant ER/LA Opioid Analgesic Prescribers Completing Training by Profession during the Reporting Period (May 11, 2013 – February 28, 2014)



N = 19,198 ER/LA opioid prescribers; data collected May 11, 2013 through February 28, 2014

Figure 3 provides data according to the practice type, or the clinical practice focus of the ER/LA opioid analgesic prescriber. Practice type was an optional category of metrics captured by some CE Providers for those ER/LA opioid analgesic prescribers completing the RPC-supported, REMS-compliant training. These data were collected on 7,993 ER/LA opioid analgesic prescribers in this reporting period, which represents 41.6% of all ER/LA opioid analgesic prescribers completing an RPC-supported REMS-compliant CE activity. For those prescribers for whom a practice area was reported, 72.4% were primary care physicians.

Figure 3: ER/LA Opioid Analgesic Prescribers Completing RPC-Supported, REMS-Compliant Training by Practice Type during the Reporting Period (May 11, 2013 – February 28, 2014)



N = 7,993 ER/LA opioid ER/LA opioid prescribers of the total 19,198 who received training; data collected May 11, 2013 through February 28, 2014

3.1.6.2.2. ER/LA Opioid Analgesic Prescriber Training Format Types

RPC-supported, REMS-compliant training activities (n=262) have been provided in both live, which includes *Congress Symposium or Session; Grand Rounds; Meeting Series; Symposium; Live-Webinar; Teleconference* (n=236) and internet formats (n=26). The majority of ER/LA opioid analgesic prescribers who completed training participated in live training activities.

3.1.7. New Grant Request for Applications

For the 2013 RFA cycle, fewer grant proposals were received than in response to the 2012 RFAs. This, the RPC decided to include any accredited provider in the 2014 RFA, including medical education communication companies (MECCs).

On March 19, 2014 the RPC issued a RFA, CE RFA 040314, which was posted on the RPC website and Grant Management System (GMS). The RFA specified that grant proposals should include a number of critical components intended to inform RPC's selection of those grant applications most likely to achieve the REMS goals. These key components include:

- Collaboration with organizations whose constituents comprise the primary REMS education audiences
- Broad geographic coverage
- Innovative learning formats to meet learner preferences and timing/practice needs
- Thorough program overview including details of how the full FDA Blueprint will be integrated into the activity

- Details on performance of the activity assessments to test knowledge across all sections of the FDA Blueprint
- Attestation that proposed activities are fully compliant with all applicable standards of the primary Accrediting Body, as well as other relevant standards, guidelines, and requirements as they apply to the conduct of independent medical education

The 2014 RFA included several modifications from the 2013 RFA:

- Requested detailed description of strategies to engage ER/LA opioid analgesic prescribers in activities through to completion of education on entire Blueprint.
- Updated sections related to the: 1) needs assessment including outcomes/surveys specific to audience; timing of educational activities to be best aligned with FDA progress reporting requirements; 2) scope/populations to be educated; and 3) greater clarity regarding the independent audit by the CE Accrediting Bodies
- Broadened the Requestor definition to include any Accredited Provider who will serve as the Provider of Record for the proposed activities, with the goal of increasing the number of grant applications in response to our Request for Proposal (RFP).
- Included an appendix which provided background on overdose deaths related to ER/LA opioid analgesics and demographic information on ER/LA opioid analgesic prescribers.

A comprehensive list of grant request submission requirements can be found in Appendix B RPC assured broad awareness of the RFA through mass e-mail dissemination to Accrediting Bodies, national CE provider organizations, CE Providers, and other CE stakeholders. Additionally, the RPC CE Sub-team hosted an informational webinar for all interested CE stakeholders on March 27, 2014. The goal of the webinar was to review the RFA and how it differed from past years, provide key learnings from the past thirteen months, and answer any questions.

A total of 21 RFA responses were received by RPC by the due date of April 30, 2014.

3.1.8. Conclusion

Since the approval of the ER/LA Opioid Analgesic REMS on July 9, 2012, the RPC has planned, designed and deployed the infrastructure needed to support REMS-compliant CE activities. As of February 28, 2013, the launch of the first REMS-compliant CE activity, the RPC has:

- collaborated extensively with the National Accrediting Bodies, Accredited CE Providers, the FDA, and other key CE stakeholder groups on:
    - funding, tracking, and monitoring compliance of educational activities
    - data reporting and aggregation
    - designing and implementing a process for independent audits of REMS-compliant CE activities
    - determining best practices to conduct long-term evaluations
- funded 12 providers through 3 RFA cycles and extension grants

Extension grants were awarded to some 2012 grant recipients in 2013, allowing CE providers to efficiently use previously-developed REMS-compliant education and educational tools/pieces. This enables Providers to extend the reach of their education and engage additional ER/LA

opioid analgesic prescribers via similar educational formats and/or by introducing additional activities.

CE Providers have informed the RPC that it is considerably more challenging than expected to attract ER/LA opioid analgesic prescribers to their REMS-compliant activities and to engage them to completion. Additionally, CE Providers have reported that as many as 50% of HCPs completing the education had in fact not written a prescription for an ER/LA opioid analgesic in the past year. Although CE Providers indicate that non-prescribing healthcare professionals are critically important in the care and safety of patients, they do not help to meet performance goals of the ER/LA Opioid Analgesics REMS. In order to address these observations, these organizations have been executing exhaustive, creative awareness campaigns, engaging in CE Provider and Accreditor information exchange calls hosted by the RPC CE Sub-team to ensure collaboration among stakeholders as the RPC continues to work diligently to achieve the FDA REMS goals.

In all, many milestones were reached during the second year that ER/LA Opioid Analgesic REMS CE was available. The RPC collaborators enabled the provision of quality education that was supported by an audit structure and included appropriate data gathering to allow assessment of progress toward REMS CE goals. The effort and commitment of these stakeholders became evident with the production of 262 RPC-supported activities that generated 19,198 ER/LA opioid analgesic CE Program completers. Additionally, the formation of new coalitions of providers and other organizations such as CCCE, and the enhanced CE standards set by Medbiquitous will leave a lasting contribution to quality CE development and uniform reporting.

4. ASSESSMENT ELEMENT 2 – INDEPENDENT AUDIT OF CONTINUING EDUCATION ACTIVITIES

In order to assure the overall content and quality of the accredited certified educational activities comply with the FDA Blueprint, the RPC will have audits conducted by a party that is independent of industry and acceptable to the FDA and CE accrediting bodies. This will allow the educational offerings to be assessed and will continue to allow compliance with accreditation policies. The audits must:

- Be conducted by an auditor independent of the NDA/ANDA holders. (Accreditation bodies of CE providers would be considered independent of the NDA/ANDA holders and would be eligible to conduct the audits.)
- Evaluate:
    - whether the content is factually correct
    - whether the content of the training covers all sections of the FDA Blueprint approved as part of the REMS;
    - whether the post-course knowledge assessment measures knowledge of all sections of the FDA Blueprint; and
    - whether the training was conducted, by CE providers, in accordance with the standards for CE of the ACCME, or of other accrediting bodies' standards and are independent of the pharmaceutical industry's influence, and the content is free from promotional material.
- Be conducted on a random sample of at least 10% of the RPC-supported, REMS-compliant CE activities and REMS-compliant training not funded by the RPC but that will be counted towards meeting the REMS performance goals.

Currently, there are 5 nationally recognized Accrediting Bodies that have submitted independent audit reports as shown in Table 5. The operational logistics for the independent audit process were reported in the Twelve-Month FDA Assessment Report.

Table 5: SUMMARY OF SUCCESSFUL INDEPENDENT AUDIT REPORTS

ACCREDITING BODY	NUMBER OF AUDIT REPORTS RECEIVED	NUMBER OF AUDIT REPORTS MEETING CRITERIA FOR REMS COMPLIANT CE *(AS DEFINED IN REMS SUPPORTING DOCUMENT)*	RESULTS		
			CONTENT OF THE TRAINING COVERS ALL COMPONENTS OF THE FDA BLUEPRINT APPROVED AS PART OF THE REMS	POST-COURSE KNOWLEDGE ASSESSMENT MEASURES KNOWLEDGE OF ALL SECTIONS OF THE FDA BLUEPRINT	CE TRAINING WAS CONDUCTED IN ACCORDANCE WITH THE STANDARDS FOR CE OF THE ACCME®, OR OF ANOTHER CE ACCREDITING BODY APPROPRIATE TO THE PRESCRIBERS' MEDICAL SPECIALTY OR HEALTHCARE PROFESSION
ACCME	13	8	✓	✓	✓
AAFP	8	8	✓	✓	✓
AANP	2	2	✓	✓	✓
AOA	3	3	✓	✓	✓
ANCC	1	1	✓	✓	✓
TOTAL	27	22			

Of the 27 total audit reports received, 22 (82%) met all criteria for REMS-compliant CE as defined in the REMS Supporting Document and the FDA Blueprint. ACCME noted observations for 6 of the 13 activities they audited. One of the activities did not meet expectations with respect to scope of evaluation; however, ACCME noted that this could not yet be assessed because the activity was still underway at the time of the audit. ACCME noted that the remaining five activities did not meet expectations with respect to the ACCME Standards for Commercial Support relating to obtaining and prominently displaying financial relationships of faculty and/or staff involved in the activity. Details are provided below in Table 6.

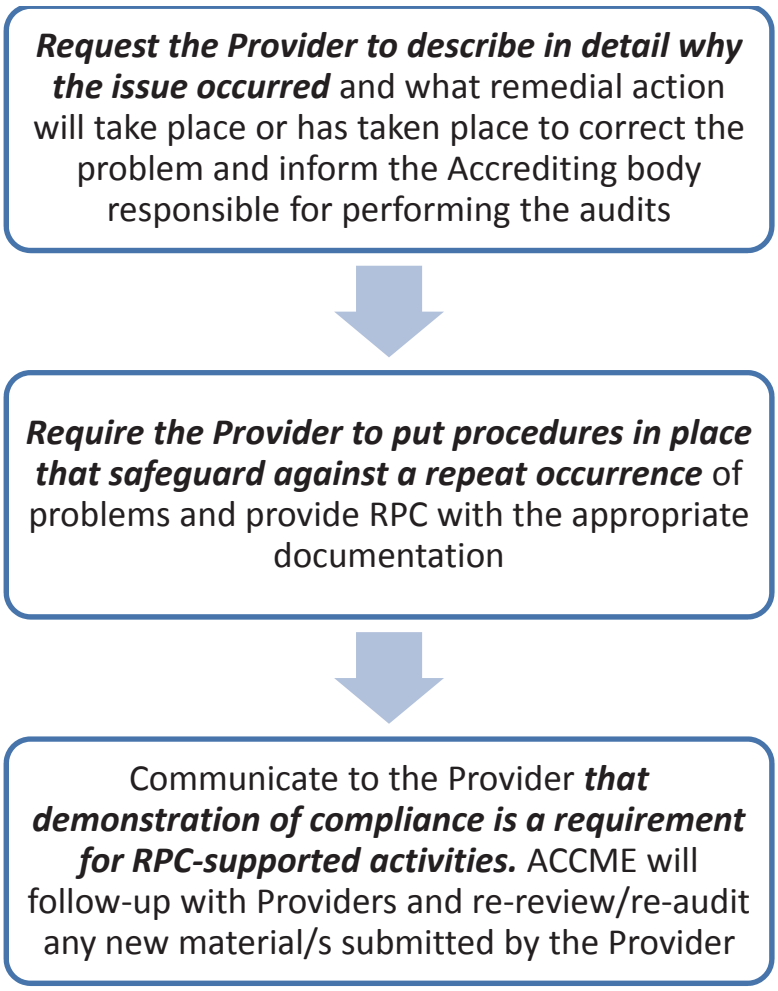
Table 6: SUMMARY OF ACCME INDEPENDENT AUDIT REPORTS WITH OBSERVATIONS RELATED TO DISCLOSURE OF FINANCIAL RELATIONSHIPS

	AUDIT OBSERVATIONS		STATUS
	THE RELEVANT FINANCIAL RELATIONSHIPS THAT EACH INDIVIDUAL IN A POSITION TO CONTROL THE CONTENT OF THE CE ACTIVITY DISCLOSED TO THE PROVIDER	EVIDENCE THAT DISCLOSURE OF RELEVANT (OR NO) FINANCIAL RELATIONSHIPS WAS MADE TO LEARNERS PRIOR TO THE BEGINNING OF THE ACTIVITY	PROVIDER TAKING CORRECTIVE ACTION WITH ACCREDITING BODY
Activity 1		X	✓
Activity 2	X	X	✓
Activity 3	X	X	✓
Activity 4	X		✓
Activity 5	X		✓

RPC has reviewed the documentation for the above referenced 5 ACCME audit reports and views the issues as important but not impacting content. The RPC is following up with each provider to ensure appropriate remediation.

Due to significant work required to design and implement the required independent CE audits, the process was implemented following the launch of REMS-compliant CE. Thus, some activities that underwent or will undergo audits are already in progress or were completed prior to the audit. Below is a depiction of the current follow up process that will help ensure that observations identified in current or past activities are adequately addressed (Figure 4). In the future, CE providers will be required to submit activities for audit prior to launch so that any observations can be remediated prior to the program going live.

Figure 4: Independent Audit Follow-Up Process



5. ASSESSMENT ELEMENT 3B – LONG-TERM EVALUATION

RPC-funded REMS-compliant CE activities have been available for 16 months and planning for the LTE is well underway. The LTE will be designed to assess prescribers' knowledge and practice changes 6 months to one year after completing a REMS-compliant CE course.

To enhance collaborations between CE Providers and outcomes organizations or vendors qualified to perform the LTE (referred to as the LTE Coordinating Organization), the RPC hosted a well-attended webinar on April 3, 2014. Feedback received as a result of the webinar and input from additional committees within the RPC was integrated into a RFP which was disseminated on April 25, 2014. Proposals were due to RPC on May 14, 2014; four proposals were received and the vendor selection process is underway. The RPC's goal is to have a contract in place by mid-September 2014. The protocol for the LTE will be submitted for FDA's 90-day review. The results of the LTE will be included in the Thirty-Six Month FDA Assessment Report.

6. ASSESSMENT ELEMENT 4 – PATIENT SURVEY

To assess patient knowledge of the safe use of ER/LA opioid analgesic products following implementation of the REMS, a cross-sectional patient survey was conducted by a vendor on behalf of the RPC. To understand the impact of the core messages in the FDA Blueprint that could be assessed from the patient perspective, the survey also identified patient-reported prescriber behaviors, including appropriate screening and counseling. The evaluation of whether patient access to ER/LA opioid analgesic medication and patient satisfaction with access to pain management has been impacted by the REMS is further detailed in Assessment Element 8.

6.1. Survey Design and Methods

The survey population was identified from medical and pharmacy claims in the HealthCore Integrated Research Database^{SM} (HIRD) and consisted of commercially-insured adult patients who filled at least one prescription for an ER/LA opioid analgesic class product between December 1, 2012 and November 30, 2013. A total of 413 patient surveys were completed.

The patient survey included questions assessing the respondents' knowledge about the safe use of ER/LA opioid analgesics, the receipt and comprehension of the Medication Guide and Patient Counseling Document (PCD), and perceived access and satisfaction of access to pain medication. The patient protocol and survey have been included in the appendix of this report. Responses to the FDA comments on the draft Protocol received on March 19, 2014 are shown in Appendix C.

6.1.1. Pretesting

Prior to conducting the patient survey, a pretest was used to identify any limitations with the survey instrument or process. Results of the pretest are included in Appendix C. There were 21 surveys conducted during pretest, which represented approximately 5% of the targeted number of 400 completed surveys required for the main patient survey. A strong understanding of key messages was demonstrated. Additionally a small number of questions were rephrased and survey skip patterns revised, based on feedback received during the pretesting as well as FDA feedback.

6.1.2. Survey Administration

A total of 413 patient surveys were completed during this reporting period. Eligible respondents were identified through a third party and pre-notification letters were sent to patients via postal mail with invitations to complete the survey either online or by telephone. The patients that did not respond to the invitation were then contacted by telephone and invited to participate. Patients were excluded if they failed to validate their name and date of birth, stated that they had not filled a prescription for an ER/LA opioid analgesic in the 12 months prior to the survey date, were employed as a licensed physician, were unsure of their ER/LA opioid analgesic or class, or were employed or had family members that were current or former employees of vendor companies who developed and/or implemented the survey; the FDA; or members of the RPC. The survey averaged approximately 20 minutes in duration. Patients who completed the survey received a $20 payment for their time and participation.

6.1.3. Survey Analysis

Six stratifications were analyzed:

1. ER/LA opioid analgesic type (methadone, transdermal delivery systems, oral products);
2. Medication Guide receipt/read/comprehension status;
3. PCD receipt/provider referenced/comprehension status;
4. Combined receipt/read/comprehension status for both the Medication Guide and PCD versus neither the Medication Guide nor the PCD;
5. Receipt of only one versus more than one ER/LA opioid analgesic; and
6. Knowledge Assessment Score (KAS; i.e., the proportion of questions that the respondent answered correctly concerning the safe use and storage of ER/LA opioid analgesics) threshold of <70% versus ≥70%.

The following analyses were performed:

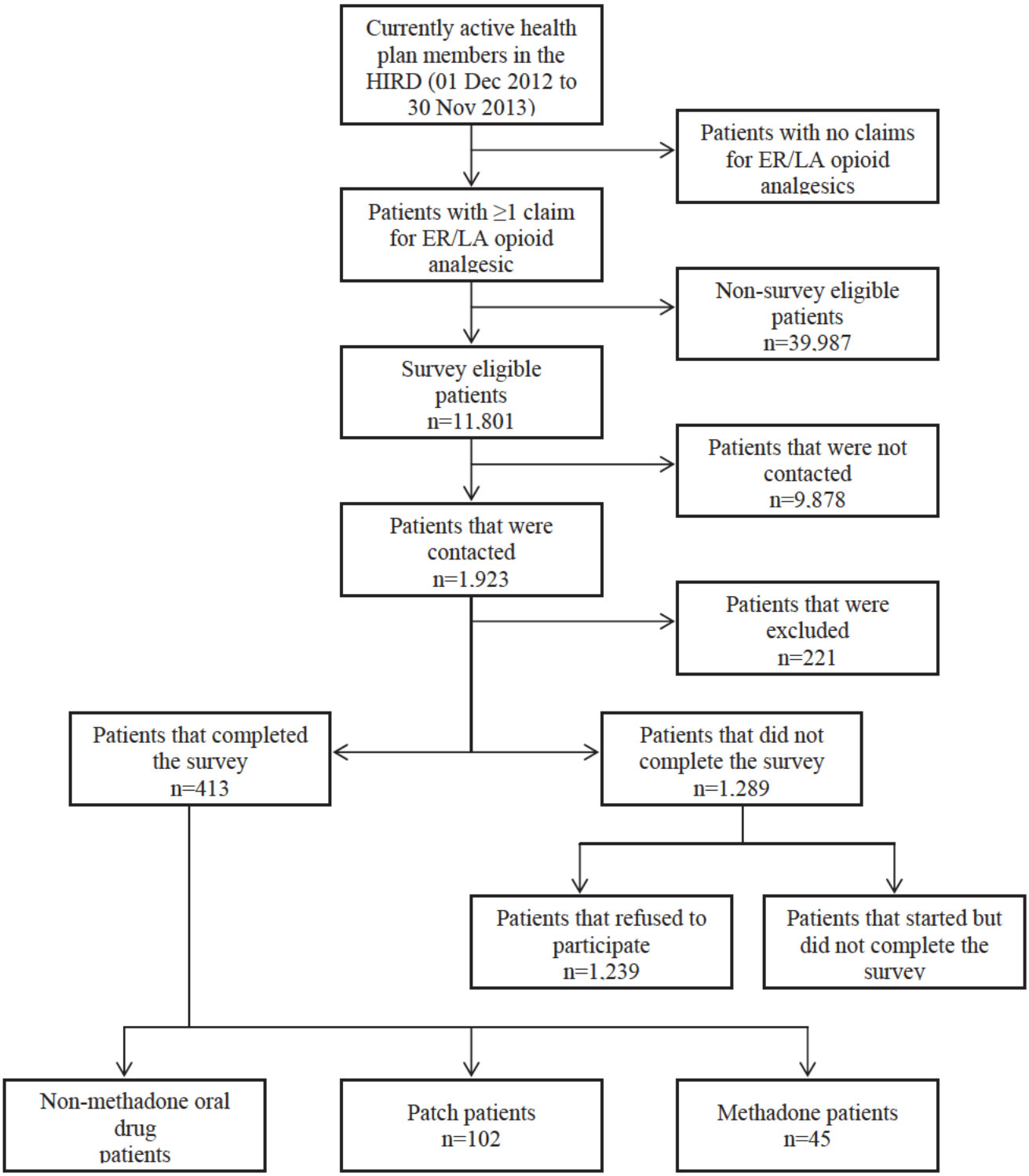
- Comparison of respondents and non-respondents in terms of demographic and clinical characteristics identified in the HIRD claims data;
- Characterization of respondent demographic characteristics identified in the survey and HIRD claims data;
- Characterization of respondent drug use by specific product;
- Identification of the proportion of respondents that received or read the Medication Guide;
- Identification of the proportion of respondents that received or had a provider that referenced the PCD;
- Identification of the proportion of respondents responding correctly to each KAS component question;
- Identification of the proportion of respondents reporting satisfaction with access to treatment (results described in FDA Assessment Element 8);
- Identification of the proportion of respondents reporting key healthcare provider screening and counseling activities;
- Distribution of KAS scores; and
- Analysis of risk factors for a poor KAS (<70%) via logistic regression.

All analyses were performed using SAS® software version 9.4 or later (SAS Institute Inc., Cary, NC). Only aggregated data were presented. Complete details of the analyses performed will be provided to the FDA when available.

6.1.4. Survey Results

The main survey patient list consisted of the contact information of 11,801 individuals who met the claims-based study inclusion/exclusion criteria; 8,005 (68%) used non-methadone oral products only, 2,733 (23%) used patch products, and 1,063 (9%) used methadone. Of these 11,801 patients, 1,923 (16%) patients were successfully contacted, of which 221 (11%) were excluded at the time of the survey based on screening criteria. Of the remaining 1,702 contacted patients, 413 (24%) completed the survey, 50 (3%) started but did not complete the survey, and 1,239 (73%) refused to participate. Among the 9,878 potentially eligible patients who were not contacted, 2,834 (29%) patients had invalid contact information, 245 (2%) could not be contacted after the maximum number of 5 survey attempts had been made, and 6,799 (69%) were still potentially eligible at the time the targeted number of completed surveys was reached (Figure 5).

Figure 5: Patient Identification



The 413 survey respondents were similar to non-respondents in terms of age, US region of residence, and type of ER/LA opioid analgesic used. Respondents were more often female (62% versus 52%) and diagnosed with chronic pain, fibromyalgia, and unspecified abdominal pain. Respondents also had more previous dispensings of ER/LA opioid analgesics (respondents: mean 9.0, standard deviation [SD] 8.96 versus non-respondents: mean 7.7, SD 8.97) and a higher total number of distinct drug classes dispensed in the six months preceding the survey (respondents: mean 9.4, SD 5.59 versus non-respondents: mean 8.3, SD 5.30).

Over 90% of survey respondents were Caucasian, which is typical for the HIRD population. Almost three fourths were married or living with a partner (71%) and over half had a total household annual income at least $50,000 in 2013 (59%). Half had completed college and/or graduate school. Only 17% reported that they were new users of their current ER/LA opioid analgesic. However, 54% stated that their last prescription was filled within the last month and 50% had seen their healthcare provider in that timeframe. 54% reported that their healthcare provider first prescribed their ER/LA opioid analgesic at least 12 months prior to the survey date. Pain specialists were the prescribers for 43% of survey respondents. The most common agents used were Oxycontin ER (25%), oxycodone slow release (17%) and fentanyl (18%).

Comparing respondents based on the type of ER/LA opioid analgesic used, a higher proportion of the methadone cohort was female (73% versus 62% of non-methadone oral product and 57% of patch product users) and had their ER/LA opioid analgesic prescribed by a pain specialist (67% versus 36% of non-methadone oral product and 51% of patch product users). Only 7% of methadone respondents were new users, and 69% were first prescribed their ER/LA opioid analgesic more than 12 months prior to the survey.

Comparing respondents with more than one recorded dispensing of ER/LA opioid analgesics based on claims data (n = 315) versus respondents with only one dispensing (n = 98), a larger proportion of one time users were prescribed oral drugs (81% versus 59%). Fewer of these respondents had filled an ER/LA opioid analgesic prescription within six months prior to survey (50% versus 90%), and the most common prescriber type was “non-pain specialist” (62% versus 21%).

Medication Guide and PCD

There were 389 (94%) respondents who reported receipt of a Medication Guide and 399 (97%) who reported that they read at least some of the Medication Guide at least once. Of the 405 respondents who either received or read the Medication Guide, 396 (98%) reported that they understood at least half of the information and 92% received it at their most recent dispensing. Respondents who received the Medication Guide less often reported a total household annual income in 2013 below $25,000 (11% versus 21%). Fewer were first time users (16% versus 29%), and more had seen their healthcare provider or filled a prescription for ER/LA Opioid analgesics in the past month (52% versus 29% and 55% versus 29%, respectively). Among 405 respondents that received or read at least some of the Medication Guide at least once, 92% described their pharmacist as the source at their most recent dispensing and 96% described the Medication Guide as somewhat or very useful. Given that only 10 respondents did not understand the Medication Guide, it is difficult to assess differences in education between respondents that did and did not understand the Medication Guide. (Among 413 respondents, 175 (42%) received the PCD and 109 (26%) reported that their providers referenced the document; 141 (34%) neither received nor had a provider who referenced it, and 117 (28%) were unsure about whether they received or had a provider who referenced the PCD. Among 187

respondents who received or had a provider who referenced the PCD, 182 (97%) stated that they understood at least half of the PCD. Among 53 who stated that they were not sure whether they had received or had a provider who referenced the PCD, there were 38 (72%) respondents who subsequently stated that they understood at least half of the PCD. Compared to non-recipients, PCD recipients had more often seen a healthcare provider or filled an ER/LA opioid analgesic prescription in the past month (58% versus 45% and 60% versus 49%, respectively). Less than 1% of respondents who had received or had a healthcare provider who referenced the PCD reported that they did not understand it at all.

There were 94 (23%) respondents that received, read/had a provider who referenced, and understood both the Medication Guide and PCD; only five (1%) respondents did not receive, read/have a provider who referenced, nor understand both the Medication Guide and PCD.

Knowledge Assessment

A large majority of respondents correctly answered most questions concerning the serious risks of ER/LA opioid analgesic use, what to do in the case of overdose, proper storage, the importance of not sharing medication, and safe use. The KAS (i.e., proportion of knowledge questions that a respondent answered correctly) had a mean of 85.6% (SD 10.38) and ranged from 42% to 100%. There were 33 (8%) respondents with a KAS below the threshold of 70%, defining poor knowledge, and 99 (24%) with a KAS below 80%. Results by key risk message were as follows:

- *Patient understanding of the serious risks associated with the use of their ER/LA opioid analgesic*
    - Overall, 94% of respondents correctly identified that overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death and 84% that ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.
- *The patient knows what to do if they take too much drug*
    - 97% of respondents were aware of the need to seek emergency medical care for respiratory, chest, or facial swelling side effects, and 88% knew to seek emergency medical care for an overdose even if the patient felt fine.
- *The patient understands the need to store the drug in a safe place*
    - The risk of death in children using the respondent's ER/LA opioid analgesic was recognized by 93% of the respondents and 91% recognized that ER/LA opioid analgesics should not be thrown away in the trash.
    - Fewer respondents (66%) were aware that ER/LA opioid analgesics should not be stored in a medicine cabinet next to other household medications.
- *The patient knows they should not share the drug with anyone*
    - Respondents recognized that ER/LA opioid analgesics should not be given to others with the same condition (98%) and that selling or giving away these medications is against the law (97%).
- *The patient understands how to use the drug safely*
    - A high proportion of respondents were aware of the necessity of informing their healthcare providers about all other medications being used (96%), over-the-counter medications (89%), any history of substance or prescription drug abuse, alcohol addiction, or mental health problems (91%), and whether to take more medication if the current dose was not controlling their pain (94%); 84%

identified the need to talk to a healthcare provider prior to stopping ER/LA opioid analgesics.
- The need to abstain from alcohol was recognized by 93% of respondents.
- Only 56% of respondents correctly identified the need to read the attached Medication Guide at each dispensing.
- A small number of questions were asked only to respondents using a particular ER/LA opioid analgesic type:
  - Among respondents using oral products, 77% recognized that pills should not be split or crushed, and 92% recognized that more medication should not be taken after a missed dose.
  - Among respondents using transdermal products, 73% knew to inform their healthcare provider of any fever, 82% knew not to use a hot tub or sauna while using ER/LA opioid analgesics and 82% knew that the patch should not be cut in half to use less medicine.

A negative control question concerning whether it is okay to drink caffeine while using ER/LA opioid analgesics was answered in the affirmative by 49% of respondents.

The mean KAS was comparable across ER/LA opioid analgesic types (non-methadone oral products: 85.4, SD 10.38 versus patch products: 85.5, SD 10.16 and methadone users: 86.9, SD 10.99). Scores were generally similar across each key risk message. A higher proportion of methadone users knew to seek emergency medical help for an overdose even if the respondent feels fine (96%) and not to store their medication with other medications in the household (82%). A lower proportion of oral product users correctly identified the need to talk to a healthcare provider prior to stopping ER/LA opioid analgesic use (78%).

Respondents stating that they did not understand the Medication Guide (n = 10) had a slightly lower overall KAS (mean 76.6, SD 9.26 versus mean 85.8, SD 10.30 among respondents who stated that they understood the Medication Guide). These respondents more often answered questions about safe storage and safe use incorrectly. Respondents who received the PCD or had a healthcare provider who referenced or understood the PCD had similar KAS values compared with those who did not (mean 86.3, SD 10.15 for those who received the PCD versus mean 85.0, SD 10.53 for those who did not). However, respondents whose providers did not give or reference the PCD less often understood benefits and risks, safe discontinuation, and what to do in the event of a missed dose based on their self reported comprehension. Respondents with only one ER/LA opioid analgesic dispensing had slightly lower KAS scores than those with multiple dispensings (mean 82.3, SD 12.03 versus mean 86.6, SD 9.59.

The 33 respondents with a low KAS showed knowledge deficits in most of the key risk message areas, but were aware that they should not share the drug with others with the same condition (94%). Only 18% of respondents with a low KAS were aware of the need to read the attached Medication Guide at each dispensing.

Risk Factors for KAS <70%

In the univariate analyses, respondents most likely to have a KAS <70% were single/never married, male, and had not been prescribed ER/LA opioid analgesics by a pain specialist. A longer interval since the last prescription fill or healthcare provider visit was also associated with a low KAS. Respondents diagnosed with neuropathic pain were less likely to have a low KAS. Education was not a strong predictor of KAS <70%; college graduates had a small numerically

elevated OR compared to non-college graduates (odds ratio (OR) 1.39, 95% confidence interval (CI) 0.68 - 2.85). An adjusted model identified a stronger risk for lower KAS for individuals that were not married or living with a partner (OR 1.90, 95% CI 0.90 - 3.99), did not have neuropathic pain (OR 3.40, 95% CI 1.00 - 11.52), did not have their medication prescribed by a pain specialist (OR 2.70, 95% CI 1.13 - 6.44), or were of male gender (OR 1.99, 95% CI 0.96 - 4.14).

Provider Screening and Counseling

Over 90% of respondents reported that their healthcare providers discussed medical history and how much medication to use when their ER/LA opioid analgesic was first prescribed; however only 53% reported discussion of proper disposal of extra medication. In the 12 months prior to the survey, 48% of respondents reported that they were instructed on the proper disposal of unused medication, and 56% on safe discontinuation. Discussions to keep ER/LA opioid analgesics safe and away from children was reported by 61%, not sharing medication by 64%, risks of overdose by 69%, and common side effects by 73% of respondents regarding healthcare provider activities. Only 40% of the prescribing healthcare providers always, regularly, or sometimes used a PCD when discussing ER/LA opioid analgesics.

Safe discontinuation was more often discussed with respondents using methadone (64%). Respondents who received the Medication Guide more often reported that their healthcare providers had discussed these key points except for discontinuation, and a higher proportion of respondents who had read, had a provider that referenced, and/or reported that they understood the PCD stated that their providers had addressed each of the key points. A lower proportion of patients receiving only one dispensing, of ER/LA opioid analgesics and of individuals with a KAS <70% reported that their healthcare provider had discussed these key points.

6.1.5. Conclusion

In a sample of commercially-insured ER/LA opioid analgesic users, we assessed patient knowledge of the safe use of these products. A large majority of respondents reported that they received, read, and understood the Medication Guide. A smaller majority reported that they received, had a healthcare provider who referenced, and understood the PCD. Knowledge of safe use measured through the KAS was high; only 8% of respondents had a KAS below 70%. The only general knowledge questions that less than 80% of respondents answered correctly concerned storing ER/LA opioid analgesics away from other household medications, the need to read the Medication Guide at each pharmacy dispensing, never splitting or crushing pills (oral product users only), and informing a healthcare provider of fever (patch product users only).

To understand those core messages of the FDA Blueprint that can be evaluated through the patient perspective, we also identified patient recall of prescriber behaviors, including appropriate screening and counseling. Approximately half of respondents reported that their healthcare providers used the PCD for discussion or discussed safe discontinuation and disposal. However, the majority of respondents correctly answered KAS questions related to these and other key risk messages.

This study utilized an administrative claims database to identify patients eligible to complete the survey and is subject to the limitations inherent in the use of such data. The HIRD is representative of the commercially-insured population in the US; however, it may not be representative of individuals without medical insurance or those with government-sponsored insurance such as Medicaid or Medicare.

Because the study population was limited to adults with commercial insurance, representation of patients 65 years of age and older is limited to those patients who receive medical and pharmacy benefits through continued coverage by an employer (or a spouse's employer).

Despite these limitations, this patient survey provides key insights concerning the knowledge and experience of ER/LA opioid analgesic users following implementation of the REMS. Within this sample of commercially-insured patients, key messages from the Medication Guide and PCD were well-recognized. Improvements can be made by promoting and counseling, especially pertaining to safe discontinuation and disposal.

7. ASSESSMENT ELEMENT 5 – SURVEILLANCE MONITORING

A number of sources were used to collect surveillance data regarding misuse, abuse, overdose, addiction, and death for this Twenty-Four Month FDA Assessment Report. These sources include:

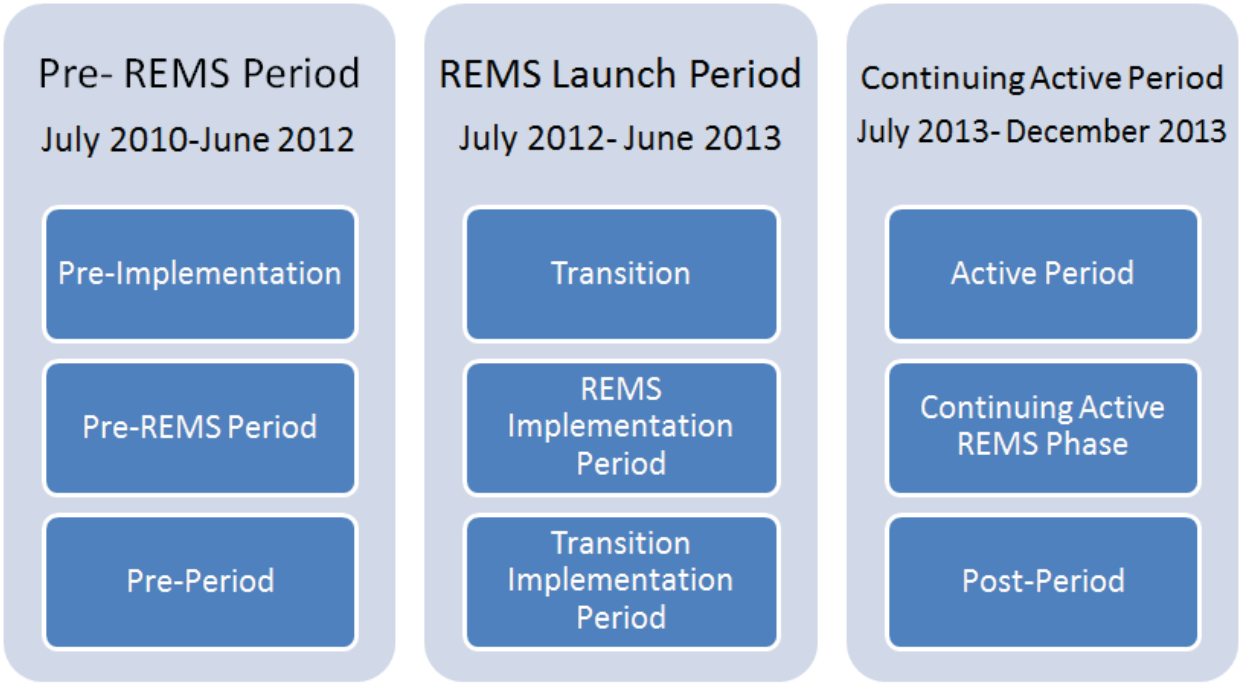
- Intentional exposures among adolescents and adults, including severity and deaths, using nationally-based poison control surveillance data
- Unintentional exposures among infants and children, including severity and deaths, using nationally-based poison control surveillance data
- Rates of individuals in substance abuse treatment programs abusing ER/LA opioid analgesics, as well as source of acquiring the ER/LA opioid analgesics, as compared to comparator immediate-release (IR) opioids and benzodiazepines using the national surveillance systems among substance abuse treatment seekers
- Surveys of abuse in adolescents and adults to assess trends in reported abuse of opioids, not specifically ER/LA opioid analgesics, using the NSDUH and MTF publically-accessible annual reports

There are two additional Assessment Element 5 components included in the REMS Supporting Document. A status update on these two components is included within this Twenty-Four Month FDA Assessment Report. Data for these items is planned to be included within the Thirty-Six Month FDA Assessment Report.

- Emergency department (ED) visits for opioid overdose and poisoning events using either a national representative database of ED visits, subject to availability, or an analysis of public and/or private insurance claims databases (a commercial insurance plan claims database plus a Medicaid claims database linked to a mortality database).
    - The first phase of this assessment was to validate the code of opioid overdose for use in measuring ED visits, and the second phase is to use the code for opioid overdose emergency department visits to measure the effect of the REMS on this outcome. Data on the first phase are in included in this Twenty-Four Month FDA Assessment Report the data for the second are planned for inclusion in the Thirty-Six Month FDA Assessment Report.
- Mortality rates resulting from drug poisoning associated with active pharmaceutical ingredients included in the ER/LA Opioid Analgesic REMS, but not specifically those formulations covered by the class REMS using state medical examiner databases from multiple states, including but not limited to Florida and Washington states.

Three time periods were taken into consideration for Assessment Element 5, 6, and 7 so that the effectiveness of the REMS may be measured over time. Since multiple vendors/data sources are used to achieve the requirements of Assessment Element 5, 6, and 7, terminology used within each report (and associated tables/figures) may vary. While terminology may differ, data periods described are maintained across all data sources. The table below describes the relationships between the terminologies used by each data source. When possible, text within this report has been standardized to follow the below referenced time period terminology.

Figure 6: Surveillance Monitoring Time Periods



7.1. Emergency Department Visits for Opioid Overdose and Poisoning Events

7.1.1. Assessment of the Positive Predictive Value of ICD-9 Codes for Opioid Poisoning/Overdose in Electronic Health Records for Use in Measuring the Effect of the REMS on Emergency Department Visits for Opioid Poisoning/Overdose

7.1.1.1. Purpose

The purpose of this study was to compare diagnoses of opioid overdose and poisoning (OOP) events identified by electronic medical record (EMR) diagnoses, particularly ICD-9 and ICD-10 codes, against diagnoses confirmed by medical chart review to be OOP events, and thereby to determine the positive predictive value of ICD-9 and ICD-10 codes in identifying OOP events. The study was conducted by investigators at the Center for Health Research, Kaiser Permanente Northwest (KPNW).

7.1.1.2. Methods

7.1.1.2.1. Sample of Events

The sample includes OOP events identified among KPNW and Kaiser Permanente Northern California (KPNC) members between August 2008 and October 2012. The former has a membership population of approximately 475,000 members and the latter approximately three million members. EMR chart audits were conducted between July 2008 and June 2012. Initially, ICD-9 codes for non-fatal events and ICD-10 codes for death records in Table 7 were searched for in the Kaiser Permanente Northwest and Northern California EMR databases, starting from August 2008. The potential OOP events identified from the ICD codes used in the table below were audited through medical chart reviews by trained chart auditors to determine if the potential OOP event identified by ICD code was a true OOP event. Chart reviews are divided into 5 categories based on whether the Kaiser Prescription Database identifies an opioid prescription for the potential OOP event. The 5 categories of OOP events, based on their prescription for an opioid, are the following a) prescriptions for OxyContin or generic ER oxycodone equivalents, b) prescriptions for immediate-release oxycodone, c) prescriptions for other extended-release or long-acting opioid (i.e., ER/LA opioid analgesic class REMS), d) prescriptions for other opioids (i.e., other immediate-release opioids or extended-release less potent opioids) and e) no prescription for an opioid within the prior 12 months of the event. All potential OOP events in category (a), and a random proportional sample of those in categories (b), (c), (d) and (e), were audited against chart review.

7.1.1.2.2. Selection of ICD-9 and ICD-10 Codes

Initial ICD-9 and ICD-10 codes were selected based on a previously published study that used ICD-9 and ICD-10 codes to identify OOP events and partially validated the ICD codes against medical chart review by skilled, impartial reviewers (Dunn et al.)[1]. The Dunn et al. study was conducted within the Group Health Cooperative membership and identified potential opioid-related overdoses from electronic medical records and conducted medical record reviews to classify and validate overdose events. Dunn et al. identified potential cases from the electronic medical records by using the following 2 case group definitions:

- Case 1: ICD code indicating opioid-related poisoning (Table 7), or
- Case 2: ICD code indicating an adverse opioid-related event plus a diagnosis code on the same date considered to identify an overdose

In addition, the Kaiser Permanente (KP) study expanded on the case definitions used in the Dunn et al. study to capture opioid poisoning by heroin and the Healthcare Common Procedure Coding System (HCPCS) code for injection for naloxone hydrochloride.

Table 7: INTERNATIONAL CLASSIFICATION OF DISEASES (ICD) CODES FOR IDENTIFYING POTENTIAL OPIOID-RELATED OVERDOSES, BY VERSION, USED IN PREVIOUSLY PUBLISHED STUDIES AND MODIFICATIONS MADE SPECIFIC TO THE KP STUDY.

Case 1 Definitions: Opioid-related poisoning codes	
ICD code	***Description***
ICD-9	
965.0*	Poisoning by opioids and related narcotics
E850.1	Accidental poisoning by methadone
E950.0	Suicide and self-inflicted poisoning by analgesics, antipyretics, and anti-rheumatics
E980.0	Undetermined poisoning by analgesics, antipyretics, and anti-rheumatics
ICD-10	
T40.0	Poisoning by opium
T40.1	Poisoning by heroin (not included in Dunn et al.)
T40.2	Poisoning by other opioids
T40.3	Poisoning by methadone
T40.4	Poisoning by other synthetic narcotics
X42	Accidental poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified
X62	Intentional self-poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified
Y12	Undetermined poisoning by and exposure to narcotics and psychodysleptics, not elsewhere classified
Case 2A definition: Opioid-specific adverse event (AE) codes†	
ICD-9	
E935.0	Adverse effects of heroin
E935.1	Adverse effects of methadone
E935.2	Adverse effects of other opioids and related narcotics
ICD-10	
Y45.0	Adverse effects of opioids and related analgesics
Case 2B definition: Overdose diagnostic codes †	
ICD-9	
276.4	Mixed acid–base balance disorder
292.1	Drug-induced psychotic disorders (including 292.11 and 292.12)
292.81	Drug-induced delirium
292.8*	Drug-induced mental disorder (excluding 292.81)
486	Pneumonia, organism unspecified
496	Chronic airway obstruction, not elsewhere classified
518.81	Acute respiratory failure
518.82	Other pulmonary insufficiency, not elsewhere classified
780.0*	Alteration of consciousness
780.97	Altered mental state
786.03	Apnea
786.05	Shortness of breath
786.09	Dyspnea and respiratory abnormalities — other
786.52	Painful respiration

Table 7: INTERNATIONAL CLASSIFICATION OF DISEASES (ICD) CODES FOR IDENTIFYING POTENTIAL OPIOID-RELATED OVERDOSES, BY VERSION, USED IN PREVIOUSLY PUBLISHED STUDIES AND MODIFICATIONS MADE SPECIFIC TO THE KP STUDY.

799.0*	Asphyxia and hypoxemia
E950–E959	Suicide and self-inflicted injury
HCPCS Code	
J2310	Injection, naloxone hydrochloride (not included in Dunn et al.)

* Includes all sub-codes beginning with this code.

† Case definition 2 is met when participants have a code for an opioid-specific AE code (Case 2A definition) plus Case 2B definition: Overdose diagnostic codes

7.1.1.2.3. Chart Audit, Training, and Adjudication Process

Events were identified by research analysts at both sites. Chart auditors were provided with health record numbers, event dates, and inclusion diagnoses. They scanned the EMR chart to locate the identified event for each person and printed all associated records for that event. Records used, if available, included History & Physical, Discharge Summary, Medication Activity Report, Telephone Encounter, and/or any other related documentation that might be present in the electronic chart for the specified event.

The training process began with a sample of events that were reviewed by all chart audit staff, adjudicators, and project investigators at each site to identify problems with the chart audit form, clarify questions, and ensure consistency in review. A weekly teleconference call with chart audit staff, investigators, expert adjudicators, and administrative staff was held to identify and resolve ongoing questions related to the events and the chart audit process. One hundred percent of the first sample of charts at each site (n = 200) were adjudicated. Once the chart review form and associated instructions were finalized, abstractors began working on individualized event lists.

Each audit file was reviewed for missing data prior to data entry; if forms were incomplete, the file was returned to the staff person who collected the data for completion. Then, 10% percent of charts were reviewed by two reviewers to assess and maintain high inter-rater reliability (>95%). All identified errors were discussed and corrected and if patterns exist in the errors found, all charts were re-reviewed to ensure abstraction was correct. Once abstraction files were complete, data was entered into an electronic database using double entry verification until adequate accuracy was obtained (e.g., less than 1 error/100 entries). Once this level was achieved, 10% of data were double-entered as a continuous check. Following entry, data files were merged from both sites for analysis.

7.1.1.2.4. Analysis of Chart Audit Data

Analyses compared concordance, including the specificity of the individual ICD codes, of the EMR-identified OOP events to results of the chart audit summary stratified by several covariates. These covariates included ICD code, case definition diagnosis, category of opioids prescribed, and length of opioid prescriptions used.

7.1.1.3. Results

(b) (4)

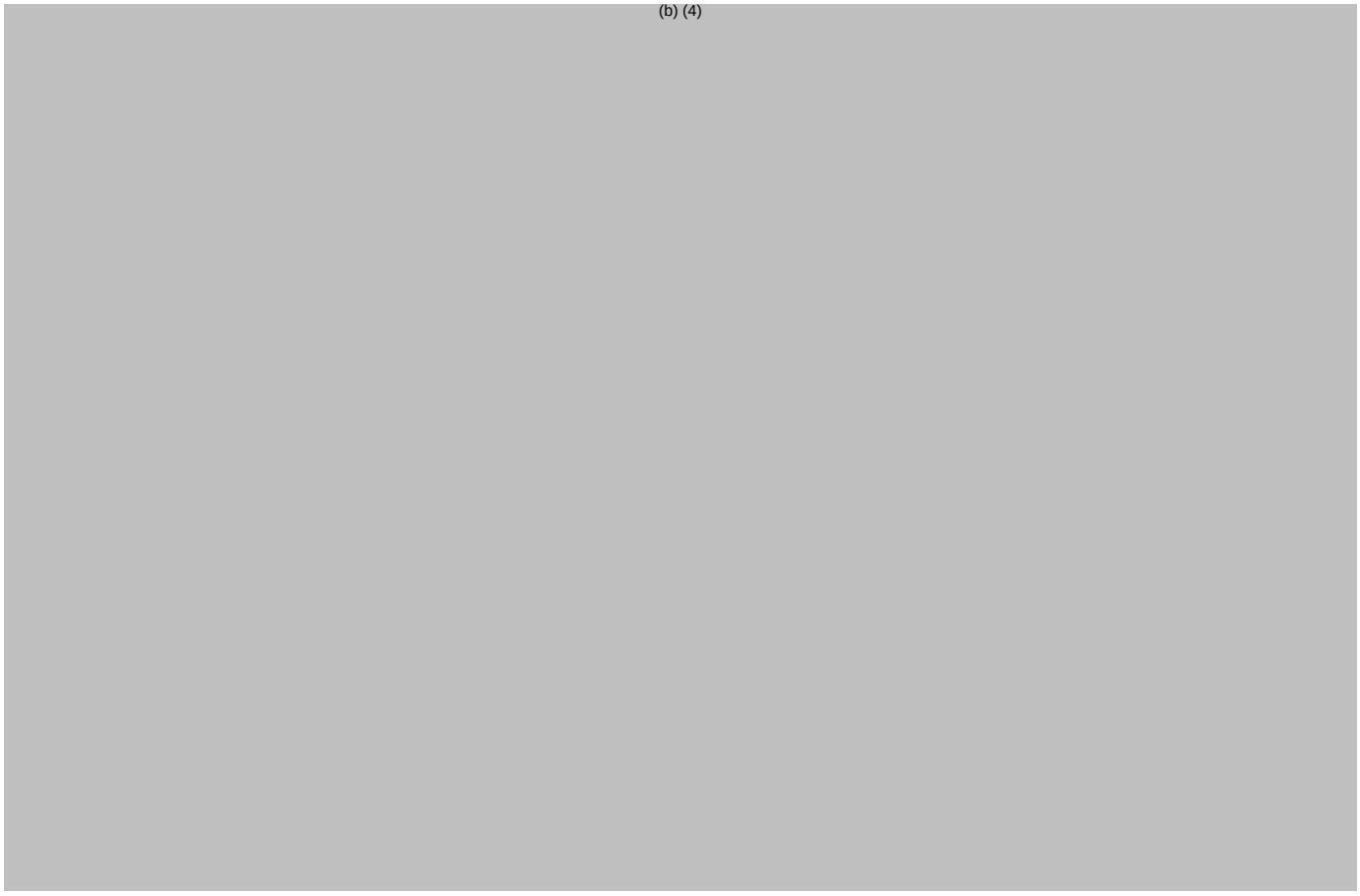
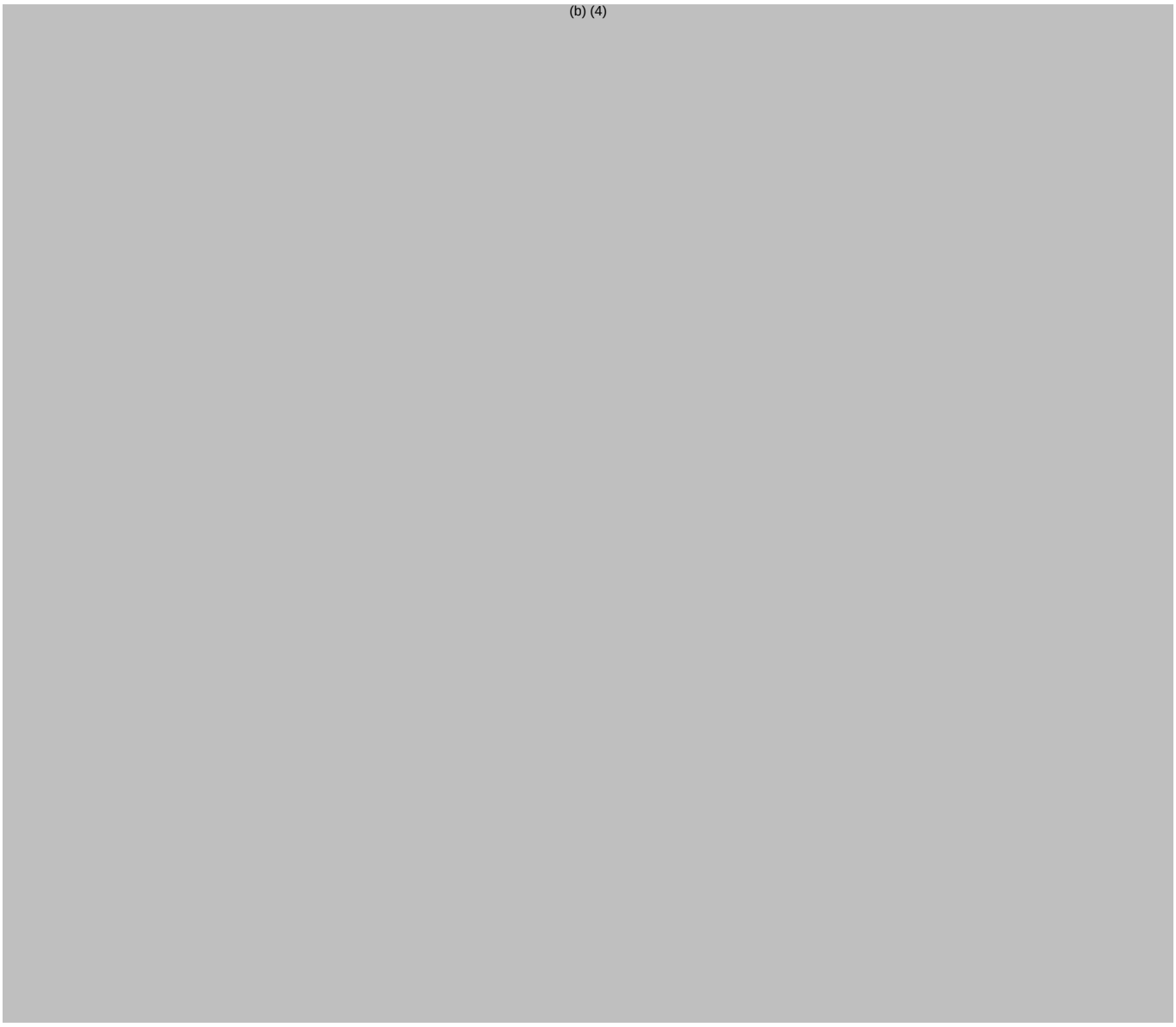


Figure 7: Figure Evaluation of ICD-9 Codes for Opioid Poisoning Relative to Medical Chart Review for Opioid Overdose or Poisoning

(b) (4)

[1]Miscode: event documentation does not match with EMR codes used to identify event, meaning that the code does not match what happened at the time of the event

[2]Unintentional events include both medical errors and misuse/abuse events



7.1.1.4. Conclusion

The ICD-9 codes for opioid-related poisoning had a positive predictive value of (b) (4) % to detect opioid overdose/poisoning events.

The positive predictive value could be increased to (b) (4) if analgesic-related overdose/poisonings could be excluded by a diagnostic algorithm that excluded cases that had a surgery code or anesthetic procedure code on the day of or within 2 days preceding the overdose event. The positive predictive value could be further increased to (b) (4) if a diagnostic algorithm using coded medical terminologies can be developed to differentiate between opioid overdose and poisoning events versus opioid AEs that are not overdoses.

PMR study 2065-3 for ER/LA opioid analgesics will evaluate the feasibility of developing diagnostic algorithms to exclude analgesic-related overdose/poisonings and opioid AEs that are not overdoses, as well as to differentiate between unintentional and suicide overdoses. In

addition, PMR 2065-3 will evaluate the feasibility of using medical record text search, natural language processing, and/or machine learning to search for opioid overdose codes not identified by ICD codes, thereby improving the sensitivity of detecting opioid overdoses.

7.1.1.5. Request for Proposal Process

Information and data obtained through the study to assess the positive predictive value of ICD-9 codes for opioid poisoning/overdose in electronic health records and PMR 2065-3 (both described above) will be applied as appropriate to meet the requirements of this Assessment 5 component. The RPC's Metrics Sub-team has developed a RFP to solicit proposals concerning surveillance monitoring studies of ED visits for opioid overdose and poisoning events. The RFP has been issued to organizations that have capabilities relevant to this component of Assessment 5. The RPC will evaluate proposals and plans to select an organization to conduct the ED surveillance monitoring study for inclusion in the Thirty-Six Month FDA Assessment Report.

7.2. Poison Center Programs

The following two components of Assessment Element 5 examine exposures through a Poison Center Program:

- Intentional exposures among adolescents and adults, including severity and deaths
- Unintentional exposures among infants and children, including severity and deaths

Both of these components utilize RADARS System data. The RADARS System Poison Center Program obtains data from individuals within the general population and from healthcare providers who are seeking advice regarding potential toxic exposures, including prescription opioids and prescription stimulants. The objectives of the Poison Center Program are to detect product-specific prescription drug abuse and misuse in near-real-time and to identify geographic sites with disproportionately high rates of abuse and misuse. Poison center data collected through the RADARS System provide an estimate of change in intentional abuse, misuse, and deaths associated with these drugs. The Poison Center Program gathers data from 49 regional US Poison Centers in 46 states, including urban, suburban, and rural regions (covering over 90% of the US population). Investigators at each participating poison center collect data using a nationally standardized electronic health record. In addition to obtaining exposure and substance data, the Poison Center Program collects demographic, clinical effects, treatment, and medical outcomes information. The Poison Center Program was initiated in 2002.

7.2.1. Intentional Exposures among Adolescents and Adults

The primary objective of this Assessment Element component is to explore intentional exposures among adolescents and adults, including severity and deaths, using a Poison Center Program. Measures were evaluated in reference to rates per 100,000 population, rates per 1,000 prescriptions, and rates per 100,000 dosing units. Rates are presented for ER/LA opioid analgesics, as well as IR prescription opioids and prescription stimulants which are used as comparators. The solid grey lines presented in each figure represent the 95% CI. The average is depicted by the dotted lines.

7.2.1.1. Intentional Abuse Exposures

Figure 9 through Figure 11 show the observed and predicted rates of abuse exposure for 3 denominators (population, prescription dispensed, and dosing unit dispensed) and 95% confidence intervals for ER/LA opioid analgesics and comparator drugs during Pre-Implementation, Transition, and Active Period time periods.

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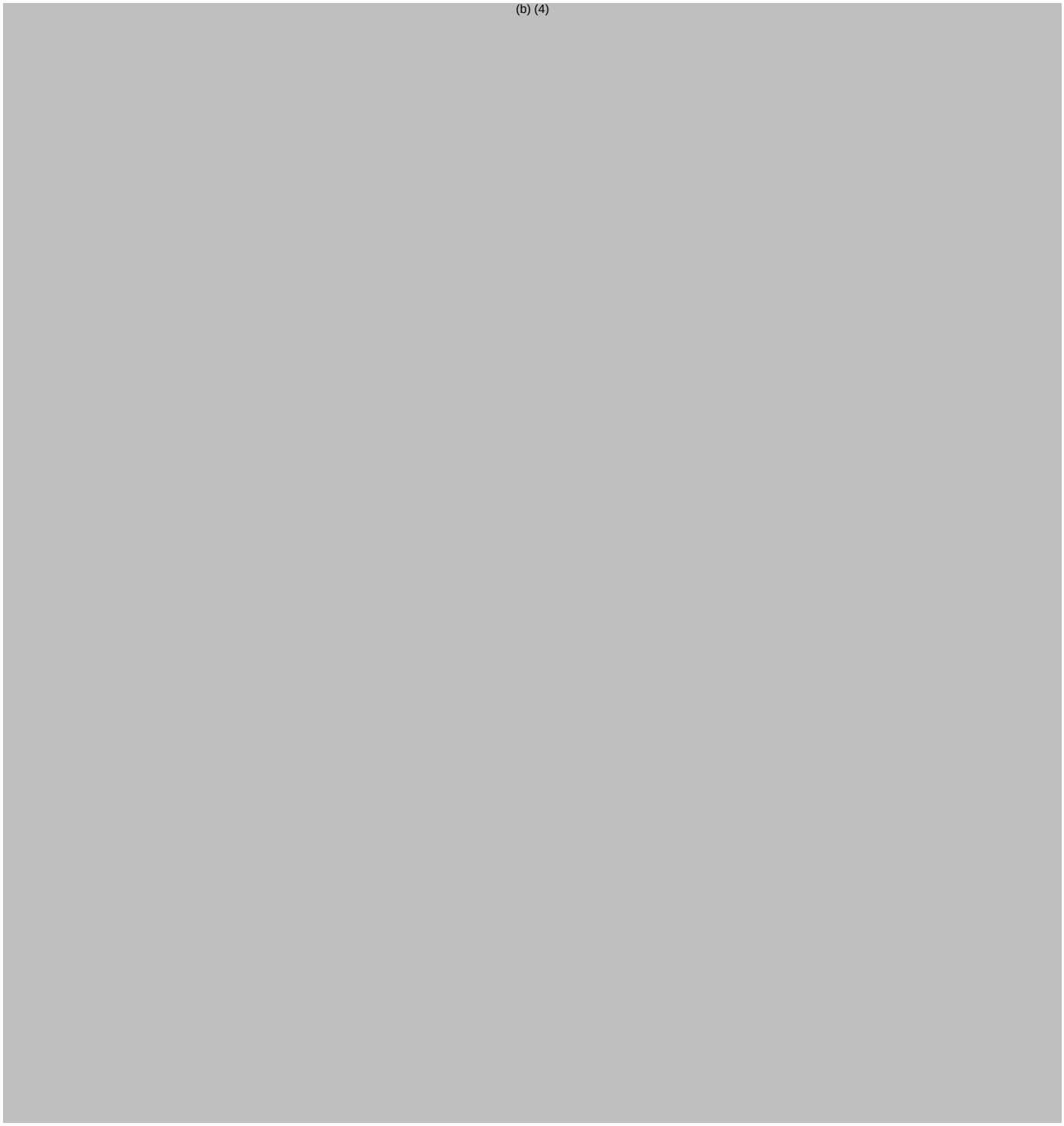

7.2.3. Poison Center Program Conclusion

Mean decreases for the ER/LA opioid analgesics from the Pre-Implementation to Active Period were significant for Poison Center population rates of abuse; misuse; major medical outcome, hospitalization or death; and adolescent abuse. Furthermore, the decrease in the ER/LA Opioid Analgesic REMS group population rate was significantly different than decreases seen for IR

prescription opioids for adolescent abuse. The population rate decrease was significantly different from prescription stimulants for abuse; misuse; major medical outcomes, hospitalization, or death; and adolescent abuse. Mean decreases for the ER/LA opioid analgesics REMS from the Pre-Implementation to Active Period were significant for Poison Center prescription rates of abuse; misuse; and major medical outcome, hospitalization or death. The decrease in the ER/LA Opioid Analgesic REMS prescription rate was significantly different than the decreases seen for IR prescription opioids for abuse, and misuse. The prescription rate decrease was significantly different from prescription stimulants for Poison Center abuse.

7.2.4. Rates of People in Substance Abuse Treatment Programs Abusing ER/LA Opioid Analgesics

Two vendors chosen by the RPC examined rates of substance abuse among individuals in substance abuse treatment abuse treatment programs abusing ER/LA opioid analgesics. One vendor compared ER/LA opioid analgesic abuse with IR opioids and benzodiazepines, and includes examination of the source of the ER/LA opioid analgesics. This analysis relied on two proprietary data streams within the NAVIPPRO, the ASI-MV for adults and CHAT for adolescents. The second vendor provided an additional comparison of ER/LA opioid analgesic abuse with IR opioids as a comparator using data from RADARS System Treatment Center Programs.

7.3. NAVIPPRO ASI-MV,® and CHAT Analyses

The objective for this analysis was to evaluate trends in abuse and source of ER/LA opioid analgesics before and after the shared REMS intervention was implemented in order to assess for changes in past 30-day abuse (in relation to the point in time each individual completed the assessment) within the ASI-MV and CHAT samples across three time periods (pre-REMS period, REMS implementation period, continuing active REMS phase).

Analyses were conducted for all ER/LA opioid analgesics included in the class-wide REMS and, at the compound or sub-group level for morphine ER, oxymorphone ER, methadone, a group of transdermal fentanyl and buprenorphine, and an “other” ER opioid group. The “other” ER opioid group was a combination of oxycodone ER, hydromorphone ER, and tapentadol ER. Sources of procurement included: one’s own prescription, one’s own prescription from several doctors, family member or friend and “illicit” (i.e., bought it online without a doctor’s visit, bought it from a dealer [a known seller], wrote or bought a fake prescription, stole them, traded for it, and “other”).

7.4. Summary of findings from ASI-MV analyses

(b) (4)

7.5. Summary of key findings from CHAT analyses

(b) (4)

7.5.1. RADARS System Analyses

The objective for this analysis was similar to that of the NAVIPPRO ASI-MV, and CHAT Analysis. The RADARS System Treatment Center program data was used to evaluate trends in abuse of ER/LA opioid analgesics before and after the shared REMS intervention was implemented.

Figure 23 through Figure 24 show the past 30-day mention observed and predicted population, prescriptions dispensed, and dosing unit rates and 95% confidence intervals for ER/LA opioid analgesics and comparator drugs during Pre-Implementation, Transition, and Active Period time periods. Additional details can be found in Appendix F.

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The mean ER/LA opioid analgesics past 30-day mention population rate decreased significantly between the Pre-Implementation and Active Period time periods. This decrease was not significantly different than the decrease in mean past 30-day mention population rate for IR prescription opioids. Results are similar for prescription rates but the difference in decreases achieves significance compared to IR prescription opioids.

7.5.2. Conclusion

Within the ASI-MV network of substance abuse treatment centers, between July 2010 and December 2013, the prevalence of opioid abuse, including abuse of ER/LA opioid analgesics, increased by about 2 cases per 100 ASI-MV assessments. There was evidence of reduction in ER/LA opioid analgesics being obtained from the abusers' own prescriptions. This is contradictory to the significant mean decrease for the ER/LA opioid analgesics REMS Analgesics from the Pre-Implementation to the Active Period found in the RADARS System analysis. These discrepancies may in fact be a result of the different data sources and the means in which data are obtained. For example, the RADARS System data are restricted to individuals who are seeking treatment for opioid abuse while NAVIPPRO collects data from individuals seeking treatment for any substance abuse. For reasons such as these further monitoring and exploration of substance abuse among individuals in substance abuse treatment abuse treatment programs abusing ER/LA opioid analgesics is warranted and ongoing.

As the REMS mitigation programs continue in the coming years, it will continue to be important to examine the potential role played by the substance abuse treatment data, such as those reflected in the ASI-MV and CHAT data streams. The ASI-MV data stream does have has well-documented limitations. However, the network of high-risk sentinel treatment sites, does offer many strengths, including: (1) near real-time data, (2) product specificity, (3) a relatively large volume of data that can capture abuse of specific products, and (4) an assessment methodology that collects patient data in a way that is systematic and consistent over time and geography. Furthermore, as the active period of the REMS intervention increases beyond December 2013, the level of exposure for the REMS intervention will increase, presumably increasing the potential national impact. Such an impact may be observed in a concordant reduction in ER/LA opioid analgesic abuse among adults assessed for substance abuse treatment via the ASI-MV, as well as possible shifts in reported source of procurement among those who continue to obtain and abuse ER/LA opioid analgesics.

Finally, as with any uncontrolled observational study, causality cannot be determined with any confidence. There are, however, some factors that could be considered when evaluating the findings presented here as well as expectations for future analyses. These include:

- If a result of the REMS program is a reduction in the number of ER/LA opioid analgesic prescriptions, it is possible that abusers could respond to this decrease in availability by seeking treatment.
- An additional possible outcome is that changes in prescribing patterns might result in a leveling off of the upward trend in ER/LA opioid analgesic abuse prior to the REMS implementation.
- The observed increase in ER/LA opioid analgesic abuse in the NAVIPPRO system across the study time period should be viewed in the context of the ASI-MV limitations. The

estimates are not intended to be generalized to all individuals in substance abuse treatment. The contribution from geographic regions within the US varies within the ASI-MV network, and findings from different geographic areas may likewise vary. The ASI-MV network is also heterogeneous with respect to types of treatment facilities and modalities of treatment offered (e.g., inpatient/residential, outpatient, detox, methadone maintenance, criminal justice evaluations, and so forth). Future exploration on the impact of geographic region, treatment modalities/settings, and other possible subgroups on findings may be enlightening with respect to understanding the impact of the REMS program.

- The extent to which the number of ER/LA opioid analgesic prescriptions dispensed during the study time period increased in those states from which the ASI-MV population is drawn, may have contributed to the increase in ER/LA opioid analgesic abuse observed within the ASI-MV system for this report.

Finally, the observed decrease in medical providers as a reported source (i.e., own prescription from one doctor and own prescription from several doctors) could be an early indicator of greater medical awareness on the part of practitioners as a result of various efforts (the REMS program, general level of awareness of a prescription opioid problem, prescription monitoring programs, and so forth). Individuals who continue to abuse these medications may increasingly turn to illicit sources.

7.6. Mortality Rates Resulting From Drug Poisoning

An RFP has been developed and will be issued to potential vendors that can assist in identifying mortality rates resulting from drug poisoning associated with active pharmaceutical ingredients included in the ER/LA Opioid Analgesic REMS. The RFP will be issued, a vendor will be selected and additional details will be included in the Thirty-Six Month FDA Assessment Report.

7.7. Surveys of Abuse in Adolescents and Adults to Assess Trends in Reported Abuse of Opioids

Two sources are used to assess trends in adolescents and adults in reported abuse of opioids. One of the sources used is the NSDUH[2]. The NSDUH is an annual survey sponsored by the Substance Abuse and Mental Health Services Administration (SAMHSA), US Department of Health and Human Services. The most recent publically available NSDUH was released in September 2013, and includes data from 2012. The report also describes trend data from 2002 through 2012 for some exposures.

The NSDUH describes use of illicit drugs, and is a source of information on non-medical use of prescription drugs including pain relievers. It cannot, however, be used to specifically identify exposures to ER/LA opioid analgesics.

Another data source utilized for this assessment is MTF. MTF studies are conducted annually by the University of Michigan's Institute for Social Research. MTF provides data on the substance use of American adolescents, college students, and adults through age 55. Since data from high school students are released separately from college students and adults, the data available for this Twenty-Four Month FDA Assessment Report includes a high-level analysis of 2013 data for

8th, 10th, and 12th grade students[3] and an in-depth analysis of 2012 data for 8th, 10th, and 12th grade students[4,5], college students, and adults through the age of 55[6]. The MTF studies collect data on use of opioids without a prescription and specifically include questions about use of OxyContin and Vicodin.

Both the NSDUH and MTF include national samples and have shown similar long-term trends in prevalence of non-medical use of prescription drugs. There are some differences, however, between the data provided by the NSDUH survey and the MTF studies. First, the NSDUH only includes cross-sectional surveys, while the MTF includes longitudinal follow-up of age cohorts in addition to cross-sectional surveys. Second, the NSDUH survey sampling includes school dropouts; MTF by design excludes dropouts and adolescents absent from school on the day of the survey. These groups are known to have higher rates of illicit drug use (CBHSQ, 2012a[7]; Gfroerer et al., 1997b[8]). Lastly, the NSDUH has traditionally shown lower rate of youth substance use than the MTF.

Since the ER/LA Opioid Analgesics REMS was approved on July 9, 2012, the NSDUH and MTF data in this analysis will serve as a foundation for future surveillance monitoring which will evaluate trends in non-medical use and abuse of opioids throughout the course of the REMS implementation. There are some measures that extended to 2013 and these measures are consistent with declining rates of abuse occurring concurrently with the introduction of the REMS. These measures and additional discussion on the limitations of data from these sources are included within the conclusion of this section.

7.7.1. Report Highlights

7.7.1.1. NSDUH 2012

- An estimated 23.9 million Americans aged 12 or older (9.2% of the US population age 12 and above) had used an illicit drug (marijuana/hashish, cocaine [including crack], heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics such as pain relievers, tranquilizers, stimulants and sedatives) during the month prior to the survey interview.
- Approximately 2.4 million persons are estimated to have used psychotherapeutics non-medically for the first time within the past year, which is an average of approximately 6,700 initiates per day.
- Rates of use of psychotherapeutic drugs was highest in the age group 18 – 25 (5.3%) and lowest in adults aged 26 and older (2.1%).
- The number and percentage of persons aged 12 or older estimated to be current non-medical users of pain relievers in 2012 (4.9 million or 1.9 %) were similar to those in 2011 (4.5 million or 1.7 %) and in 2007 to 2010 (ranging from 4.7 million to 5.3 million and from 1.9% to 2.1 %). Among youth aged 12 – 17, non-medical users of pain relievers was highest among 16 and 17 year olds (3.1%). Overall among youth aged 12 - 17, current non-medical use of pain relievers decreased between 2002 (3.2%) and 2012 (2.2%).
- The rate of current non-medical use of pain relievers among young adults aged 18-25 in 2012 (3.8 %) was similar to the 2011 rate (3.6 %), but it was lower than the rates between 2003 (4.7 %) and 2010 (4.4 %).
- Of those persons aged 12 or older in 2011-2012 who used pain relievers non-medically in the past year, 54.0% reported obtaining their most recently used drug from a friend or

relative for free; 19.7% reported receiving them through a prescription from one doctor and 10.9% purchased them from a friend or relative.

- In 2012, an estimated 7.3 million persons age 12 and over had illicit drug dependence or abuse, and 2.1 million of these had pain reliever dependence or abuse. This number was similar to the number in each year from 2007 through 2011 and was higher than the number in each year from 2002 through 2006.

7.7.1.2. MTF 2013

- Percentages of 12th graders who reported trying a narcotic drug other than heroin in their lifetime, in the last year and in the last 30 days were 11.1%, 7% and 2.8%, respectively.
- There was a decrease of 1.1% from 2012 and 1.9% from 2010 in 12th graders who reported that they had tried a narcotic drug other than heroin at some point in their life.
- Approximately 7.1% of 12th graders reported that they had used a narcotic drug other than heroin in the last year.
- Since 2010 there has been a decrease of 1.6% in the annual prevalence of narcotics other than heroin in 12th graders.
- Since 2010 there has been a gradual decline in the reported use of narcotics other than heroin within the past 30 days (3.6% in 2010 to 2.8% in 2013).
- OxyContin and Vicodin® use:
    - Use of OxyContin within the past year was reported by 2.0%, 3.4%, and 3.6% of 8th, 10th, and 12th graders respectively. Compared to 2012, these figures represent an increase of 0.4% in both 8th and 10th graders, but a decline of 0.7% in 12th graders.
    - Use of Vicodin was reported by 1.4%, 4.6% and 5.3% of 8th, 10th and 12th graders, respectively. Compared to 2012, these figures represent a stable rate for 8th graders, an increase of 0.2% for 10th graders and a decline of 2.2% for 12th graders.
- When asked how difficult they thought it would be to get narcotic drugs other than heroin, 9.7%, 22.5%, 46.5% of 8th, 10th, and 12th graders said they would be fairly easy or very easy to get.
- A total of 18.5% of those aged 19-30 surveyed had used a narcotic other than heroin in their lifetime, and approximately 7% reported use within the last year.
- While about 33%, 31%, 25%, and 27% of 35, 40, 45, and 50 year olds reported trying a narcotic other than heroin in their lifetime, only approximately 2% of each of these age groups reporting using a narcotic other than heroin within the past 30 days.

Further details on the NSDUH and the MTF are described below.

7.7.2. National Survey on Drug Use and Health (NSDUH)

The NSDUH is planned and managed by SAMHSA's Center for Behavioral Health Statistics and Quality (CBHSQ). Approximately 67,500 persons 12 years old or older are interviewed in NSDUH each year, providing information on the use of illicit drugs, alcohol, and tobacco in the civilian, non-institutionalized population of the US. A scientific random sample of households is selected across the US. Since the survey is based on a random sample, each selected person represents more than 4,500 US residents.

7.7.2.1. Design & Methods

The sample design for the 2012 NSDUH was an extension of a coordinated five-year survey design which provided estimates for all 50 States plus the District of Columbia from 2005 through 2009, then through 2012. The NSDUH survey covers residents of households (e.g., persons living in houses/townhouses, apartments, condominiums; civilians living in houses on military bases) and persons in non-institutional group quarters (e.g., shelters, rooming/boarding houses, college dormitories, migratory workers' camps, halfway houses). The survey excludes persons with no fixed household address such as homeless persons who do not use shelters, military personnel on active duty, and residents of institutional group quarters (e.g., jails and hospitals). The survey sampling frame is designed to ensure that there was a sufficient sample in every State to support State estimation.

The NSDUH collects information on nine categories of illicit drug use: use of marijuana, cocaine, heroin, hallucinogens, and inhalants, as well as the non-medical use of four prescription-type drug groups: pain relievers, tranquilizers, stimulants, and sedatives. Prescription-type drugs include numerous medications that currently are or have been available by prescription. Respondents are asked to report only "non-medical" use of these drugs. Non-medical use is defined as use without a prescription of the individual's own or simply for the experience or feeling the drug causes. The four prescription-type drug groups are combined and reported under the category of "psychotherapeutics".

7.7.2.2. Data Collection

The NSDUH collects data through in-person interviews with sample persons. The interview can be completed in English or Spanish. To increase cooperation and willingness to report honestly, confidentially is stressed in all written and oral communication and computer-assisted interviewing (CAI) methods are used. The CAI records of collected data do not include any personal identifying information about the respondent.

The interview utilizes a combination of CAPI (computer-assisted personal interviewing, in which the interviewer reads the questions) and ACASI (audio computer-assisted self-interviewing) and is conducted away from other household members in a private area of the household identified by the respondent. The average interview time is approximately one hour.

The NSDUH interview consist of core and non-core (i.e., supplemental) sections. Core questions, which are covered in the first part of the interview, are used for basic trend measurement of prevalence estimates. These questions remain in the survey every year and include initial demographic information and questions pertaining to the use of tobacco, alcohol, marijuana, cocaine, crack cocaine, heroin, hallucinogens, inhalants, pain relievers, tranquilizers, stimulants, and sedatives. After the demographic information is complete, the respondent can read the questions silently on the computer screen and/or listen to the questions read through headphones and enter his or her responses directly into the computer.

The remainder of the interview includes non-core questions which are questions that may be revised, dropped, or added from year to year. Non-core questions include both questions that are self-administered and interviewer administered. Non-core questions that are self-administered include topics of injection drug use, perceived risks of substance use, substance dependence or abuse, arrests, treatment for substance use problems, pregnancy, health care issues, and mental health issues. Interviewer administered questions may address demographic topics such as

immigration, current school enrollment, employment and workplace issues, health insurance coverage, and income. After completion of the full interview the respondent is given a $30 cash payment as a token of appreciation for his or her time.

7.7.2.3. Trend Analysis

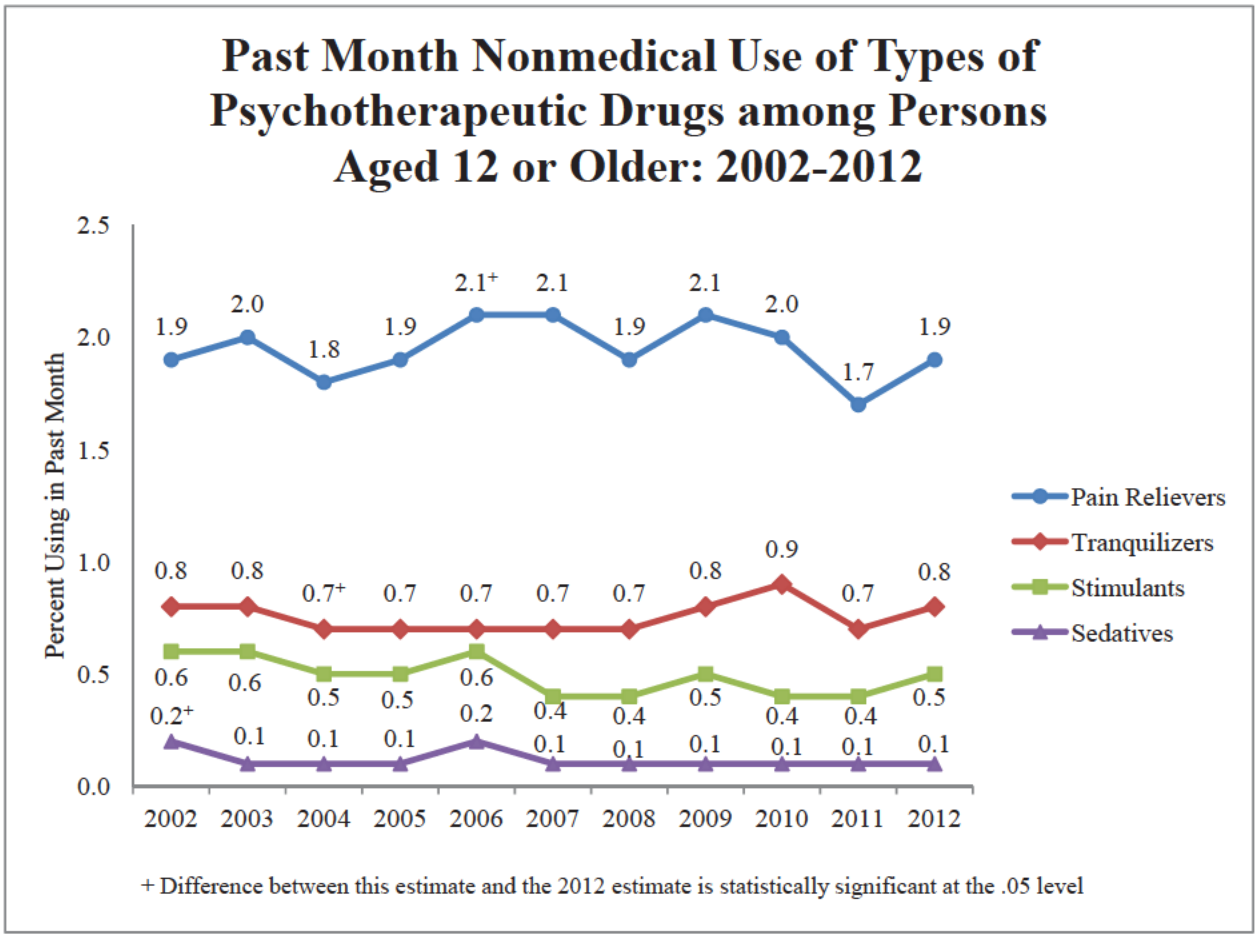
While the NSDUH has been conducted since 1971, trend analysis is limited to 2002 to 2012 due to methodology changes in 1999 and 2002, making results prior to 2002 not comparable to surveys conducted in 2002 through 2012. Additionally, due to changes in the questionnaire, estimates for methamphetamine, stimulants, and psychotherapeutics should not be compared with corresponding estimates presented in previous reports for data years prior to 2007. Estimates for 2002 to 2006 for these drug categories in this report, as well as in the 2007 and 2008 reports, incorporate statistical adjustments that enable year-to-year comparisons to be made over the period from 2002 to 2012.

It is not possible to evaluate trends in non-medical use of the ER/LA opioid analgesics based on the NSDUH because all pain relievers are grouped together and reported under the general category of psychotherapeutics. However, where possible, rates of non-medical use of pain relievers will be discussed.

7.7.2.4. Results

The 2012 NSDUH survey was conducted from January through December 2012. Screening was completed at 153,873 addresses, and 68,309 completed interviews were obtained. The survey asks respondents to indicate their use of illicit drugs in the previous month. Results from the 2012 NSDUH showed that an estimated 23.9 million Americans aged 12 or older were current (past month) illicit drug users, meaning they had used an illicit drug during the month prior to the survey interview. This estimate represents 9.2% of the population aged 12 or older, which is similar to the rates reported from 2009 to 2011 (ranging from 8.7 to 8.9%), but it was higher than the rates in the years from 2002 to 2008. The highest rate of current illicit drug use was among 18 to 20 year olds (23.9%), with the next highest rate occurring among 21 to 25 year olds (19.7%). Overall, the rate of current use of illicit drugs among young adults aged 18 to 25 increased from 19.7% in 2008 to 21.3% in 2012. Thereafter, the rate of current drug use generally declined with age although not all declines between consecutive age groups were significant**.** An estimated 6.8 million persons aged 12 or older (2.6% of the population) used psychotherapeutic drugs (prescription-type pain relievers, tranquilizers, stimulants and sedatives) non-medically in 2012, which is comparable to 2011 estimates of 6.1 million or 2.4% of the population. In 2012, males were more likely than females to be current non-medical users of psychotherapeutic drugs (2.8% vs. 2.4%). The number and percentage of non-medical users of pain relievers (4.9 million or 1.9%) were similar to the estimates from 2011 (4.5 million, 1.7%) and from 2007 to 2010 (ranging from 4.7 million to 5.3 million and from 1.9 to 2.1%). The number of new non-medical users of pain relievers in 2012 (1.9 million) was similar to the estimates in 2007, 2010, and 2011, but was lower than the numbers in 2002 through 2006 and in 2008 and 2009 (ranging from 2.2 million to 2.5 million). The average age at first non-medical use of pain relievers was 22.3 years in 2012, similar to the corresponding estimate in 2011.

Figure 26: Past Month Non-medical Use of Types of Psychotherapeutic Drug among Persons Aged 12 or Older: 2002 – 2012



Source: National Survey on Drug Use and Health: Summary of National Findings 2012

7.7.2.5. Youths Aged 12-17

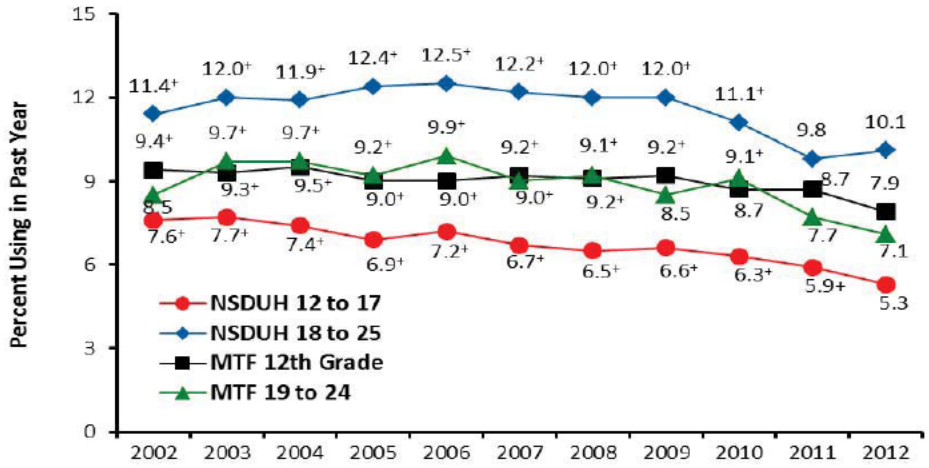
In 2012, non-medical use of psychotherapeutic drugs was reported in 2.8% of youths aged 12 to 17. Across all survey participants in this age range, current non-medical use of pain relievers was reported by 2.2%, a decrease from 3.2% in 2002 and 2003. However, the rates of non-medical use of pain relievers varied by age, being reported by 1.5% of 12 or 13 year olds, 2.2% of 14 or 15 year olds, and 3.1% of 16 or 17 year olds.

7.7.2.6. Young Adults Aged 18-25

Reported rates of current non-medical use of psychotherapeutic drugs among respondents aged 18 to 25 was similar to the rates in 2010 and 2011 (5.3%), but was lower than the rates reported in 2003 and 2007. Respondents aged 18 to 25 also reported the highest rate of use over the past month, past year and over a lifetime as compared to other age groups. The reported rate of current non-medical use of pain relievers was also similar to the 2011 rate at 3.8% and 3.6% respectively.

Similar to the MTF Survey, the NSDUH indicates a decline in past year and past month non-medical use of pain relievers among young adults between 2010 and 2012(Figure 27). However, the trends identified by the NSDUH were significant whereas the MTF declines did not reach the level of statistical significance.

Figure 27: Past Year Non-medical Pain Reliever Use among Youths and Young Adults in NSDUH and MTF: 2002-2012



MTF = Monitoring the Further: NSDUH = National Survey on Drug Use and Health.
* Difference between this estimate and the 2012 estimate is statistically significant at the .05 level.
Note: Data for MTF are for "narcotics other than heroin."

Source: National Survey on Drug Use and Health: Summary of National Findings 2012

7.7.2.7. Adults Aged 26-50

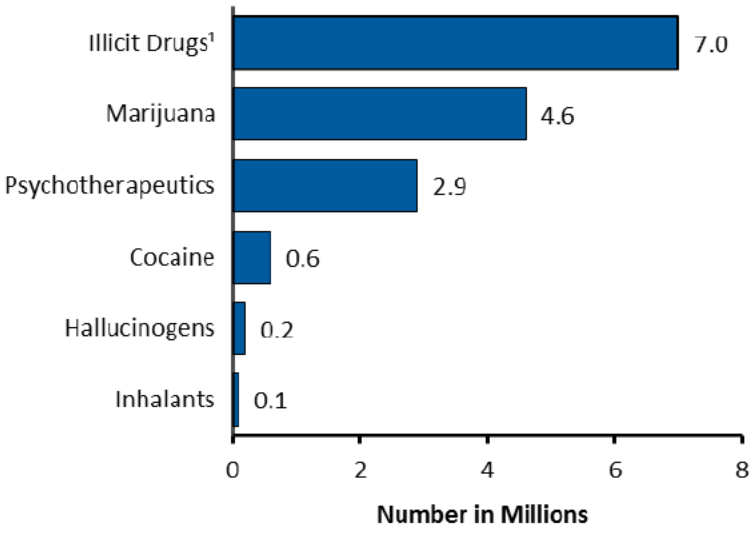
In 2012, the rate of current (past month) illicit drug use among adults aged 26 or older was 7.0%, which was higher than the rate in 2011 and in 2002 through 2009. The rate of current non-medical use of psychotherapeutics among adults aged 26 and older was 2.1% which was the lowest rate among all age groups. Further analysis regarding trends in non-medical use of psychotherapeutics or pain relievers in this age group was not included in the 2012 NSDUH report.

7.7.2.8. Adults Aged 50 or Older

NSDUH data indicate that the rates of current illicit drug use among persons aged 50 to 64 increased from 2002 to 2012, with marijuana and non-medical use of prescription psychotherapeutic drugs being the most commonly used substances in the past year (Figure 28). Much of this increase can be attributed to the aging of the baby boom cohort (born between 1946 and 1964) into the 50 or older age group. This cohort, particularly those born after 1950, had

much higher rates of illicit drug use as teenagers and young adults than older cohorts. This generational shift in drug use is still evident in the most recent data.

Figure 28: Past Year Illicit Drug Use among Persons Aged 50 or Older: 2012



[1]Illicit Drugs include marijuana/hashish, cocaine including crack), heroin, hallucinogens, inhalants, or prescription-type psychotherapeutics used non-medically.

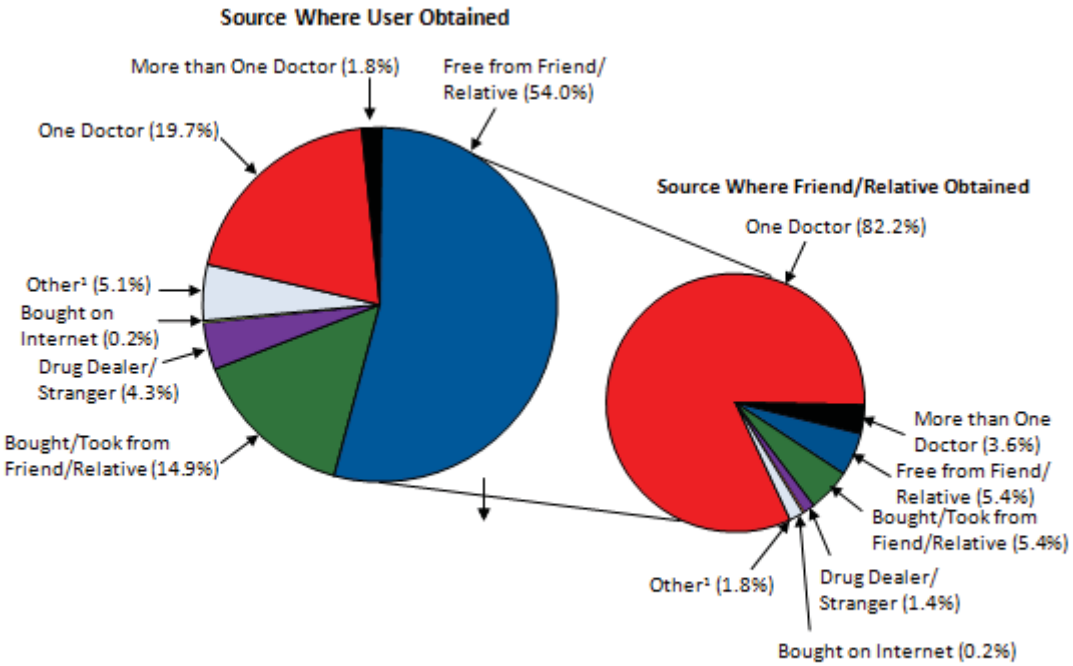
Note: The estimated number of past year heroin users aged 50 or older rounds to fewer than 0 1 million persons and is not shown

Source: National Survey on Drug Use and Health: Summary of National Findings 2012

7.7.2.9. Sources of Illicit Drugs

The NSDUH also seeks information on how respondents obtained the drugs they most recently used non-medically (Figure 29). Of those persons aged 12 or older in 2011-2012 who reported using pain relievers non-medically in the past year, the most common sources were from a friend or relative for free (54.0%, 82.2% of which reported that the friend or relative obtained the drugs from just one doctor) a prescription from one doctor (19.7%), bought from a friend or relative (10.9%), took pain relievers from a friend or relative without asking (4.0%), and obtained pain relievers from a drug dealer or other stranger (4.3%). Other sources are detailed in the figure below.

Figure 29: Source Where Pain Relievers Were Obtained for Most Recent Non-medical Use among Past Year Users Aged 12 or Older: 2011-2012

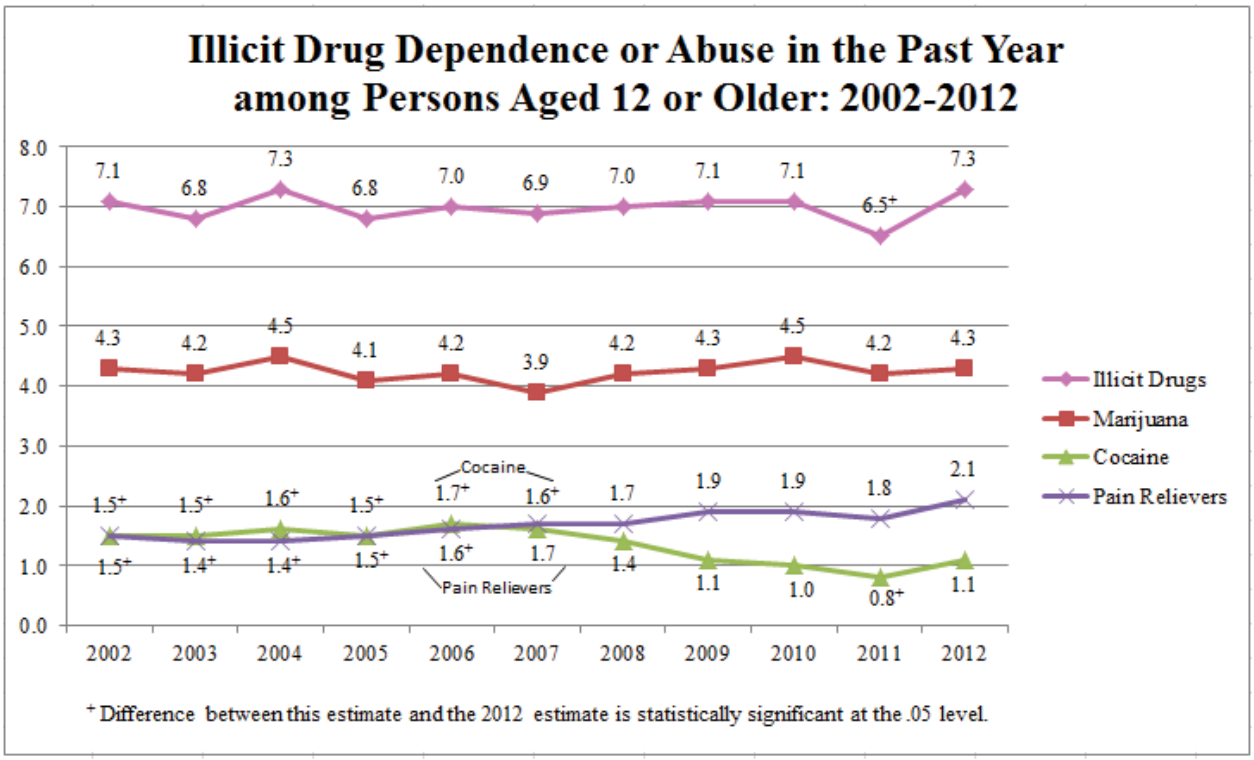


Source: National Survey on Drug Use and Health: Summary of National Findings 2012 (page 30)

7.7.2.10. Past Year Dependence or Abuse

In 2012, an estimated 7.3 million persons aged 12 or older had illicit drug dependence or abuse with marijuana, pain relievers and cocaine being the most common drugs associated with these events. Pain reliever dependence or abuse was estimated to have occurred in 2.1 million persons in 2012, similar to the estimates from each year from 2007 through 2011 (1.7 million in 2007 and 2008, 1.9 million in 2009 and 2010, and 1.8 million in 2011), but higher than the estimates from 2002 through 2006 (1.5 million in 2002, 1.4 million in 2003 and 2004, 1.5 million in 2005, and 1.6 million in 2006) (Figure 30).

Figure 30: Illicit Drug Dependence or Abuse in the Past Year among Persons Aged 12 or Older: 2002 – 2012



Source: National Survey on Drug Use and Health: Summary of National Findings 2012

7.7.2.11. Initiation of Substance Use

The number of new non-medical users of pain relievers in 2012 (1.9 million) was similar to the estimates in 2007, 2010, and 2011, but was lower than the numbers in 2002 through 2006 and in 2008 and 2009 (ranging from 2.2 million to 2.5 million). Average age at first non-medical use of pain relievers was 22.3 years in 2012, compared to 22.1 years for stimulants, 23.6 years for tranquilizers and 26.2 years for sedatives. All of these 2012 estimates were similar to the corresponding estimates in 2011.

In 2012, the number of new non-medical users of OxyContin aged 12 or older was 372,000, which was similar to the 2011 estimate of 483,000, but lower than the 2010 estimate of 600,000. The average age at first use of OxyContin among past year initiates aged 12 to 49 was similar in 2011 and 2012 (22.8 and 22.0 years, respectively).

7.7.3. Monitoring the Future

MTF is a long-term study conducted annually since 1975 by the University of Michigan's Institute for Social Research. The MTF is supported under a series of investigator-initiated, competing research grants from the National Institute on Drug Abuse (NIDA) and provides data on the substance use of American adolescents, college students, and adults through age 50.

This summary covers a high-level analysis on 2013 data for 8th, 10th, and 12th grade students and an in-depth analysis of 2012 data for 8th, 10th, and 12th grade students, college students, and adults through the age of 55. Data from a total of four published reports was used in the following summary. [Findings from 2013 on college students and adults through age 55 will be

released later in 2014 separate from data for 8th, 10th, and 12th grade students and were not available in time for inclusion in this report.]

7.7.3.1. Design & Methods

MTF includes data collection through a variety of methods:

- Annual cross-sectional surveys which allow assessment of change across history by age segments of the population and among sub-groups
    - 8th graders
    - 10th graders
    - 12th graders
- Follow-up surveys are conducted biannually with a sample of members of the cohort (panel) identified in 12th grade. To ensure that the drug-using population is adequately represented, 12th graders reporting 20 or more occasions of marijuana use in the previous 30 days (i.e., daily users), or any use of the other illicit drugs in the previous 30 days, are selected with higher probability than the remaining 12th graders. From the total number of 12th graders originally surveyed in a senior class (13,000-19,000), approximately 2,400 are randomly selected for inclusion in biannual follow-up surveys. This provides an examination of developmental change in the same individuals as they assume adult responsibilities, enter and leave various adult roles and environments, and continue further into adulthood is provided through the panel studies. Follow-up survey data are provided for the following groups:
    - college students
    - their age peers not attending college
    - young adult high school graduates aged 19-30
    - high school graduates at the specific later modal ages of 35, 40, 45, and 50
    - 55-year olds (beginning in 2013)

7.7.3.2. Sample

The nationwide sample of 12th graders is created through a multistage random sampling procedure. Particular geographic areas are selected in Stage 1, followed by selection of one or more high schools in each area (with probability proportionate to size) in Stage 2, and finally the selection of 12th graders within each high school in Stage 3. Weights are used to compensate for differential probabilities of selection at each stage of sampling.

Schools are invited to participate in the MTF study for a two-year period. In the event that a school declines participation, a similar school (in terms of size, geographic area, urbanicity, etc.) is recruited as a replacement. The schools participating in the MTF study are provided payment as an incentive to participate. Typically, each school that participates in the first year has agreed to participate in the second year. At each grade level, half of each year's sample is schools that started their participation the previous year and half is schools that began participating in the current year. Both samples are drawn to be nationally representative. This approach allows for a check on possible errors in the year-to-year trend estimates due to school turnover.

To provide an accurate representative cross-section of 12th graders throughout the coterminous US, typically between 120 and 146 public and private high schools are selected. Up to approximately 350 twelfth graders in each school may be included. Individuals who drop out of high school prior to graduation are excluded from the MTF study. According to the US Census statistics this includes approximately 10-15% of each age cohort nationally. For most purposes, the small proportion of students who drop out sets outer limits on the bias created by this exclusion. Additionally, since the bias from missing dropouts should remain relatively constant, little or no bias should be introduced in change estimates.

A similar sampling method is used for 8th and 10th grade students. Overall, approximately 16,000 8th grade students in about 150 schools and approximately 15,000 10th grade students in about 130 schools are surveyed each year.

7.7.3.3. Data Collection

Multiple questionnaire forms are administered to students randomly at each grade level. This increases coverage of attitudes and behaviors relevant to substance use. Since not all of the questions are contained in all forms, a particular statistic from the results of the survey may be based on less than the total sample size.

Usage levels for the various drugs (excluding cigarettes and smokeless tobacco) are determined through a standard set of three questions that use the same answer scale of 0, 1-2, 3-5, 6-9, 10-19, 20-39, 40 or more occasions. For example, the survey will ask: "On how many occasions (if any) have you used a narcotic other than heroin… (a)…in your lifetime? (b)…during the past 12 months? (c)… during the last 30 days?". For questions regarding psychotherapeutic drugs, respondents are instructed to only answer based on use "on your own- that is, without a doctor telling you to take them." Perceived risk is measured through a question such as: "How much do you think people risk harming themselves (physically or in other ways), if they try marijuana once or twice." The respondent would be asked to answer using the following categories: "no risk," "slight risk," "moderate risk," "great risk," and "can't say, drug unfamiliar."

Additionally the MTF survey measures disapproval and perceived availability. Disapproval is measured by a question such as "Do YOU disapprove of people doing each of the following", followed by a list of drugs. Respondents are asked to select from the answer categories "don't disapprove," "disapprove," and "strongly disapprove." The survey will ask the respondent to select one of the following categories for a perceived availability question such as "How difficult do you think it would be for you to get each of the following types of drugs, if you wanted some": "probably impossible," "very difficult," "fairly difficult," "fairly easy," and "very easy."

Questionnaires completed by 8th and 10th graders are fully anonymous. Respondents in 12th grade complete a tear-off card providing their name, address, phone number(s), and email address to be included in follow-up surveys after graduation.

Follow-up surveys that parallel the questionnaires used in 12th grade are implemented over time for a representative sample of the total 12th grade class respondents. From the total number of 12th graders originally surveyed in a senior class (13,000-19,000), approximately 2,400 are randomly selected for inclusion in biannual follow-up surveys. To limit respondent burden, half of the participants are surveyed in the spring on even-numbered calendar years and the other half

of participants is surveyed in the spring on odd-numbered years. This approach also allows MTF to collect data from every graduating class each year (through age 30 or six biennial surveys).

After the sixth biennial survey, additional follow-up occur 5-year intervals until completion of a survey at age 50 (i.e., at modal ages 35, 40, 45, and 50). For the five-year surveys beginning at age 35, only one questionnaire form is used and both half-samples from a class cohort are surveyed at the same time. Questionnaire content is similar the biennial survey content, but is streamlined with a focus on the major family and work issues relevant to respondents ages 35 to 50. Additionally the questionnaire includes added measures of substance use disorders and health outcomes. Starting in 2013, follow-up will also occur at modal age 55.

Throughout the course of the follow-up survey implementation, reminder letters and postcards are sent at fixed intervals. Additionally, telephone calls are made to gather up-to-date location information for those respondents with whom MTF is trying to make contact. For those whom are contacted but have not responded, the Survey Research Center makes a prompting phone call to the respondent. No questionnaire content is administered by phone, but if requested a second copy of the questionnaire is sent. Attached to each questionnaire is a check made payable to the respondent.

7.7.3.4. Results

Due to the phased release of data from the MTF activities, results for college students and adults aged through 55 can only be provided for 2012. Results for these respondents for 2013 surveys will be available later in 2014 and will be included in the summary provided in the 2015 ER/LA Opioid Analgesics REMS Assessment Report. Since preliminary data collected from 8th, 10th, and 12th graders were released in early 2014 both 2012 and 2013 data for 8th, 10th, and 12th graders is included in this summary in order to provide overall depiction of trends and leverage the most current data available.

7.7.3.5. 2012 & 2013 MTF 8th, 10th, and 12th Grade Results

In 2012, the MTF survey collected data from about 45,400 students in 395 secondary schools, including about 15,700, 15,400, and 14,300 8th, 10th, and 12th graders respectively. The 2013 MTF survey collected data from approximately 41,700 8th, 10th, and 12th grade students in 389 secondary schools nationwide including 15,200, 13,300 and 15,200 8th, 10th, and 12th graders respectively.

Since data regarding use of narcotic drugs other than heroin are considered unreliable as reported by 8th and 10th graders, narcotic use is only reported for 12th graders. In 2013, 11.1% of 12th graders reported that they had tried a narcotic drug other than heroin at some point in their life, a decrease of 1.1% from 2012 and 1.9% from 2010. Approximately 7.1% of 12th graders reported that they had used a narcotic drug other than heroin in the last year. While only a decrease of 0.8% was seen from 2012 to 2013, since 2010 there has been a decrease of 1.6% in the annual prevalence of narcotics other than heroin in 12th graders. Similarly, since 2010 there has been a gradual decline in the reported use of narcotics other than heroin within the past 30 days (3.6% in 2010 to 2.8% in 2013).

The MTF survey collects specific data on use rates of for two narcotics of recent interest (OxyContin and Vicodin) from 8th, 10th, and 12th graders. Use of OxyContin within the past year

was reported by 2.0%, 3.4%, and 3.6% of 8th, 10th, and 12th graders respectively. While the percent that reported use of OxyContin increased by 0.4% by both 8th and 10th graders, there was a decline of 0.7% in 12th graders. The Vicodin use within the past year as reported by 8th graders remained similar to 2012 at 1.4% while an increase was seen in 10th graders (4.6%, + 0.2%) and a significant decline was noted in 12th graders (its annual prevalence fell from 7.5% in 2012 to 5.3% in 2013; a difference of -2.2%) While overall use has declined significantly in all grades since 2008, the lower grades (8th and 10th) showed virtually no change in annual prevalence from 2012 to 2013.

As shown in Table 24, perceptions of harmfulness of trying OxyContin or Vicodin and taking OxyContin or Vicodin occasionally was also collected. When asked how much do you think people risk harming themselves (physically or in other ways) if they try OxyContin once or twice or take OxyContin occasionally, 19.9% and 32.6% of 8th graders, 29.4% and 44.7% of 10th graders respectively reported that it was a great risk. When asked the same questions about Vicodin, 15.0% and 26.2% of 8th graders, and 21.0% and 36.0% of 10th graders responded that it was a great risk. Twelfth graders were asked similar questions to those posed to 8th and 10th graders. When asked whether they thought people risk harming themselves (physically or in other ways), if they try any narcotic other than heroin (codeine, Vicodin, OxyContin, Percocet, etc.) once or twice, occasionally, or regularly the percentage of 12th graders who reported it was a great risk was 43.1, 57.3, and 75.8% respectively. An increase from 2012 to 2013 was seen on each of these items (+ 4.8, + 3.5, + 1.9).

Table 24: TRENDS IN HARMFULNESS OF DRUGS AS PERCEIVED BY 8TH, 10TH, AND 12TH GRADERS: PERCENTAGE SAYING GREAT RISK

HOW MUCH DO YOU THINK PEOPLE RISK HARMING THEMSELVES (PHYSICALLY OR IN OTHER WAYS), IF THEY…	2010	2011	2012			2013			2012-2013 CHANGE		
	12th	12th	8th	10th	12th	8th	10th	12th	8th	10th	12th
Try OxyContin® once or twice	-	-	21.9	30.9	-	19.9	29.4	-	-2.0	-1.5	-
Take OxyContin® occasionally	-	-	35.3	48.3	-	32.6	44.7	-	-2.8	-3.6	-
Try Vicodin once or twice	-	-	17.5	23.2	-	15.0	21.0	-	-2.5	-2.2	-
Take Vicodin occasionally	-	-	29.4	40.3	-	26.2	36.0	-	-3.2	-4.2	-
Try any narcotic other than heroin (codeine, Vicodin, OxyContin®, Percocet, etc.) once or twice	40.4	39.9	-	-	38.4	-	-	43.1	-	-	+ 4.8
Take any narcotic other than heroin occasionally	54.3	54.8	-	-	53.8	-	-	57.3	-	-	+ 3.5
Take any narcotic other than heroin regularly	74.9	75.5	-	-	73.9	-	-	75.8	-	-	+ 1.9

*significance of at least 0.05
Source: Monitoring the Future Study 2013, Overview

Data regarding availability of narcotic drugs other than heroin (taken as a class) is also collected from 8th, 10th, and 12th graders. Perceived availability increased gradually among 12th graders from 1978 through 2001. In contrast, perceived availability has declined among 8th and 10th graders since the late 1990s. The considerable jump in reported availability in 2010 is presumably due to a change in question wording in 2010 to include OxyContin and Vicodin as examples of narcotics other than heroin. In 2013, when asked how difficult they thought it would be to get narcotic drugs other than heroin, 9.7%, 22.5% and 46.5% of 8th, 10th, and 12th graders, respectively, said they would be fairly easy or very easy to get. This was a decrease across all grades from 2012 to 2013 (-0.9%, -1.9%,-3.9%).

7.7.3.6. MTF 2012 College Students and Adults through the Age of 55

The MTF follow-up surveys conducted in 2012 provided data from 1977 through 2012 of the graduating high school classes of 1976 through 2011. The representative samples from each graduating class from 1999 to 2011 are considered the "young adult" sample. This sample corresponds to respondents at modal ages 19 through 30 and includes college students. Surveys that are conducted at modal age 35 and at five-year intervals thereafter cover respondents in middle adulthood.

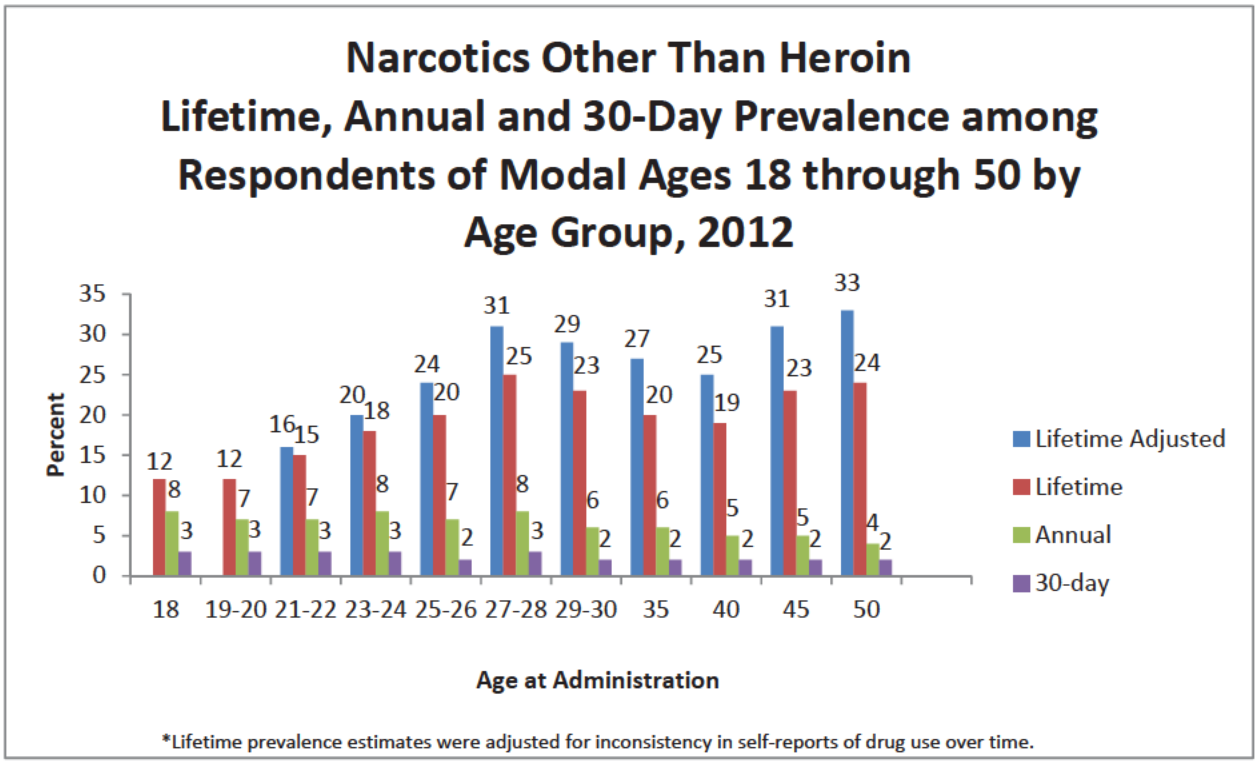
A total of 18.5% of those aged 19-30 surveyed had used a narcotic other than heroin in their lifetime. Respondents aged 27-28 were most likely to have used a narcotic other than heroin in their lifetime (24.7%), while respondents aged 19-20 were the least likely (11.9%). Males were more likely than females (21.1% vs. 16.7%) to have used one in their lifetime and higher usage was noted in from the West region (20.7%) and Northeast region (20.0%) of the US than the Midwest (18.3%) and Southern (16.7%) regions.

Approximately 7% of respondents had used a narcotic other than heroin within the last year. The rate of males reporting using a narcotic other than heroin within the last year was higher than that of females (8.1% vs. 6.4%). The highest percentage of use was reported in those aged 27-28 (8.2%) and those living in the West or Northeast region of the use (8.5% and 8.1%).

Some similar trends as mentioned previously for lifetime and annual prevalence of use were seen in 30-day prevalence of use. A total of 3.1% of males and 2.4% of females reported using a narcotic other than heroin in the last 30 days, and the highest percentages of use were seen in the Northeast and West regions (22% and 19.8%). However, unlike the lifetime and annual prevalence of use findings, the highest reporting of use of narcotics other than heroin within the last 30 days were respondents aged 23-24 (3.3%), 19-20 (2.8%), 21-22, and 27-28 (both at 2.7%). While about 33%, 31%, 25%, and 27% of 35-, 40-, 45-, and 50-year-olds, respectively, reported trying a narcotic other than heroin in their lifetime (based on the adjusted lifetime estimate), approximately 2% of each of these age groups reporting using a narcotic other than heroin within the past 30 days (Figure 31).

In 2002, specific questions were added for Vicodin and OxyContin, and the observed prevalence rates suggest that these two drugs likely help to account for the upturn in use of the general class of narcotics other than heroin. In 2003, Vicodin had attained high prevalence rates among college students (7.5%), and among young adults (8.6%). In 2012 the rates were down in both age groups (3.8%, and 6.3%, respectively). OxyContin started with lower annual prevalence rates than those for Vicodin across both age groups in 2002 but, annual prevalence for OxyContin increased in 2003 with slight further increases and leveling through 2011. In 2012 it dropped somewhat in both the college student and young adult populations to annual prevalence rates below the 2003 levels (1.2%, and 2.3% respectively).

Figure 31: Narcotics Other Than Heroin (Lifetime, Annual and 30-Day Prevalence among Respondents of Modal Ages 18 through 50 by Age Group 2012)



Source: Monitoring the Future Study 2012, Volume II

7.7.4. Conclusion

Both the NSDUH survey and the MTF surveys provide demographic data and substance use data for a large portion of the US population. Comparisons between the NSDUH and MTF studies have shown that while there is a difference in the reported rate of non-medical use of pain relievers between the studies, the data show overall comparable trends. While there are certain limitations of the data collected the results contained in these annual reports serve as an influential public health source on demographics and trends in substance use.

As described by Biondo and Chilcoat in 2013[9], while data for prevalence of past year oxycodone non-medical use from both the NSDUH and MTF surveys has been steady over time, estimates in the MTF have been 2.5-3 times higher compared to the NSDUH. This difference in reported prevalence could be a reflection of the overall methodological differences between the two surveys. Specifically, the NSDUH provides pill cards with pictures of specific pain relievers which may increase the accurate identification and reporting of the pain reliever(s) used by a participant. The MTF, which does not include such graphic aides, may capture inaccurate responses due to a participant's mis-identification of a product. For example, a participant may report using OxyContin when in fact the pain reliever used was oxycodone. Another important limitation of this data are that data specific to ER/LA opioid analgesics (other than OxyContin) is not provided. Lack of this specific data limits the ability to use these sources as a means to evaluate the effectiveness of the REMS.

Overall from 2009 to 2012, there has been a decline in the reported lifetime prevalence estimate of non-medical use of pain relievers in both the NSDUH and the MTF studies. The NSDUH reported a decline from 24.5% in 2009 to 22.4% in 2012 while the MTF studies reported a decline from 17.2% to 14.7%. For past 30-day prevalence of pain reliever use estimates among young adults from 2010 to 2012 the same relative trend was also seen with declines from 4.4% to 3.8% for the NSDUH and from 3.5% to 2.9% in the MTF studies. Preliminary results from the MTF 2013 survey also indicate a continued decline in reported use of narcotics other than heroin at some point in the respondents' lifetime or in the past 30 days in 8th, 10th, and 12th graders.

Since the primary data only covers 2012 with 6 months into the REMS Launch Period, the NSDUH and MTF results summarized in this Twenty-Four Month FDA Assessment Report will be utilized as a baseline for future FDA Assessment Reports. As previously described there are some measures that extended to 2013 and these measures are consistent with declining rates of abuse occurring concurrently with the introduction of the REMS.

8. ASSESSMENT ELEMENT 6 – EVALUATION OF DRUG UTILIZATION PATTERNS

Assessment Element 6 is the evaluation of drug utilization patterns which was conducted in order to describe trends in the number of prescriptions for ER/LA opioid analgesics and comparator products using a national prescription database system. The specific objectives of this analysis included:

1. To estimate trends by month in the number of prescriptions for a one-year period before, and each month after, the implementation of the REMS
2. To compare average number of prescriptions per 3-month period in the 2 years before as compared to the same measure in transition implementation period and post-period
3. To compare the trends in prescribing, both number of prescriptions and patients, by prescriber specialty. These trends and changes over time will be estimated for the following groups of opioids:
    - All ER/LA opioid analgesics included in the class REMS versus immediate-release opioids not in the class
    - Immediate-versus extended-release formulations of each drug substance
    - Each product in the ER/LA opioid analgesic class
4. To show switches (absolute and rates of switching) from ER/LA opioid analgesics to comparator analgesics with introduction of REMS

To evaluate the above objectives, a retrospective cross-sectional study using data drawn from the IMS Health, National Prescription Audit™ (NPA™) and IMS Health, LifeLink™ patient-level longitudinal prescription (LRx) database was conducted. Comparators were broken into three categories:

- IR opioid analgesics not covered by the class REMS for ER/LA opioid analgesics. These products included oral forms, and were assessed at the product group level. For example, fentanyl, fentanyl citrate, hydrocodone-acetaminophen, hydrocodone-ibuprofen, hydromorphone, morphine sulfate, oxycodone, oxymorphone, and tapentadol.

- Prescription Non-steroidal Anti-Inflammatory Drug (NSAID), celecoxib, as an "analgesic control" group. Celecoxib was selected as the only NSAID comparator because all celecoxib strengths require prescriptions. This is not the case with many other NSAIDs, which do not require prescriptions or do not require prescriptions for some dosage strengths. As a result, data would not be available in IMS or other claims databases. In addition, just as with the ER/LA opioid analgesics, celecoxib is more likely to be used for longer term pain due to its lower risk of gastrointestinal bleeding as compared to other NSAIDs that are generally more often used for acute pain than chronic pain.
- Benzodiazepines as an "abuse control" group since this class of prescription drugs is subject to abuse. These products were assessed at product group level (e.g., alprazolam, chlordiazepoxide, clorazepate dipotassium, diazepam, halazepam, lorazepam, and oxazepam).

Patients meeting *all* of the following criteria were selected for inclusion:

- At least one prescription in the market of interest
- Continuous eligibility in the LRx database
- Activity by patients in the LRx database

All measures described below were aggregated monthly and/or quarterly in the pre-period, transition implementation period, and post-period. Monthly and quarterly assessment of prescription volume was based on individual product level for ER/LA opioid analgesics and on product group level for comparator products. Data on unique patients prescribed ER/LA opioid analgesics is presented by product strength, while data are available on product level for comparator products. As a result, monthly and quarterly assessment of patient volume was conducted on individual product strength level for ER/LA opioid analgesics and on product group level for comparator products.

Prescription and patient counts were projected to the national level based on the LRx prescription sample with projection factors derived from the prescriptions in LRx relative to NPA total prescription (see Appendix H for description of methodology).

8.1. Objective 1

Trends and changes per month were estimated for all REMS ER/LA opioid analgesics and all comparator products. The specific outcome measured for this objective was monthly prescription volume, and was based on all ER/LA opioid analgesics and comparator products prescriptions filled in the pre REMS period (July 1, 2011 through June 30, 2012), during the transition implementation period (July 1, 2012 through June 30, 2013) and after the implementation of REMS (July 1, 2012 through December 31, 2013). Monthly prescription volume was defined as the total number of prescription filled for ER/LA opioid analgesics and comparator products within a calendar-month. Counts of prescription volumes (n) were aggregated for ER/LA opioid analgesics and comparator products.

8.2. Objective 2

Trends and changes per quarter were estimated for all REMS ER/LA opioid analgesics and all comparator products. This analysis included all prescriptions for ER/LA opioid analgesics and comparator products filled in the pre-period (July 1, 2010 through June 30, 2012), transition implementation period (July 1, 2012 through June 30, 2013), and post-period (July 1, 2013 through December 31, 2013). Specific outcomes measured for this objective were:

- Average prescription volumes per quarter (three calendar-months) in pre-period, transition implementation period, and post-period
- Average prescription volumes per quarter in the pre-period, transition implementation period, and post-period, stratified by select patient characteristics which includes:
    - Age group, computed based on patient's year of birth and the date of the index prescription of interest: ≤18, 19-40, 41-64, ≥65
    - Gender: Male and female
    - Pay type (Cash, Medicaid, Medicare Part D, Third Party)
    - Prescriber specialty, defined as the specialty of the prescribing physician for each prescription: Dentist, emergency medicine, hospice and palliative medicine, oncology, pain, primary care physician, surgery, other
- Pre-transition implementation and pre-post changes in average quarterly number of prescriptions as a % change

Mean and 95% confidence interval were calculated for average prescription volumes. Changes in prescribing before and after REMS implementation were performed by calculating and comparing prescription volume between the pre-period and the transition implementation and post-periods. Differences in the average change in quarterly volume were assessed for statistical significance using student's t-test. P-values less than 0.05 were considered significant.

8.3. Objective 3

Trends and changes over time were estimated by prescriber specialty for all REMS ER/LA opioid analgesics and all comparator products. This analysis included all prescriptions for ER/LA opioid analgesics and comparator products filled in the pre-period (July 1, 2010 through June 30, 2012), transition implementation period (July 1, 2012 through June 30, 2013), and post-period (July 1, 2013 through December 31, 2013). Specific outcomes measured for this objective were:

- Average prescription volumes per quarter (three calendar-months) in pre-period, transition implementation period, and post-period, by prescriber specialty by product
- Average patient volumes per quarter (three calendar-months) in pre-period, transition implementation period, and post-period, by prescriber specialty by product
- Pre-transition implementation and pre-post changes in average quarterly number of prescriptions as a % change

Mean and 95% confidence interval were calculated for average prescription volumes. Changes in prescribing before and after REMS implementation were performed by calculating and comparing the average percent changes in prescription and patient volume between the pre-period and the transition implementation and post-periods. Differences in the average change in quarterly volume were assessed for statistical significance using student's t-test. P-values less than 0.05 were considered significant.

8.4. Objective 4

Switching from an ER/LA opioid analgesic to other products was evaluated among all patients with a prescription for ER/LA opioid during the pre-period (July 1, 2010 through June 30, 2012, transition implementation period (July 1, 2012 through June 30, 2013), and post-period (July 1, 2013 through December 31, 2013). Switching was defined as filling a prescription for a new product that is different from the prescription in the previous 3 months. If a patient filled multiple prescriptions in the previous 3 months, only the most recent prescription (i.e., most recent fill date) were evaluated. Patients meeting the definition for switching were defined as switchers. Patients without a prescription for any ER/LA opioid analgesic in the previous 3 months, but who have a prescription for an ER/LA opioid analgesic in the current month were defined as new patients. Patients with a prescription for the same ER/LA opioid analgesics in the previous 3 months and in the current months were defined as continuing patients. Switching assessment was also stratified by prescribing specialty. Specific outcomes measured for this objective were:

- Monthly volume of patients who switch from REMS products to IR opioid analgesics or celecoxib
- Rates of switching

8.5. Monthly trend

Results of the monthly prescription trend are presented in Figure 32.

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9. ASSESSMENT ELEMENT 7 – EVALUATION OF CHANGES IN PRESCRIBING BEHAVIORS

Assessment Element 7 is an evaluation of changes in prescribing behavior (e.g., prescriptions to non-opioid tolerant patients, excessive prescriptions for early refills). The specific objectives of this analysis included:

- For products that are indicated for use in opioid tolerant patients only (i.e., fentanyl transdermal patches and extended-release hydromorphone pills), describe trends in the proportion of prescriptions for these products to opioid-non-tolerant patients in the year preceding the availability of REMS-compliant CE courses and compare the proportion of prescriptions to opioid non-tolerant patients pre-versus post-REMS CE course availability
- For products whose labels indicate that higher dosage strengths should only be used in opioid tolerant patients, describe trends in the proportion of prescriptions prescribed to opioid non-tolerant patients with a high starting dosage strength; compare the proportion of prescriptions for such products that are prescribed to opioid non-tolerant patients with a high starting dosage strength pre-versus post-REMS CE course availability
- Describe trends in the proportion of prescriptions for ER/LA opioid analgesics prescribed to patients that have early refills of prescriptions and compare this proportion pre-versus post-REMS CE course availability
- To compare the concomitant use of benzodiazepines with ER/LA opioid analgesics before and after REMS implementation

These objectives were evaluated through the same retrospective cross-sectional study (drug utilization patterns), described in Assessment Element 6.

All measures described below were aggregated monthly and/or quarterly in the pre-period (July 1, 2010 through June 30, 2012), transition implementation period (July 1, 2012 through June 30, 2013), and post-period (July 1, 2013 through December 31, 2013). Monthly and quarterly assessment of prescription volume was based on individual product level for ER/LA opioid analgesics and on product group level for comparator products. Data on unique patients prescribed ER/LA opioid analgesics is only available by product strength, while data are available on product level for comparator products. As a result, monthly and quarterly assessment of patient volume was conducted on individual product strength level for ER/LA opioid analgesics and on product group level for comparator products.

Unless otherwise stated, prescription and patient counts were projected to the national level based on the LRx prescription sample with projection factors derived from the prescriptions in LRx relative to NPA total prescription (see Appendix H for description of methodology).

9.1. Objective 1: Assess the prescription of opioids to opioid non-tolerant patients

This objective was addressed using a subset of patients who filled prescriptions for products that are indicated for use only in opioid tolerant patients. These products include fentanyl transdermal patches and ER hydromorphone pills. This analysis assessed whether these prescriptions were being filled by opioid tolerant patients or non-opioid tolerant patients (or opioid naïve). Non-opioid tolerant patient is defined as an individual who has not received an opioid for 6 months. The following outcomes were calculated:

- Monthly volume of prescriptions in opioid tolerant patients
- Monthly volume of prescriptions in non-opioid tolerant patients
- Monthly proportion of patients that are non-opioid tolerant
- Average prescription volumes in the 12 months pre-period, transition implementation period, and post-period
- Pre-transition implementation and pre-post changes in average quarterly number of prescriptions as a % change

For the monthly volumes, counts of prescription volumes (n) for fentanyl transdermal patches and ER hydromorphone pills were aggregated for opioid tolerant patients and non-opioid tolerant patients. Mean and 95% CI were calculated for average prescription volumes within each period. Differences in the average change in quarterly volume were assessed for statistical significance using student's t-test. P-values less than 0.05 were considered significant.

9.2. Objective 2: Metrics of Appropriate Prescribing Behavior for Starting Dose

This objective was addressed using a subset of patients who a filled prescription for products whose labels indicate that higher dosage strengths should only be used in opioid tolerant patients (For example, from the AVINZA label, "AVINZA 90 mg and 120 mg capsules are for use only in patients in whom tolerance to an opioid of comparable potency has been established." Non-opioid tolerant was defined as an individual who has not received an opioid for 6 months.

Table 30: Product Strengths Exceeding Recommended Starting Dose for Non-Opioid Dependent Patients

PRODUCT	DOSE STRENGTH EXCEEDING RECOMMENDED STARTING DOSE FOR NON-OPIOID DEPENDENT PATIENTS
Buprenorphine	10 mcg/ hr, 15 mcg/ hr, & 20 mcg/ hr
Morphine Sulfate	100 mg, 100 mg/12 hr, 100 mg/24 hr, 130 mg/24 hr, 150 mg/24 hr, 200 mg, & 200 mg/24 hr
Morphine Sulfate Capsules	90 mg/24 hr & 120 mg/24 hr
Oxycodone	15 mg, 20 mg, 20 mg/12 hr, 30 mg, 40 mg, 40 mg/12 hr, 60 mg, 80 mg, 80 mg, & 160 mg/12 hr
Oxymorphone	7.5 mg, 7.5 mg/12 hr, 10 mg, 10 mg/12 hr, 15 mg, 15 mg/12 hr, 20 mg, 20 mg/12 hr, 30 mg, 30 mg/12 hr, 40 mg, & 40 mg/12 hr
Tapentadol	100 mg/12 hr, 150 mg/12 hr, 200 mg/12 hr, & 250 mg/12 hr

The following outcome measures were calculated:

- Monthly volume of high-starting dose prescriptions in opioid tolerant patients
- Monthly volume of high starting dose prescriptions in non-opioid tolerant patients
- Proportion of non-opioid tolerant patients that have high-starting dose prescriptions
- Average prescription volumes in the 12 months pre-period, transition implementation period, and post-period
- Pre-transition implementation and pre-post changes in average quarterly number of prescriptions as a % change

For the monthly volumes, counts of prescription volumes (n) were aggregated for opioid tolerant patients and non-opioid tolerant patients. Mean and 95% confidence interval were calculated for average prescription volumes within each period. Differences in the average change in quarterly volume were assessed for statistical significance using student's t-test. Calculated p- values of less than 0.05 were considered significant.

9.3. Objective 3: Assess the frequency of early refills

For this objective, early refills among patients who are new-to-therapy were assessed for the pre-period (July 1, 2010 through June 30, 2012), and transition implementation period (July 1, 2012 through June 30, 2013). Early refill was defined as two consecutive prescriptions for the same individual and the same drug with the number of days between prescriptions >15% lower than the number of days of supply in the first prescription. Because the data used for this objective only went through December 2013, the last usable study month (leaving a 6 month look-forward period) is June 2013. Previously published studies have used a threshold for early refills of 10%, but the published studies have reported that patients may frequently get refills three days early on a 30-day prescription within the course of usual clinical practice.[10,11, 12]The resulting data for this objective were not projected, because the same projection factor will be applied to the numerator

and denominator, and this will cancel out when the proportion of patients or rate of early refill are calculated.

Specific outcome measures calculated for this objective were:

- Volume of early refills by monthly patient cohort
- Volume of normal refills by monthly patient cohort
- Proportion of patients receiving early refills
- Early refill rate by monthly patient cohort

All outcome measures were stratified by individual level ER/LA opioid analgesics. Counts of prescription volumes (n) were aggregated for patient cohorts by month. Percentages were calculated for rates and proportions of early refill by month.

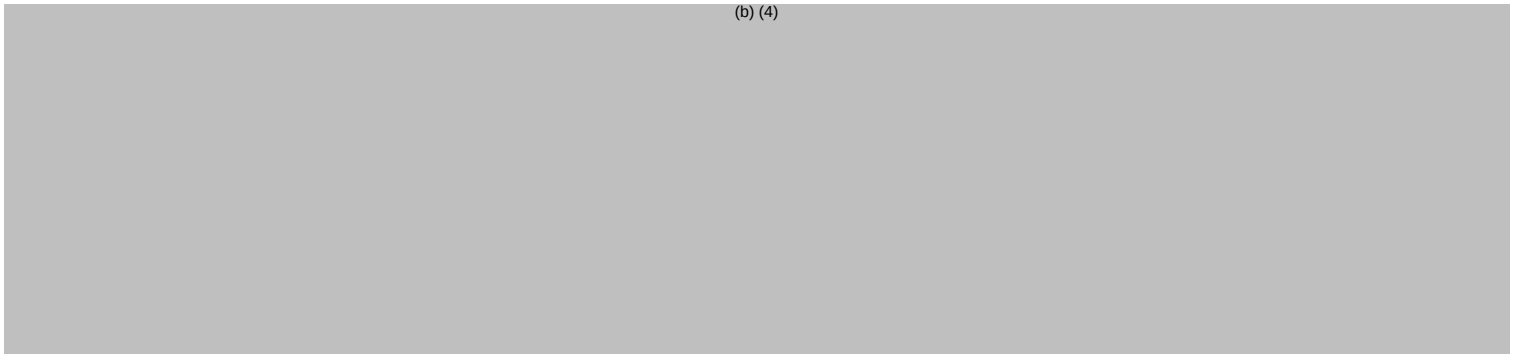
9.4. Objective 4: REMS products and benzodiazapines used concomitantly

This objective used a subset of patients who are using a REMS product and a product in the benzodiazepine group concomitantly. Concomitant use was defined as filling a benzodiazepine prescription in the previous 3 months. The main outcome assessed was monthly volume of patients who are using a REMS product and a benzodiazepine concomitantly.

For the monthly volumes, counts of prescription volumes (n) were aggregated were presented. Mean and 95% CI were calculated for average prescription volumes within each period. Differences in the average change in quarterly volume were assessed for statistical significance using student's t-test. P-values less than 0.05 were considered significant.

9.4.1. Monthly volume of prescriptions for drugs indicated for use in opioid tolerant patients

(b) (4)



(b) (4)

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9.4.2.1. Conclusion

This report presents the results from a retrospective cross-sectional assessment evaluating changes in drug utilization and changes in prescribing for opioids covered by the class-wide REMS during the periods before, during the transition and after the implementation of the REMS. This assessment revealed that the total ER/LA opioid analgesics had a significant decrease in prescriptions dispensed and patients treated from the pre-period to the post-period. There was a (b) (4) % decrease in the average quarterly prescription volume from the pre-period compared to the post-period. While overall prescription volumes decreased, oxycodone, morphine sulfate, fentanyl, and methadone retained the largest prescription share of all the ER/LA opioid analgesics evaluated during the study period.

When the ER/LA opioid analgesics were individually assessed, morphine sulfate, buprenorphine, and hydromorphone showed an increase in prescription volume from either the pre-period to the transition implementation period or from the pre-period to the post-period. In contrast, oxymorphone, morphine sulfate capsules, oxycodone, and methadone had a decrease in prescription volume from the pre-period to the transition implementation period or from the pre-period to the post-period. Hydromorphone had the largest percent increase in volume across periods, (pre to transition implementation period: (b) (4)

The total prescription volume for the comparator products remained relatively stable throughout the study periods. Benzodiazepine was the only product group to have an increase in prescription volume during the study period (b) (4)). Celecoxib had a significant decrease in prescription volume between the pre-period and transition implementation period; however, there was no significant change in prescription volume from the transition period to the post-period ((b) (4)). The IR opioid group showed a decrease in prescription volume; however only the decrease between the pre-period and post-period was significant ((b) (4)

Differences were observed in the absolute prescription volume and trends among patient groups during the period before and after the implementation of the REMS. When stratified by age, the 41 to 64 age group had the highest prescription volume for the total ER/LA opioid analgesics. A decrease in the average quarterly prescription volume was observed for all age groups under 65 years for the total REMS products; while an overall increase in the average quarterly prescription volume observed for the 65 and older age group. There was a decrease in the average quarterly prescription volume for both men and women from the pre to post-period for the total REMS products. A decrease in average quarterly prescription volume was observed across nearly all pay types, with Medicaid having the highest percent decrease from the pre-period to the implementation period (b) (4)) and from the pre-period to the post-period (b) (4) Medicare Part D was the only pay type to have an increase in prescription volume for the total REMS product from the pre-period to the implementation

period [redacted] and from the pre-period to the post-period [redacted]).

Change in the prescription volume before and after the implementation of the REMS was assessed by prescriber specialty. For ER/LA opioid analgesics, primary care physicians (PCP), pain specialists, surgeons, and oncologists had the largest prescription volume. Total ER/LA opioid analgesics exhibited a decrease in average quarterly prescription volume for most of the specialties from the pre to transition and the transition to post-periods, the exceptions being "other" and pain specialty, as well as, for the hospice and palliative medicine specialty groups. The largest significant decreases in average prescription volume per quarter were observed for dentists (pre to transition implementation period: [redacted]). Across the largest part of the prescribing specialties, hydromorphone had the largest increase in prescription volume, while morphine sulfate capsules had the largest decrease in volume.

Switching from REMS products to the non-REMS opioid group or celecoxib was assessed overall and by prescriber specialty. The switch rate from REMS products to the IR opioids was highest for the oncology, pain, and hospice and palliative medicine specialties, with switch rates of approximately [redacted]%, respectively. The switch rate from REMS products to celecoxib was also highest within the oncology, pain and, hospice and palliative medicine specialties. The monthly switch rate from REMS products to celecoxib fluctuated among the majority of prescribing specialties, with the fluctuation for hospice and palliative care being the most notable (ranging from [redacted]%).

Changes in prescribing behavior of prescribers were also analyzed. Relative to the overall number of patients prescribed these drugs, the proportion of non-tolerant patients decreased for these products.

The trend in the proportion of prescriptions prescribed to non-tolerant opioid patients with a high starting dose was evaluated. Different trends were noted depending on the product and strength. All the high starting doses for tapentadol and nearly all the high starting doses for buprenorphine showed a trend towards an increase in the average number of non-tolerant opioid patients prescribed these drugs. For morphine sulfate capsules, there was a decrease in the average number of non-tolerant opioid patients with a prescription. The majority of the high starting doses for morphine sulfate, oxycodone, and oxymorphone showed a trend towards a decrease in the average number of non-tolerant opioid patients prescribed these drugs.

When early refill for the REMS products was analyzed, different patterns in change were seen for the proportion of patients with early refills. The proportion of patients with early refills slightly decreased over time for buprenorphine, oxycodone and hydromorphone, while a slight increase was observed for morphine sulfate capsules and methadone. For oxymorphone and tapentadol, the proportion of patients with an early refill decreased in the early part of the pre-period, but eventually increased in the months closest to the transition implementation period. The proportion of patients with early refills for morphine sulfate and fentanyl remained the same throughout the study periods. On the contrary, a trend towards a decrease in the rate of early

refills was observed for the majority of the ER/LA opioid analgesics over the assessment period. The rate of refills remained relatively stable for methadone and fentanyl.

The change across periods for the concomitant use of benzodiazepine in combination with ER/LA opioid analgesics also differed depending on the product. There was an increase in the average monthly number of patients using benzodiazepine in combination with the majority of the strengths for buprenorphine, hydromorphone, and tapentadol. In contrast, the average number of patients who used concomitant benzodiazepine decreased across all strengths for morphine sulfate capsules. For the other ER/LA opioid analgesic products, the average number of patients who used concomitant benzodiazepine varied among products and product strengths across periods.

10. ASSESSMENT ELEMENT 8-MONITORING PATTERNS OF PRESCRIBING TO IDENTIFY CHANGES IN ACCESS TO ER/LA OPIOID ANALGESICS

Assessment Element 8 concerns changes in access to ER/LA opioid analgesics. This Assessment Element has two main components. The first component compares changes in number of prescriptions for prescriber types with less (e.g., Dentist) and more (e.g., Oncologist, Hospice Care) compelling reasons to prescribe ER/LA opioid analgesics are assessed. The second component relied on survey questions to assess whether prescribers and patients perceive and impact of the ER/LA Opioid Analgesic REMS on access to treatment. For prescribers, switch in medications that they prescribe and their perception of a change in access for patients will be assessed. For patients, survey items will assessed whether patients perceive a change following implementation of the REMS in, 1) Physicians prescribing pain medication, 2) access to medication to treat pain, and 3) satisfaction with access to pain treatment.

The RPC worked with three vendors to conduct Assessment Element 8 and its multiple components the results of which are presented below.

10.1. Changes in number of prescriptions for prescriber types with less and more compelling reasons to prescribe ER/LA opioid analgesics

For this component prescriptions from prescriber specialties that are hypothesized to have less compelling reasons to prescribe ER/LA opioid analgesics (e.g., Dentists) and those that have more compelling reasons to prescribe ER/LA opioid analgesics (such as oncologists and hospice providers) were segmented and compared. This component was also accomplished through the retrospective cross-sectional study described in Assessment 6 and Assessment 7, using data from the IMS Health, NPA™, and IMS Health Lifeline™ patient-level LRx database.

The specific outcomes measured among the REMS versus the comparator products were:

- Monthly volume of prescriptions from specialties hypothesized to be relatively unaffected by the REMS
- Monthly volume of prescriptions from specialties hypothesized to be more affected by the REMS

Measurements of changes in prescribing before, during the transition implementation period, and after REMS implementation were performed. The average percent changes in volumes from the pre-period, transition period, and post-periods, and 95% CI were calculated. The statistical significance of these changes was estimated by T-test. P-values less than 0.05 were considered significant. SAS 9.2 (Cary, NC) was used to perform statistical tests for significance.

Table 37: MONTHLY TREND IN PRESCRIPTION OF ER/LA OPIOID ANALGESICS BY PRESCRIBER SPECIALTY BEFORE AND AFTER IMPLEMENTATION OF REMS

(b) (4)

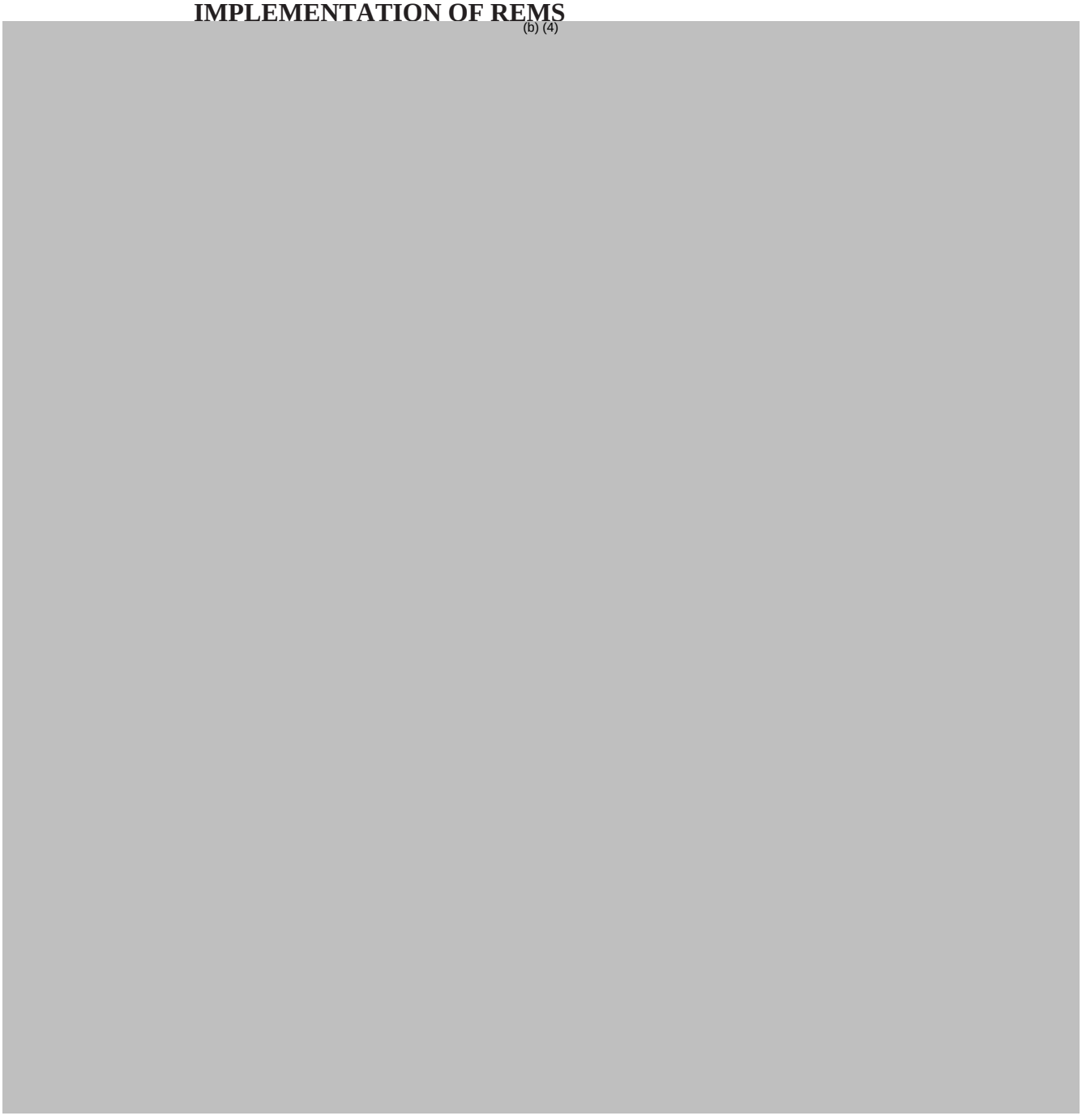
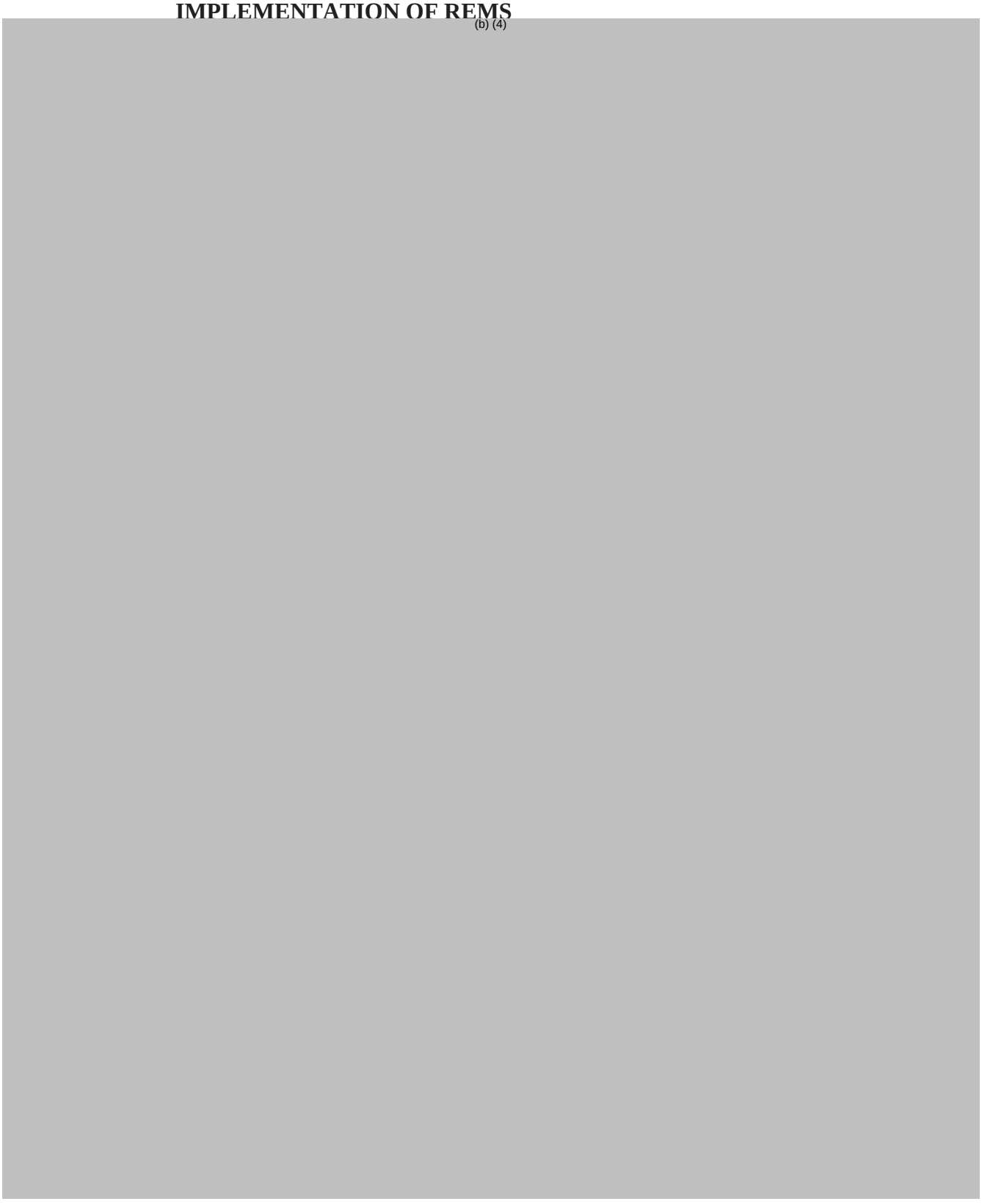


Table 37: MONTHLY TREND IN PRESCRIPTION OF ER/LA OPIOID ANALGESICS BY PRESCRIBER SPECIALTY BEFORE AND AFTER IMPLEMENTATION OF REMS

(b) (4)



The prescription volume for the total ER/LA opioid analgesics prescribed by hospice and palliative care medicine and pain specialists did not significantly change after the REMS was launched. The prescriber specialty with the largest decrease in prescription volume was dentists. For these prescribers, a (b) (4) % decrease in prescription volume for the total ER/LA opioid analgesics was observed between the pre-period and transition implementation period, and a (b) (4) % decrease was observed between the pre-period and post-period.

For the non-REMS products, the volume of benzodiazepines prescribed by PCPs, dentists, and emergency medicine specialists did not significantly change over the study period. For the majority of other specialists, the prescribed volume for benzodiazepines decreased across periods. Hospice and palliative medicine specialists had the largest percent decrease, with a (b) (4) % decrease from the pre-period to the transition implementation period, and a (b) (4) % decrease from the pre-period to the post-period. A significant increase in prescription volume for benzodiazepines was observed for the other prescriber specialty group.

There was no significant change in the volume of celecoxib prescribed by pain specialists and the other prescriber specialty group over the study period. The majority of the other prescriber specialists had a decrease in the volume of celecoxib prescribed. Hospice and palliative medicine specialty had the largest percent decrease, with a (b) (4) % decrease from the pre-period to the transition implementation period, and a (b) (4) % decrease from the pre-period to the post-period.

For the IR opioids, the volume prescribed by most of the specialists remained the same between the pre-period and transition implementation period. However, the volume prescribed between the pre-period and post-period decreased for the majority of the specialists. The largest decrease ((b) (4) %) between the pre-period and the post-period was observed for the hospice and palliative medicine specialists.

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10.1.1. Conclusion

Despite the prescriber specialty, the prescription volume for the majority of the REMS products either had no significant change or significant decrease from the pre-period to the end of the study period. Few REMS products had an increase in their prescription volume.

When evaluated by prescriber specialty, the average quarterly prescription volume for the majority of the ER/LA opioid analgesics prescribed by hospice and palliative care and pain specialists remained stable over the duration of the study period. The prescription volume for the majority of the specialists significantly decreased over the study period. Dentists had the largest percent decrease in the average quarterly prescription volume for total ER/LA opioid analgesics, with a (b) (4)) decrease between the pre-period and transition implementation period, and a (b) (4)) decrease between the pre-period and post-period. An increase was observed only for the "other" prescriber specialist group; however, this was significant only for the volume prescribed between the pre-period and transition implementation period.

This retrospective cross-sectional assessment evaluates change in access to opioids covered by the class-wide REMS during the periods before, during the transition and after the implementation of the REMS. Results of this study showed that, irrespective of the prescriber specialty, the prescription volume for the majority of the REMS products either had no significant change or significantly decreased from the pre-period to the end of the study period.

For comparator products, there was a general decrease or no change in average quarterly prescription volume from pre-period to post-period for the majority of the prescriber specialties. However, the average quarterly prescription volume for benzodiazepine prescribed by the "other" prescriber specialty group increased between the pre-period and transition implementation period, as well as between the pre-period and the post-period.

10.2. Assessment of Whether Prescribers and Patients Perceive a Change in the Patients' Ability to Access ER/LA Opioid Analgesics

10.2.1. Prescribers Perception of Patients' Ability to Access ER/LA Opioid Analgesics

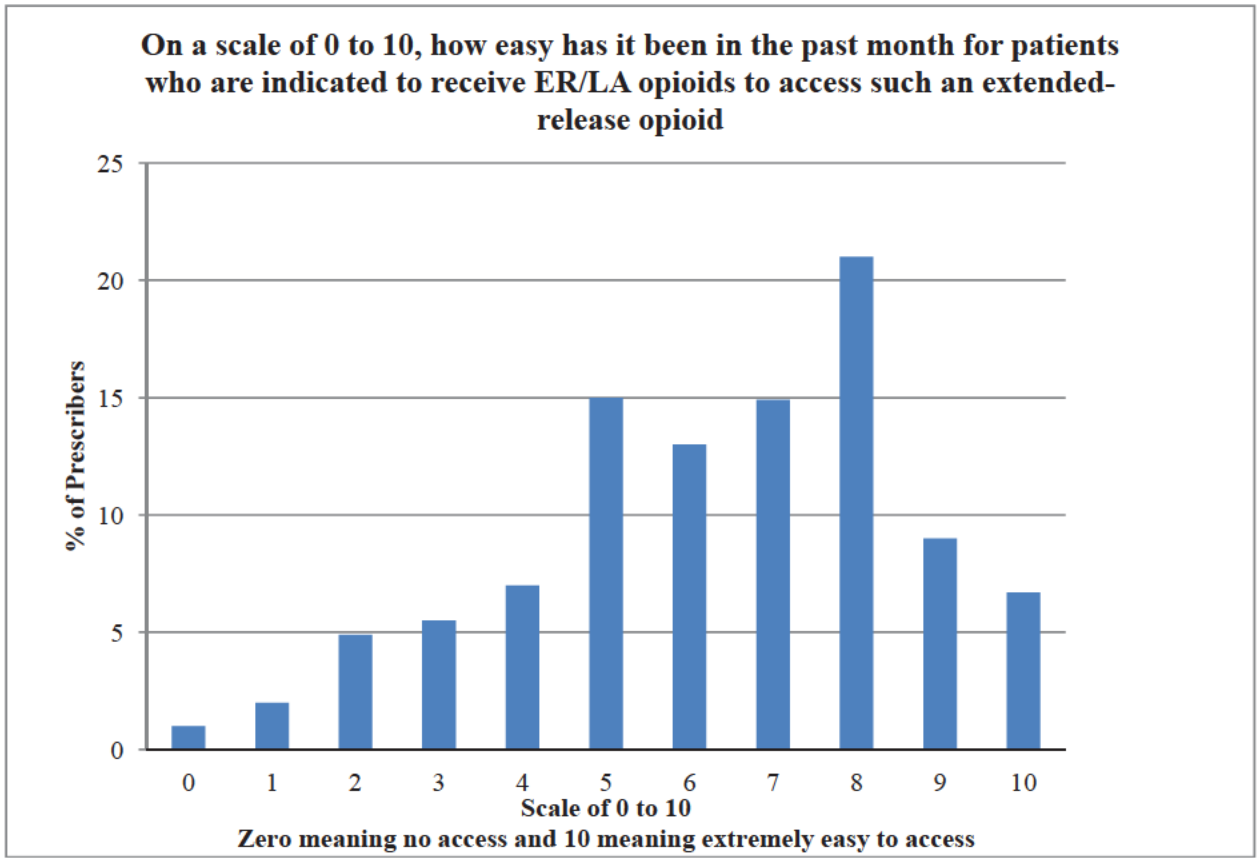
Prescribers were surveyed (in 2013) on whether they perceived a change in the patients' ability to access to ER/LA opioid analgesics because of the FDA required REMS. Survey questions were developed and pre-tested. Questions included prescribers' assessments of the ease of access to ER/LA opioid analgesics and the effect of the REMS on patient access. When asked on a scale of 0-10 (zero meaning no access and 10 meaning extremely easy to access) how easy it has been in the past month for patients who are prescribed an ER/LA opioid analgesic to access the medication, 95 (15.7%) rated access either 9 or 10 (Figure 40). Prescribers reported insurance coverage (N = 423, 69.9%) as the number one obstacle to patient access to these medicines (Table 39).

Further, a large number of prescribers indicated that, they feel the current level of access is 'about right' (N = 350, 57.9%) while 87 (14.4%) felt it is too difficult and 106 (17.5%) felt access is too easy (Table 39).

Table 39: EASE OF APPROPRIATE ACCESS TO ER/LA OPIOID ANALGESICS FOR PATIENTS

EASE OF ACCESS CAN IMPACT BOTH RISK OF OPIOID ABUSE AND PATIENTS WHO REQUIRE OPIOIDS. DO YOU THINK THE CURRENT LEVEL OF ACCESS TO ER/LA OPIOID ANALGESICS FOR PATIENTS WHO ARE INDICATED TO TAKE THEM IS:		
	N	%
Too easy	106	17.5
Too difficult	87	14.4
About right	350	57.9
I don't know	62	10.2
Total	605	100

Figure 40: Distribution of Responses Regarding Ease of Patient Access to ER/LA Opioid Analgesics, Based on a Scale of 0 To 10



When asked their opinion about the effect the FDA-required REMS has on the ability of patients who need opioids to access them, 225 (37.2%) indicated the ER/LA REMS makes it more difficult for patients to get opioids, 180 (29.8%) said that the REMS does not have an impact on patient access, and 190 (31.4%) indicated they did not know (Table 41).

Table 40: PRESCRIBERS ASSESSMENT OF PATIENT OBSTACLES TO ER/LA ACCESS

IN YOUR OPINION, WHAT HAVE THE OBSTACLES BEEN TO PATIENT ACCESS TO PRESCRIPTION OPIOIDS FOR PAIN-CONTROL MEDICAL NEEDS IN THE PAST MONTH? PLEASE SELECT ALL THAT APPLY.	N = 605	%
Insurance coverage	423	69.9
Insurance authorizations and approvals	413	68.3
Patients' ability to pay	373	61.7
Stigma regarding opioids	197	32.6
Pharmacy authorization	143	23.6
Pharmacy stocking issues	165	27.3
Physicians do not want to prescribe ER/LA opioids because they do not wish to complete REMS training	161	26.6
Patients are afraid to take ER/LA opioids because of risk warnings	125	20.7
Legal liability or malpractice concerns	247	40.8
Other	30	5.0

Table 41: PRESCRIBERS' ASSESSMENTS OF THE IMPACT OF THE FDA-REQUIRED RISK EVALUATION AND MITIGATION STRATEGY ON PATIENTS FOR ER/LA OPIOID ANALGESIC ACCESS

PRESCRIBERS' ASSESSMENTS OF THE IMPACT OF THE FDA-REQUIRED RISK EVALUATION AND MITIGATION STRATEGY (REMS)	N = 605	%
It makes it more difficult for patients to get opioids	225	37.2
It makes it easier for patients to get opioids	10	1.7
It doesn't have any impact on patient access to opioids	180	29.8
I don't know	190	31.4
Total	605	100

10.2.2. Evaluation of Changes in Access based on Patient Survey Results

10.2.2.1. Methods

To assess patient knowledge of the safe use of ER/LA opioid analgesic products following implementation of the REMS, a cross-sectional patient survey was conducted by a vendor on behalf of the RPC. The survey also assessed patient-reported satisfaction with access to treatment. Full details of the study methods are provided in Section 6, FDA Assessment Element 4.

10.2.2.2. Patient Survey Results

Among 413 survey respondents, 302 (73%) stated that they were able to obtain a prescription for ER/LA opioid analgesics from their healthcare providers when needed for pain. This did not vary by ER/LA opioid analgesic type; however, respondents who did not understand the Medication Guide or PCD, or had only one recorded ER/LA opioid analgesic dispensing less often confirmed their access to obtain a prescription (30%, 54%, and 60%, respectively). Only 52% of respondents with a KAS (i.e., proportion of knowledge questions that a respondent answered correctly) <70% confirmed access to a prescription when needed for pain. Satisfaction with their ability to get a prescription was reported by 80% of respondents, and was slightly higher for methadone users (86%). Satisfaction was reported by a lower proportion of single dispensing users (74%) and respondents with a KAS <70% (59%).

There were 336 (82%) respondents who reported general satisfaction with access to ER/LA opioid analgesic treatment, and 326 (79%) who were satisfied with their ability to get ER/LA opioid analgesics from a pharmacy. Nearly half of respondents (46%) felt that they needed to see their healthcare provider too often when more ER/LA opioid analgesics were needed. This sentiment was more common among patch users (51%) and individuals with a KAS <70% (58%).

Among 374 non-neutral respondents, compared with the 336 (90%) respondents that were satisfied with their access to ER/LA opioid analgesics, the 38 (10%) that were dissatisfied had higher income (total annual household income of at least $100,000 in 2013, 42% versus 25%), were more often non-Caucasian (13% versus 7%), and were more likely to have their ER/LA opioid analgesic prescribed by a pain specialist (71% versus 41%).

10.2.3. Patient Survey Conclusion

In a sample of commercially-insured ER/LA opioid analgesic users, the majority of respondents reported satisfaction with their access to ER/LA opioid analgesic prescriptions, their ability to obtain medication from a pharmacy, and their general access to ER/LA opioid analgesic medication. Many respondents felt that they were required to see their healthcare provider too often for more medication when needed.

As described in FDA Assessment Element 4, the generalizability of these study findings may be limited to adults similar to those in our commercially-insured, US population. Because all survey respondents have access to medical care through their private insurance, it is plausible that their experiences and satisfaction with access to ER/LA opioid analgesic treatments may differ from those individuals without similar general healthcare access. Further, it should be noted that this cross-sectional study cannot, by design, identify whether satisfaction with access to treatment has

changed since implementation of the REMS. Rather, it describes patient-reported perspectives at the time of the survey.

11. FUNCTIONAL COMPONENTS

11.1. Dear DEA-Registered Prescriber Letter 3 (DDRP Letter 3)

A series of DDRP Letters was planned as part of the prescriber outreach for the REMS.

- The first DDRP letter announced the approval of the ER/LA Opioid Analgesic REMS.
- The second DDRP letter was used to announce availability of ER/LA Opioid Analgesic REMS-related CE opportunities.

During this reporting period, a third DDRP letter (DDRP Letter 3), was used to announce the approval of the ER/LA Opioid Analgesic REMS and availability of ER/LA Opioid Analgesic REMS-related CE opportunities to newly DEA-registered Schedule II and III prescribers.

The target audience for the letter was all DEA-registered prescribers, regardless of discipline/degree. The REMS Communication Vendor that distributed the first two DDRP letters delivered this third letter to the targeted audience using the same methods as it had for delivery of DDRP Letters 1 and 2. The letter was distributed electronically by e-mail, via facsimile and via United States Postal Service (USPS). The REMS Communication Vendor used its proprietary database of HCPs who have "opted in" to receive electronic communications on drug safety alerts and REMS Communication Letters. The database of opt-in prescribers was matched to the list of DEA-registered prescribers to identify prescribers in the opt-in database to receive electronic communications. Prescribers on the DEA master registration file (DEA file), but not on the REMS Communication Vendor opt-in list, received the letter through USPS mail. Addresses for mailing the letters were obtained from the DEA list or from matching the DEA list to the American Medical Association (AMA) list of physicians. In cases where the electronic communication was undeliverable, the prescribers were sent a letter by direct mail to the address indicated on the DEA or AMA file within 30 days after sending the electronic communication.

DEA-registered Schedule II and III unique prescribers within the DEA file were identified. After removal of duplicate registrations, registrations with address errors, and records from deceased registrants, the target registrant audience for receipt of DDRP Letter 3, as of July 1, 2013, totaled 84,009.

There is currently no reliable method for tracking accurate volumes of unopened/unread e-mails. Industry standard e-mail exchange services/programs (e.g., Microsoft Exchange, Unix Sendmail) have limited ability to accurately track and report when an e-mail is opened or read. An affirmative action on the part of the recipient (i.e., downloading images or clicking on a hyperlink) is required to enable tracking of opening rates. It is not possible to know when an e-mail is read in the absence of these actions. In addition, many e-mail programs/services block images and hyperlinks by default as protection against spam and virus attacks. As well, many recipients do not download images as a matter of common practice for the same reasons. Finally, when the critical safety information for DDRP Letters and other REMS communications is embedded within the body of the communication, the recipient may choose to read some or all of it in a preview pane without ever downloading images or clicking on any hyperlinks. As a result, it is not currently possible to accurately know when the content of an e-mail is read.

Electronic (e-mail and facsimile) communications for DDPR Letter 3 were initiated on July 8, 2013, 1 day prior to the indicated deadline. Mailing of hardcopy communications was initiated on July 9, 2013. The sending of DDRP Letter 3 by all routes was completed on August 27, 2013. DDRP Letter 3 was posted on the ER/LA Opioid Analgesics REMS website on August 14, 2013.

During this reporting period, DDRP Letter 3 (Appendix I) was sent to all new DEA registrants and a number of registered hospitals/clinics. Of the 84,009 registrants targeted, a total of 78,888 registrants were reached, of which 1,724 letters were delivered by e-mail, 1,140 by fax, and 76,024 by USPS.

In addition, the Communication Vendor attempted to send hard copy DDRP Letter 3 by USPS to 799 hospitals/clinic registrants, of which 760 (95.1%) were delivered.

Undelivered letters to all recipients are put through the following 3 step process before considered undeliverable

1. Search the Communications Vendor Practitioners Database to identify potential secondary methods of contact and execute the communication.
2. Use several additional data assets including the AMA, Group Practice and other files to identify potential secondary methods of contact and execute the communication.
3. The Communications Vendor commits to using all available avenues to secure secondary communication methods for undeliverable mail.

11.1.1. Conclusion

The performance goal was successfully met for ensuring that DDRP Letter 3 was sent at least annually from the date of initial approval of the REMS. Of the 84,009 prescribers that were targeted, 93.9% of DDRP Letter 3 were delivered.

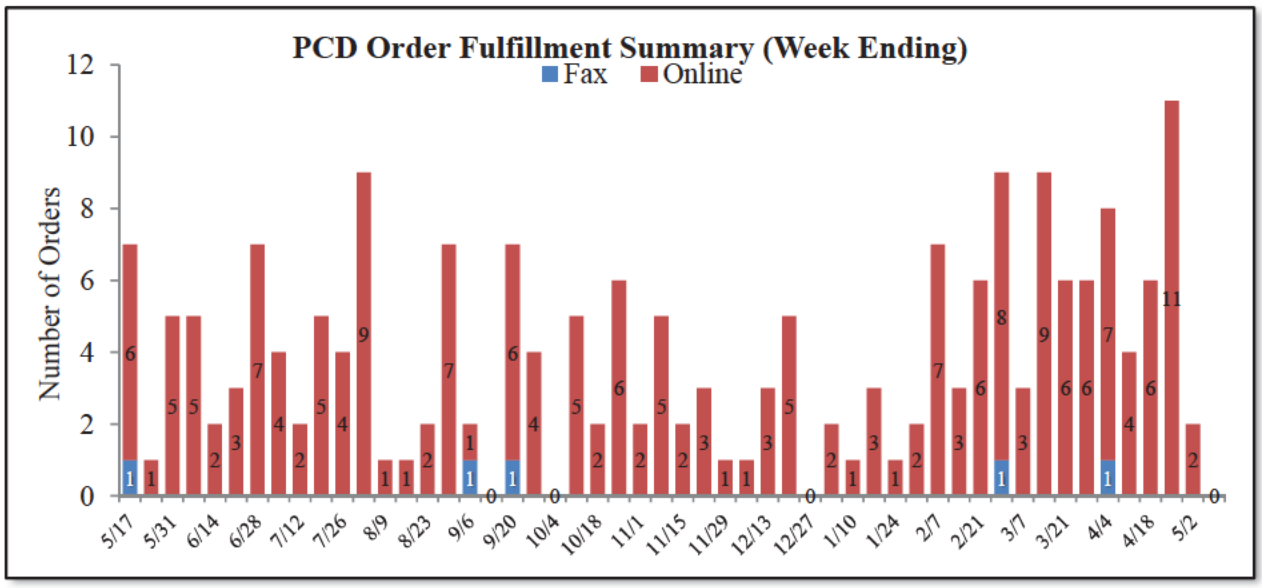
11.2. Patient Counseling Document (PCD)

The PCD on ER/LA opioid analgesics is a tool to facilitate important discussions between prescribers and patients for whom an ER/LA opioid analgesic is being prescribed. The PCD contains important safety information about the drug products covered by the REMS. Key messages outlined in the PCD include the importance of taking ER/LA opioid analgesics exactly as prescribed, the need to store ER/LA opioid analgesics safely and securely—out of the reach of children, pets, and household acquaintances—to avoid risks from unintended exposure, the importance of not sharing these medications, even if someone has the same symptoms as the patient, and the proper methods of disposal of unneeded ER/LA opioid analgesics. Additionally, the PCD has been translated into Spanish.

A Portable Document Format version of the PCD was posted on the website on July 23, 2012 (website launch). During this reporting period, from May 10, 2013 to May 9, 2014, the PCD has been downloaded (in order to view you must download) 2,461 times, and the Spanish PCD has been downloaded 196 times. No orders were placed for the PCD during this reporting period via the ER/LA Opioid Analgesic REMS Call Center. The PCD (Appendix J) was also included as an attachment in DDRP Letter 3 (Appendix I) communications (electronic and hardcopy) and is provided in the appendix of this report for reference.

Between May 10, 2013 and May 9, 2014, 202 PCD orders were placed and successfully fulfilled representing 520 pads. A total of 197 orders were placed online and 5 by fax. The PCD Portal Vendor collects and batches orders for pick-up and packing from inventoried materials every Friday. Orders received prior to 5:00 p.m. (Central Time) on Thursday ship on the following day.

Figure 41: PCD Order Fulfillment through PCD Portal during This Reporting Period, May 10, 2013 – May 9, 2014 (N = 202 Orders)



11.2.1. Conclusion

The PCD continues to be readily accessible to all stakeholders through multiple modalities.

11.3. REMS Call Center

Per the Twelve-Month FDA Assessment Report, the FDA determined that the request to modify the centralized Call Center to utilize an interactive voice mail/message retrieval system (IVRS) was acceptable. As of March 19, 2014, the ER/LA Opioid Analgesics REMS Program modified the centralized Call Center to utilize the IVRS, and user acceptance testing was conducted on the IVRS by RPC member companies prior to going live. The IVRS is available 24 hours/7 days a week and utilizes the same toll-free telephone number that was established for the centralized Call Center. The initial message for the IVRS and the initial message for each stakeholder type contain general REMS program information, including the web address for the REMS website.

The IVRS guides callers through a series of prompts for general REMS questions and specific FAQs for each stakeholder type. Using data collected from incoming calls to the previous centralized Call Center, the most often selected Frequently Asked Questions (FAQs) and responses for each stakeholder type are recorded, and stakeholders have the option to leave a voicemail if their questions are not addressed via the FAQs. The IVRS has been fully functional since its launch on March 19, 2014.

11.3.1. Utilization Data since IVRS Go-Live (03/20/2014 – 05/08/2014)

Since transitioning from the centralized Call Center to the IVRS, a total of 74 incoming calls were received, excluding test calls or wrong numbers, for an average of nine (9) calls per week. Of the total number of incoming calls, sixty-eight (68) stakeholders utilized FAQs by stakeholder type, and six (6) stakeholders left a voicemail message to be returned by an IVRS Communicator. Of the six (6) stakeholders requesting a callback, there were five (5) licensed prescribers and one (1) patient, consumer, or caregiver. From the early data, it appears that most callers had their questions addressed by the FAQ stakeholder type. RPC will continue to track utilization data for the IVRS.

Table 42: IVRS UTILIZATION DATA (Launch Through May 8, 2014)

DATE	TOTAL INCOMING CALLS	TOTAL CALLS NAVIGATED TO FAQ	EXTERNAL STAKEHOLDER REQUESTING A CALLBACK
Week Ending 3/20/14	7	7	0
Week Ending 3/27/14	10	9	1
Week Ending 4/3/14	22	19	3
Week Ending 4/10/14	8	8	0
Week Ending 4/17/14	10	10	0
Week Ending 4/24/14	5	4	1
Week Ending 5/02/14	9	8	1
Week Ending 5/08/14	3	3	0
TOTAL	74	68	6

11.3.2. Call Center Conclusion

The centralized Call Center continues to be accessible to all stakeholder types. The daily maintenance of the IVRS has shown no system interruptions to date. Monitoring will continue and FAQs will be updated based on trends in stakeholder feedback.

12. SUMMARY AND CONCLUSION

RPC has met all REMS requirements to date.

- There has been an unprecedented ramp-up of CE availability involving strong collaboration between industry and CE community.
- RPC has funded numerous providers with 262 CE activities.
- 20,345 prescribers have completed the RPC-supported, REMS-compliant training as of February 28, 2014.
    - While 20,345 prescriber completers to date would not suggest attainment of the goal of 80,000 by February 28, 2015 under the assumption of a linear rate, the CE community expects a non-linear and increasing rate of prescribers completing REMS-compliant training.
    - The RPC is aware that many more than 20,345 HCPs completed the REMS-compliant education. While not includable in the metrics, these HCPs may play important roles in disseminating important information to the public. For instance, nurses who care for ER/LA opioid patients and provide important counseling on appropriate use of medications may take the training but would not be counted. Another example would be doctors who prescribe IR opioids, but not ER/LA opioids. Other completers may take the training to learn about appropriate prescribing before starting to prescribe ER/LA opioids.
    - RPC is actively exploring efforts to increase awareness of and participation in REMS education.
- Patient Survey results indicate that the REMS requirement to make available a medication guide has been achieved, but use of the PCD can be improved.
    - A high level of patients report receiving the medication guide, reading it, and understanding it.
    - Patients have a strong understanding as reflected by high KAS scores, the proportion of questions concerning the safe use and storage of ER/LA opioids answered correctly had a mean score of 85.6%.Improvements are possible in use of PCD. The PCD is not highly recognized or used.
- Surveillance monitoring results indicate that for the most part the REMS has had a positive effect.
    - Poison center results show a marked improvement in outcomes, including decreases in abuse, misuse, as well as calls for major medical outcomes, hospitalizations, and deaths in the six months of the active period compared to the two year pre-implementation period. These include:
        - Poison center abuse exposures decreased statistically significantly by 42.6%. This decrease was much larger than comparator groups (29.0% for IR opioids and 15.1% for prescription stimulants).

- Among adolescents, abuse exposures decreased statistically significantly by 64.6%, while that for IR opioids and prescription stimulants decreased by 37.5% and 32.3%, respectively.

- Poison center misuse exposures decreased statistically significantly by 22.8% in the six months of the active period compared to the two year pre-implementation period. This decrease was much larger than comparator groups (decreases of 15.1% for IR opioids and 3.0% for prescription stimulants).
- The rate of calls to poison centers for major medical outcomes, hospitalizations, or deaths decreased significantly by 28.6%. This was greater than that for IR opioids (20.3% decrease) and prescription stimulants (1.7% decrease).

- Surveillance monitoring of abuse in substance abuse treatment center showed positive results overall, albeit with one important exception.
  - Reported abuse in the RMPDC RADARS System decreased significantly by 44.6% as compared to a decrease of 5.6% for IR opioids.
  - However, reported abuse in the NAVIPPRO ASI-MV System increased significantly by 22.0% as compared to an increase of 16.4% for IR opioids and an increase of 0.4% for benzodiazepines.
  - Reported abuse in the NAVIPPRO CHAT System among adolescents showed a non-significant decrease of 11.1% for ER/LA opioids from the pre-REMS baseline to the active period as compared to a decrease of 3.0% for IR opioids and an increase of 9.9% for benzodiazepines.
  - NAVIPPRO ASI-MV System showed source of procurement of ER/LA opioids for purposes of abuse changed significantly in a manner consistent with the expected impact of the REMS.
    - The only source of procurement that increased was the Illicit source (20.1%), whereas the Own prescription (-19.6%), My own prescription from several doctors (-43.9%), and Family member or friend (-7.2%) sources decreased.
  - A possible explanation of the difference in results between RMPDC RADARS and NAVIPPRO ASI-MV is the substantial variability in the results across geographic regions as well as by private versus public treatment center. In addition, NAVIPPRO results relate to cases of abuse per 100 ASI-MV assessments, which include subjects seeking treatment for opioid abuse as well as for abuse of other substances. Changes in the number of subjects seeking treatment for non-opioid abuse such marijuana during the three periods could also explain the results.

- Assessment of drug utilization showed changes that are consistent with the desired outcomes of the REMS. These include:
  - Although there were small reductions in prescribing ER/LA opioid analgesics and other analgesics, there was a noted increase in prescribing of benzodiazepines.

        - IMS prescription data showed a decrease of 3.2% in prescriptions of ER/LA opioid analgesics as compared to a 3.6% decrease for IR opioids, a 4.9% decrease for celecoxib, and a 4.2% increase for benzodiazepines.
    - Reductions in prescriptions for younger age groups, while those for older age groups increased.
        - IMS prescription data showed that prescriptions in the 0 - 18 category decreased by 13.6% and those in the 19 - 40 category decreased by 16.3%, while those in the 65+ category prescriptions increased by 6.4%.
    - Reductions were largest in those specialties that were hypothesized to be more affected by the REMS than other specialties.
        - Prescriptions by dentists decreased by 43.2%, those by emergency medicine physicians decreased by 22.8%, and those by primary care providers decreased by 11.3%. On the other hand, prescriptions among pain specialists increased by 0.9% and prescriptions by hospice and palliative care specialists decreased by 5.4%, while those for oncologists decreased by 8.9%.
    - Prescriptions paid for by cash (-13.9%) and Medicaid (-35.7%) decreased but those by Medicare increased (18.1%).
    - The average number of tablets per prescription decreased significantly from 92.0 to 85.4. The average number of patches per prescription decreased slightly from 10.7 to 10.3.
- Metrics of appropriate prescribing behaviors showed a reduction in prescriptions of ER/LA opioids to non-opioid tolerant patients that are indicated only for opioid tolerant patients.
    - The proportion of patients who started prescriptions of fentanyl TD who were opioid non-tolerant decreased by 5.6% from the pre-period (12.4%) to the post-period (11.7%), which was statistically significant.
    - The proportion of patients who started prescriptions of ER hydromorphone who were opioid non-tolerant by decreased by 35.4% from the pre-period (16.6%) to the post-period (10.8%), which was statistically significant.
- There is no indication that the REMS is having a negative impact on access from results of patients and prescribers surveys.
- A third DDRP letter (DDRP Letter 3) were sent to 78,888 newly DEA-registered Schedule II and III prescribers and a number of registered hospitals/clinics to announce the approval of the ER/LA Opioid Analgesic REMS and availability of ER/LA Opioid Analgesic REMS-related CE opportunities.
- The PCD was downloaded (in order to view you must download) 2,461 times, and the Spanish PCD has been downloaded 196 times. Additionally, 202 PCD orders were placed and successfully fulfilled representing 520 pads.
- The centralized Call Center was modified to utilize an IVRS. A total of 74 incoming calls have been received and no system interruptions have been reported to date.

- Overall the REMS assessments indicate substantial improvements in various indicators, including patient knowledge; misuse, abuse, and major medical outcomes including death; as well as prescribing behaviors, all while preserving access to valuable pain therapies.
- Since many interventions targeting opioid analgesics occurred during the time period of the REMS, the aforementioned effects cannot be attributed specifically to the REMS. However, the REMS was implemented as an integral part of the President's 4-part plan to decrease opioid abuse and misuse that encompassed many of these interventions.
    - As part of the President's plan, the REMS appears to have made a positive impact on its intended goals.
    - The RPC will continue to implement the REMS to build upon the positive impact seen to date.

[1] Dunn KM, Sanders KW, Rutter CM, Banta-Green CJ, Merrill JO, Sullivan MD, et al. Opioid prescriptions for chronic pain and overdose: a cohort study. Ann Inter Med. 2010;152(2):85-92.

[2] Substance Abuse and Mental Health Services Administration. Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings; 2012. Available at: http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.htm). Accessed on April 2014.

[3] Johnston LD, O'Malley PM, Miech RA, Bachman JG, Schulenberg JE. Monitoring the Future national survey results on drug use: 1975-2013: Overview, key findings on adolescent drug use. Ann Arbor: Institute for Social Research, The University of Michigan; 2014:84. http://monitoringthefuture.org/pubs/monographs/mtf-overview2013.pdf

[4] Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future national results on adolescent drug use: overview of key findings, 2012. Ann Arbor: Institute for Social Research, The University of Michigan; 2013:83. http://monitoringthefuture.org/pubs/monographs/mtf-overview2012.pdf

[5] Johnston LD, O'Malley PM, Bachman JG, Schulenberg JE. Monitoring the Future national survey results on drug use, 1975-2012. Volume I: secondary school students. Ann Arbor: Institute for Social Research, The University of Michigan; 2013:604. http://monitoringthefuture.org/pubs/monographs/mtf-vol1_2012.pdf

[6] Johnston LD, O'Malley PM, Bachman J G, Schulenberg JE. Monitoring the Future national survey results on drug use, 1975-2012. Volume II: college students and adults ages 19-50. Ann Arbor: Institute for Social Research, The University of Michigan; 2013:400. http://monitoringthefuture.org/pubs/monographs/mtf-vol2_2012.pdf

[7] Center for Behavioral Health Statistics and Quality. (2012a). *Comparing and evaluating youth substance use estimates from the National Survey on Drug Use and Health and other surveys* (HHS Publication No. SMA 12-4727, Methodology Series M-9). Rockville, MD: Substance Abuse and Mental Health Services Administration.

[8] Gfroerer, J., Wright, D., & Kopstein, A. (1997b). Prevalence of youth substance use: The impact of methodological differences between two national surveys. *Drug and Alcohol Dependence, 47*, 19-30.

[9] Biondo, G., Chilcoat, H.D. (2013). Discrepancies in prevalence estimates in two national surveys for nonmedical use of a specified opioid product versus any prescription pain reliever. *Drug and Alcohol Dependence, 134*, 396-400.

[10] Katz N, Panas L, Kim M, Audet AD, Bilansky A, Eadie J, et al. Usefulness of prescription monitoring programs for surveillance--analysis of Schedule II opioid prescription data in Massachusetts, 1996-2006. Pharmacoepidemiol Drug Saf 2010 Feb;19(2):115-123.

[11] Pradel V, Frauger E, Thirion X, Ronfle E, Lapierre V, Masut A, et al. Impact of a prescription monitoring program on doctor-shopping for high dosage buprenorphine. Pharmacoepidemiol Drug Saf. 2009;18:36-43.

[12] Pradel V, Delga C, Rouby F, Micallef J, Lapeyre-Mestre M. Assessment of abuse potential of benzodiazepines from a prescription database using 'doctor-shopping' as an indicator. CNS Drugs. 2010;24 (7): 611-620.

13. APPENDIX

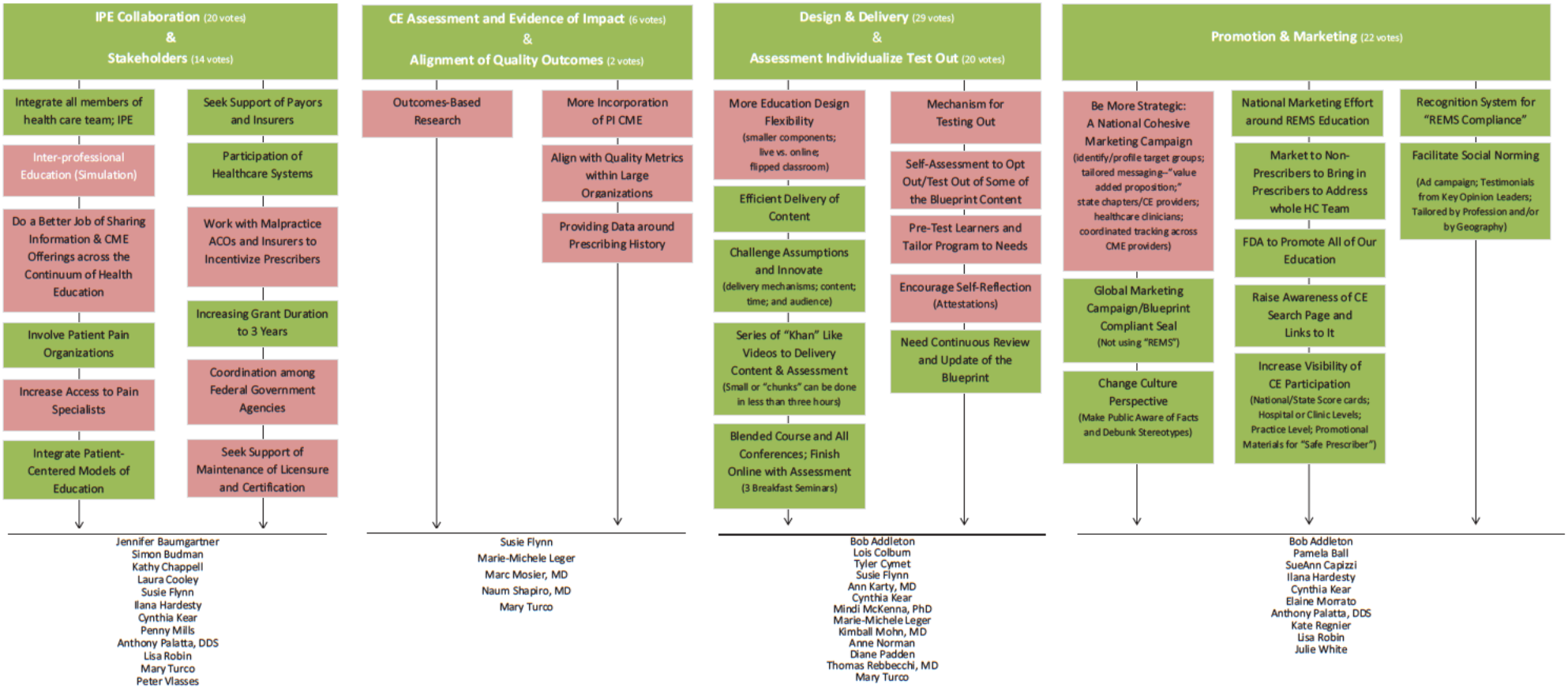
Appendix A - Strategies and Interventions

Interventions and Strategies

CCCE REMS Meeting – February 24, 2014

Feasibility

Importance



Appendix B - 2014 RFA

REQUEST FOR (GRANT) APPLICATIONS (RFA)

Overview Information

Sponsoring Organization	Risk Evaluation and Mitigation Strategy Program Companies (RPC)
RFA Title	Extended-Release and Long-Acting Opioid Analgesics: Risk Evaluation and Mitigation Strategy (REMS)
RFA Code	ER/LA 040314
RFA Goal	The goal of this RFA is to support high-quality REMS-compliant Continuing Education (CE) designed to assist in ensuring that the benefits of Extended Release/Long-Acting (ER/LA) opioid analgesics outweigh the risks (in patients whose clinicians have determined ER/LA opioid analgesics to be an appropriate treatment option). The mechanism by which this is intended to occur is by educating healthcare providers (HCPs), **particularly, as specified by the FDA REMS goals, those HCPs who prescribe ER/LA opioid analgesics**. The education will be based on the *Food & Drug Administration (FDA) Blueprint for Prescriber Education for ER/LA Opioid Analgesics* (FDA Blueprint or Blueprint), with the aim to optimize both knowledge acquisition and the translation of that knowledge into practice. Successful proposals will detail educational initiatives that ultimately assist in positively impacting safe and appropriate patient care while meeting all REMS requirements detailed in the next section.
RFA Elements Essential to Meet REMS-Compliant CE Requirements	**Educational design of proposed CE activities must incorporate all of the requirements for REMS-compliant CE training:** • All activities within each educational program must cover all FDA Blueprint elements contained within the six sections of the document. • All activities must include an assessment that covers all six sections of the FDA Blueprint. Preferred consideration will be given to grant applications that integrate the assessment throughout the activity in order to increase the likelihood of learners completing the assessment, an FDA requirement for the learner to be counted toward the REMS goals. (Please note: The related MedBiquitous specification states that "successfully completing" the REMS education means "Completing all components of an education activity and meeting education provider's

	criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation." For a full list of REMS-related definitions developed by the MedBiquitous Working Group, please see Appendix A. • The educational activities are subject to independent audit by the CE Accrediting Bodies. ➢ This audit is intended to occur prior to learners encountering the activity, and as such, Providers conducting CE under RPC-supported grants agree to submit all materials to their Accrediting Body at least 45 days before the activity start date. ➢ RPC-supported Providers whose activities are not selected for audit by the Accrediting Bodies agree to provide documentation to RPC in which a medical expert, independent of, but chosen by the Provider, attests that the activity meets the REMS-compliant CE requirements. • The activities must be conducted in accordance with the standards for accredited CE set by the appropriate Accrediting Body or Bodies (ACCME, AOA, AANP, AMA, AAFP, or ADA CERP). **FDA has set explicit definitions and goals regarding the primary target audience for REMS education and how many learners from this target audience will complete REMS-compliant CE by certain time frames (see Section 1). Since RPC is held responsible by FDA for meeting these goals, the Provider's proposed approach to engaging the primary target audience to "complete" REMS-compliant CE is a key criterion on which all proposals will be evaluated.**
Key Dates	RFA Posted: March 19th, 2014 Application Due Date: April 30th, 2014 Award Notification Date: Q3 2014
RFA Document Parameters	Grant applicants should submit applications in MS Word.
Submission Link	Grant applications must be submitted via the Grant Management System (GMS), which will be accepting new grant applications in response to this RFA beginning on **March 21st, 2014**. The GMS may be accessed by way of

	the RPC website at www.ER-LA-OpioidREMS.com via the right-hand-side link, “Continuing Education Provider Information.” For this specific RFA, the appropriate RFA code is **RFA 040314**.
Questions on RFA?	Please contact Polaris Grant Coordinator Brad Hill. Phone: 1-800-376-9756; Email: grants@er-la-opioidrems.com

Table of Contents

Section 1: Scope of Problem and Background on ER/LA Opioid REMS

Scope of the Problem

According to the 2011 Institute of Medicine (IOM) Report "*Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research,"* as many as 100 million adults in the US report having a common chronic pain condition, exceeding the number affected by heart disease, cancer, and diabetes.

The economic burden of pain to society is staggering. The IOM Report suggests that the annual health economic impact of pain represents a $560 billion to $635 billion burden to the US (in 2010 dollars) and the morbidity and disability associated with chronic pain represents a significant public health issue. At the same time, however, the misuse and abuse of opioid analgesics, one class of medications used for managing moderate-to-severe chronic pain, has emerged as a major public health/patient safety problem.

The most recent national data available indicate that:

- At the patient-health level, numerous clinical reports suggest that chronic pain remains undertreated; the percentage of patients receiving appropriate and adequate treatment has been reported to be as low as 10% to 25%.[1]

- Patients with chronic pain have difficulty finding physicians who can effectively treat their pain, with nearly 50% of patients changing physicians at least once and nearly 25% making at least three physician changes.1

- Based on the 2012 National Survey on Drug Use and Health, public health experts estimate more than 37 million Americans age 12 and older used an immediate release (IR) or ER/LA opioid analgesic for non-medical use some time in their life—an increase from about 30 million in 2002.[2]

- In 2012, there were more than 366,000 emergency department visits involving nonmedical use of opioid analgesics.[1]

- 257 million prescriptions for opioids were dispensed in 2009—a 48% increase compared with figures for 2000.[3]

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[1] Drug Abuse Warning Network 2011 http://www.samhsa.gov/data/2k13/DAWN2k11ED/DAWN2k11ED.htm#5 Accessed January 2014

[2] Substance Abuse and Mental Health Services Administration. 2012. *Results from the 2012 National Survey on Drug Use and Health: Detailed Table*, Table 1.54A.a. Rockville, MD.
http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.htm

[3] Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data*

- Total societal costs of prescription opioid abuse, including costs related to workplace, healthcare, and criminal justice, were estimated at $55.7 billion in 2009.[4]

ER/LA Opioid REMS and the REMS Program Companies

The ER/LA Opioid Analgesics REMS is designed to ensure that the benefits of ER/LA opioid analgesics outweigh the risks (in patients whose clinicians have determined ER/LA opioid analgesics to be an appropriate treatment option). The goal of this REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes of concern include addiction, unintentional overdose, and death.[5]

The FDA has developed a Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics, which is posted on the FDA website for use by accredited CE Providers to develop the actual CE activities. (http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf)

The FDA determined that a single shared system was to be implemented for all products within this drug class. As a result, the RPC was created, comprising the 19 companies[6] that have ER/LA opioid products. RPC-supported REMS education will be provided through accredited continuing education (CE) activities supported by independent educational grants from the RPC. For a complete listing of the RPC member companies, see www.ER-LA-OpioidREMS.com.

Desired Outcomes and FDA Expectations of RPC-Supported REMS Education

The desired outcome of ER/LA opioid analgesic REMS-compliant CE is to increase understanding of appropriate patient assessment and prescribing practices, as well as other information that can help reduce misuse, abuse, and overdose deaths associated with ER/LA opioids analgesics. Education that is focused on the expected results outlined below should result in healthcare professionals incorporating practices that can assist in maintaining that the benefits of opioid analgesic medications outweigh the risks.

The expected results of the REMS education as described by the FDA in the FDA Blueprint introductory section are that prescribers of ER/LA opioid analgesics will:

- Understand how to assess patients for treatment with ER/LA opioid analgesics

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Brief, *No 81*. December 2011. Hyattsville, MD. http://www.cdc.gov/nchs/data/databriefs/db81.pdf. Accessed on March30, 2012.

[4] Birnbaum, Howard G., Alan G. White, Matt Schiller, Tracy Waldman, Jody M. Cleveland, and Carl L. Roland. "Societal Costs of Prescription Opioid Abuse, Dependence, and Misuse in the United States." *Pain Medicine* 12, no. 4 (2011): 657–667.

[5] Adapted from the FDA Approved ER/LA Opioid Analgesics REMS document (October 2012 version). ER/LA Opioid Analgesics REMS (http://www.fda.gov/downloads/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/UCM311290.pdf)

[6] As of March 2013

- Be familiar with how to initiate therapy, modify dose, and discontinue use of ER/LA opioid analgesics

- Be knowledgeable about how to manage ongoing therapy with ER/LA opioid analgesics

- Know how to counsel patients and caregivers about the safe use of ER/LA opioid analgesics, including proper storage and disposal

- Be familiar with general and product-specific drug information concerning ER/LA opioid analgesics

In order to be REMS-compliant, and therefore eligible for educational grant support from the RPC, the education must address all elements of the FDA Blueprint. (http://www.fda.gov/downloads/drugs/drugsafety/informationbydrugclass/ucm277916.pdf) While these are the overall FDA REMS expectations, successful proposals should translate these into CE-compliant objectives and outcomes.

The FDA has set goals/time frames for the number of ER/LA opioid prescribers completing REMS-compliant CE.

The first FDA-mandated CE goal[7] stipulates that 80,000 ER/LA opioid analgesic prescribers will have successfully completed REMS-compliant CE, as defined at the bottom of page 1, by February 28, 2015.

Subsequent goals established by the FDA in the REMS are:

- ***160,000 ER/LA opioid analgesic prescribers will have successfully completed REMS-compliant CE by February 28, 2016.***

- ***192,000 ER/LA opioid analgesic prescribers will have successfully completed REMS-compliant CE by February 28, 2017.***

Definitions and Clarifications:

As part of the REMS, the FDA characterized prescribers that were the intended audience for the REMS CE. CE-compliant definitions were then developed and finalized by the MedBiquitous Working Group, which included representation from Accreditors, national CE Provider organizations, Providers, FDA, RPC, and other REMS CE-related stakeholders. For a full list of definitions developed by the MedBiquitous Working Group, please see Appendix A.

Key definitions relevant to this RFA include:

[7] FDA. "Blueprint for Prescriber Education for Extended-release and Long-acting Opioid Analgesics," 2013.

- ER/LA opioid prescriber: "An individual clinician who is registered with the DEA (Drug Enforcement Agency) to prescribe schedule 2 and/or 3 controlled substances and has written at least one ER/LA opioid script in the past year." (Please see MedBiquitous website for reference: http://www.medbiq.org/mems/definitions)
  Note: To be counted toward these FDA mandated CE-goals, a learner must meet the MedBiquitous definition of "prescribers successfully completing"[8] all components of an educational activity.
- "Prescribers successfully completing" a REMS educational activity: "FDA REMS defined ER/LA opioid prescribers that have completed all components of an educational activity and met the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation." (Please see definition of "prescribers_successfully _completing" at the MedBiquitous website: http://medbiq.org/mems/definitions)

The FDA Blueprint and additional information on REMS-compliant CE can be found on the RPC website at www.ER-LA-OpioidREMS.com.

[8]MedBiquitous Medical Education Metrics Definitions http://medbiq.org/mems/definitions. Accessed January 2014.

Section 2: Funding Opportunity and Award Information

Anticipated Number of Awards	The number of submissions and their ability to address the full FDA Blueprint and assessment requirements will determine the number of grants awarded in 2014. Because of the need to engage large numbers of learners in "successfully completing" all components of the educational activities described in the MedBiquitous definition,[8] grant applicants are encouraged to incorporate effective co-sponsorships, partnerships, and/or collaborations among organizations that have already established ongoing relationships/regular communication with the primary audience for REMS CE. (See Section 4, #5).
Award Budget	***Budgets should be consistent with the realistic total number of ER/LA opioid prescribers that the Provider estimates will complete both education on the full FDA Blueprint and an assessment covering all six sections of the Blueprint.*** Preference will be given to cost-effective, collaborative, and innovative educational activities that minimize redundancies in development costs and leverage potential synergies. Providers may propose budget models with multiple levels of support, which would enable RPC to award funds for a subset of activities. **Note:** The RPC will ONLY support budget proposals in full compliance with Transparency Reports and Reporting of Physician Ownership Interests provisions of the Social Security Act (42 U.S.C. 1320a-7h) (Physician Payment "Sunshine Act" or "Open Payments"). • Providers will ensure that no grant funds from the RPC will be used for payments associated with the provision of food, beverages, travel, or lodging for meeting attendees.
Award Project Period	Because of the need to report ongoing progress to the FDA, the expectations are that: • The initial activity within the proposed program must begin within four months of signing the Letter of Agreement (LOA). • If an educational program contains multiple activities, all activities

	must start within twelve months of signing the LOA. • Any portion of a proposal with a start date more than twelve months beyond the execution of the initial LOA will require a separate grant application (although an activity that begins within twelve months of LOA execution may overlap two calendar years). **Note:** The RPC is open to receiving proposals to extend grant support for CE Providers who have already been awarded funding from the RPC. • Based on the number of applications received, it is the intent of the RPC to complete the review process and notify selected grantees approximately in the middle of the third quarter, 2014.
Other Award Information	To optimize the learning opportunities, the RPC intends to fund multiple grant applications from different Accredited Providers and educational partners with different, yet complementary, initiatives. Preference will be given to those grant requests that permit the RPC to support multiple high-quality, diverse programs that will enable achievement of the education participation goals and outcomes as described in the FDA-approved ER/LA Opioid REMS. Grant applications will be considered that demonstrate how the proposed education will fully meet or exceed the criteria for being REMS-compliant, are cost-effective for the scope of the proposal, and satisfy the RFA Criteria outlined in Section 4 (e.g., innovation, number of ER/LA opioid prescribers expected to complete all components of the REMS-compliant CE, etc.).

Section 3: Applicant Eligibility Criteria

- ❒ The Requestor must be an Accredited Provider who will serve as the Provider of Record for the proposed activities.

- ❒ The Requestor must be accredited to provide CE by a national accrediting body (e.g., ACCME, AAFP, AANP, AAPA, ACPE, ADA, ANCC, AOA, or equivalent accrediting body) or by an official state accrediting agency, and must demonstrate that their organization is in good standing at the time of submission.

- ❒ The Requestor must have demonstrated capabilities in the design and successful implementation of innovative, interactive, engaging, multimodal educational activities, and effective communication skills, as evidenced by solid partnerships and collaborations.

Section 4: RFA Submission Information

Grant proposals must include *all of the following components;* Providers should use the below numbered sections in their response submission, following the outline below.

	Application Component	Description
1	**Provider of Record**	Name of Accredited Provider and person(s) responsible for this project including contact information
2	**Partner Organizations**	Name of any partner organizations involved with the proposed education, along with roles/responsibilities, and contact information
3	**Overview of Proposed Educational Program**	A one (1) to two (2) page summary description of overall project goals, target audience, findings from needs assessment, proposed educational activities to fill gaps identified in the needs assessment, method for measuring outcomes, and amount of grant funds being sought
4	**Faculty Selection Criteria/Team Member Qualifications**	• Description of methods and criteria used to select faculty, and/or individuals involved in the development and implementation of proposed educational initiatives • Description and qualifications of the members of the team responsible for implementing the project
5	**Audience(s)**	The primary audience for REMS CE, as outlined by the FDA, are clinicians who are registered with the DEA, eligible to prescribe schedule 2 or 3 drugs, and have written at least one ER/LA opioid prescription in the past year. Other audiences, who care for patients who require these medications in order to manage their pain, may be encouraged to participate in the educational activities. Within this broadly defined target audience, specify clearly your *target audience(s)*. Why this particular audience? What expertise do you have both reaching this audience and motivating them to "successfully complete" all components of your educational program (including assessment of learning)?

	Application Component	Description
6	**Scope/Populations**	Specify the scope of your educational program: • National • Regional (Multi-City, Multi-State) • State • Health System or Integrated Health System • Hospital or Medical Center • Other Community Practice Collaboratives
7	**Needs Assessment**	Needs assessment should be concise, properly referenced and include one or more of the following: (a) Evidence of knowledge and/or practice gaps of your target audience in the geographic area where the proposed program will occur, and/or in general audience where proposed program will be implemented (i.e., primary care vs. specialist). (b) Results from any surveys or assessments you have executed that provide greater detail of the knowledge and/or practice gaps of your specific target audience beyond what you provided for (a). (c) Results from any surveys or assessments you have executed with your specific target audience, where the survey tool was *specifically based on the FDA Blueprint.*

	Application Component	Description
8	**Description of Educational Program & Design** **Note: See Section 5 for details on how proposals will be reviewed and evaluated**	Detailed description of proposed educational program and its activities, and how it will: • Align with all elements of the FDA Blueprint. • Meet all REMS-compliant CE requirements (See Overview Information). • Meet the goals and close the gaps in knowledge, competence, and/or performance for your target audience based on your needs assessment. • Be based on adult learning principles, utilize instructional design principles, and employ best educational and practices/methods, so as to optimize both knowledge acquisition and the transfer of that knowledge into clinical practice for the intended audience. • Reinforce the value of including a multidisciplinary team in patient care. • Include an attestation regarding full compliance with all applicable standards of your accrediting body, as well as other relevant standards, guidelines, and requirements as they apply to the conduct of independent medical education. (Include documentation that the Provider of Record is in good standing at the time of application.) • Include a statement that your organization will cooperate with the independent third parties (independent of RPC) conducting the FDA-required Long-Term REMS Evaluations of REMS-supported CE activities six to twelve months following activity completion.

	Application Component	Description
9	**Validation of Clinical Content**	Detailed description of process by which the following will be validated: • All elements of the FDA Blueprint are covered in the educational activity/materials to ensure completeness of content. • Content of the activity reflects the most current evidence-based information and that the content of the FDA Blueprint is represented accurately. Note: Due to internal FDA review timelines, it is possible that new ER/LA opioid information may be posted to the FDA website before being integrated into the Blueprint. Prior to finalizing activity content, it is the Provider's responsibility to check the FDA REMS website for any new information that may affect the content of the REMS CE. • Provider has ensured fair balance and controlled for bias. Note, all REMS-compliant activities are subject to independent audit by the Accrediting Bodies, and all audit-required materials must be submitted to the Accrediting Bodies in advance of the activity start date, as per the timelines/processes defined by the Accreditor. The proposed process should take these requirements into account.

	Application Component	Description
10	**Outcome Evaluation/Knowledge Assessment**	Provide detailed description of how you intend to measure successful educational outcomes associated with your educational program, including the *valid and reliable measures* you intend to employ in your evaluation activities/assessment of learning. Educational impact on healthcare professional's knowledge, competence, and performance may include attitudes, perceptions, and skills. In addition to educational programs covering all elements of the FDA Blueprint, as per the FDA REMS requirements, the program must: • Include an assessment that covers all *six sections of the FDA Blueprint.* Preferred consideration will be given to grant applications which integrate the assessment throughout the activity in order to increase the likelihood of learners completing the assessment, an FDA requirement for the learner to be counted toward the REMS goals. (*To be counted toward the FDA goals, ER/LA opioid prescriber-completers must have "successfully completed" all components of an education activity* and met the education provider's criteria for passing. See MedBiquitous "FDA ER/LA Opioid REMS defined: successfully_completing"). • Be subject to independent audit by the Accreditors to confirm that conditions of the REMS education have been met.
11	**Marketing Plan for the Proposed CE Program**	Detail your *marketing strategy* for how the target audience will be reached, motivated to participate in your program, and be engaged to complete all components of the education activity, including assessment of learning. Include steps you will take if it appears you may fall short of meeting the commitments to educate the estimated number of ER/LA opioid prescribers that you proposed in your grant application.
12	**Budget**	Detail budget using the template residing in the REMS Grant Management System portal.

	Application Component	Description
		FDA has required RPC-supported CE to be provided at no cost, or at a nominal cost to the participant (e.g., a small amount to cover costs such as parking). In keeping with the FDA's requirements, the RPC thus discourages charging a fee for RPC-supported CE. In the event the provider chooses to include a nominal registration fee, this fee should not exceed $25 per participant completing CE covering the full FDA Blueprint. RPC will cover the cost of REMS service fees the Accreditors may require for reimbursement of costs the Accreditor incurs in conjunction with FDA-mandated independent audits and data aggregation/reporting. There is a specific line on the budget template which indicates how to estimate REMS Service Fees for the activities you propose. Explanation of rationale, efficiencies, and cost-effective approaches to both the live and enduring components, including an estimated cost per ER/LA opioid prescriber "completer" for both components. *Note: Rationale should include an explanation of how the proposal's estimated number of ER/LA opioid prescriber/completers was calculated.* Statement that: 1. The program activities meet the accreditation/ certification requirements and standards of the ACCME, AOA, AMA, AAFP or ADA CERP; 2. No RPC member has selected or provided suggestions for any speaker involved in the program activities; and **3.** The grant monies provided are for the program activity as a whole and are not meant to be a direct payment to any speaker since ultimate disbursement of the grant monies is within the sole control of the Provider. **Proposed cost per ER/LA opioid prescriber completer as defined in Section 1 for entire project should be calculated and provided as part of the budget.**

	Application Component	Description
13	**Timeline of Project**	Detailed project timeline for each phase and milestone. This will serve as the basis for the milestone payments in the grant as described below: • Thirty (30) days after execution of LOA and submission of initial activity listing to RPC for FDA-required CE search page: 35% • Start of first activity and upon acceptance of update report: 25% • Mid-term of grant timeline and upon acceptance of update report (including progress against the grant metrics that the Provider submitted in the approved proposal): 30% • Completion of last activity and receipt/acceptance of required grant-related documentation (including final metrics for the education activity and budget reconciliation): 10%
14	**Optional Organizational Change Elements**	See below for details

Section 5: Grant Application Review Criteria

Grant applications will be thoroughly and critically reviewed by members of the RPC Grant Review Committee and the RPC Oversight Committee. Grants will be awarded based on Providers' ability to include elements in their proposals that clearly and sufficiently address the following criteria:

Criteria	Description
Compliance	Requestor (Provider of Record) meets eligibility criteria outlined in Section 3.
Alignment[7]	Includes all elements of the FDA Blueprint and presents a detailed mapping of how all elements will be covered in educational programs/materials. Also explicitly states that all six sections of the FDA Blueprint will be covered in the assessment.
Number of ER/LA opioid prescribers fully completing the REMS-compliant CE	Relative to the FDA goals and MedBiquitous definitions described in Section 1 of this document, realistic estimate of the number of ER/LA opioid prescribers expected to fully complete CE covering all elements of the FDA Blueprint and all components of educational activity and to have met the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning that covers all six sections of the FDA Blueprint, and potentially evaluation. As described in the Budget section of the RFA on page 16, your grant application should include an explanation of how the proposal's estimated number of ER/LA opioid prescriber/completers was calculated.
Qualifications of Provider and partners	Employs effective partnerships/coalitions across professional, governmental, and/or community organizations that can achieve broad reach, engagement, and impact. Consider the inclusion of community health programs and/or patient-focused organizations.
Needs assessment [9,10,11]	Specific to the audience, ensuring the content of the educational material is relevant and adapted to the needs and clinical practice

[9] Bordage, G., B. Carlin, and P. E. Mazmanian. "Continuing Medical Education Effect on Physician Knowledge Effectiveness of Continuing Medical Education: American College of Chest Physicians Evidence-Based Educational Guidelines." CHEST Journal 135, no. 3_suppl (2009): 29S–36S.
[10] Greiner, A., and Elisa Knebel. Health Professions Education: a Bridge to Quality. National Academy Press, 2003.
[11] Moore, D. E., J. S. Green, and H. A. Gallis. "Achieving Desired Results and Improved Outcomes: Integrating Planning and Assessment Throughout Learning Activities." Journal of Continuing Education in the Health Professions 29, no. 1 (2009): 1–15.

	circumstances of the learners.
Educational design/methods[8,10,12,13,14,15,16]	• *Multi-method, multi-media:* Content is delivered using evidence-based methods and multiple *formats*—including, but not limited to, audio, visual, case discussions, role plays and other features of active learning and problem-based learning approaches—to guide learners in reflection and application of new knowledge to their practice settings. • Activities are innovative/creative in nature, motivating learners to participate and complete all activities. *Multi-exposure (education sessions):* For multi-exposure formats, content is delivered in digestible chunks or modules, over time, in ways that optimize learning.
Knowledge transfer[17]	• Principles from the field of implementation science are incorporated into overall learning program to address barriers to the application of the knowledge conveyed in the program. • *Application of CE-compliant outcomes measures of knowledge, competence, performance, etc.*
Interprofessional education[14,18]	• Facilitates interprofessional education and educational activities, particularly for healthcare providers practicing in settings in which care is delivered by multidisciplinary teams.
Valid and reliable outcome measures[14,19,20,21]	Educators should provide evidence for the validity and reliability of CE evaluation and outcome assessment methods. Preference will be given to proposals that integrate assessments throughout the

[12] Bloom, B. S. "Effects of Continuing Medical Education on Improving Physician Clinical Care and Patient Health: a Review of Systematic Reviews." International Journal of Technology Assessment in Health Care 21, no. 3 (2005): 380–385.
[13] Chiauzzi, E., K. J. Trudeau, K. Zacharoff, and K. Bond. "Identifying Primary Care Skills and Competencies in Opioid Risk Management." Journal of Continuing Education in the Health Professions 31, no. 4 (2011): 231–240.
[14] Van Hoof, T. J., and T. P. Meehan. "Integrating Essential Components of Quality Improvement into a New Paradigm for Continuing Education." Journal of Continuing Education in the Health Professions 31, no. 3 (2011): 207–214.
[15] Institute of Medicine. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. National Academy Press, 2011.
[16] Mansouri, M., and J. Lockyer. "A Meta-analysis of Continuing Medical Education Effectiveness." Journal of Continuing Education in the Health Professions 27, no. 1 (2007): 6–15.
[17] Ratanawongsa, N., P. A. Thomas, S. S. Marinopoulos, T. Dorman, L. M. Wilson, B. H. Ashar, J. L. Magaziner, R. G. Miller, G. P. Prokopowicz, and R. Qayyum. "The Reported Validity and Reliability of Methods for Evaluating Continuing Medical Education: a Systematic Review." Academic Medicine 83, no. 3 (2008): 274–283.
[18] Sargeant, J., F. Borduas, A. Sales, D. Klein, B. Lynn, and H. Stenerson. "CPD and KT: Models Used and Opportunities for Synergy." Journal of Continuing Education in the Health Professions 31, no. 3 (2011): 167–173.
[19] Marinopoulos SS, Dorman T, Ratanawongsa N, Wilson LM, Ashar BH, Magaziner JL, MillerRG, Thomas PA, Prokopowicz GP, Qayyum R, Bass EB**.** Effectiveness of Continuing MedicalEducation. Evidence Report/Technology Assessment No. 149 (Prepared by the Johns

	educational activity (versus waiting until the end of the entire activity), to optimize ER/LA opioid prescriber-completion, since completing the assessment is part of "prescribers successfully completing" the activity, as per the MedBiquitous definitions (see Appendix A).
Budget	Reasonable cost per learner given the proposed educational program (see Section 2)
Marketing plan for CE program	Detailed marketing strategy outlined for how target audience will be reached, motivated to participate in the educational activity, engaged to complete all components of the educational activity, and to meet the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning that covers all six sections of the FDA Blueprint, and potentially evaluation.

HopkinsEvidence-based Practice Center, under Contract No. 290-02-0018.) AHRQ Publication No.07-E006. Rockville, MD: Agency for Healthcare Research and Quality. January 2007.

[20] Price, D. W., E. K. Miller, A. K. Rahm, N. E. Brace, and R. S. Larson. "Assessment of Barriers to Changing Practice as CME Outcomes." Journal of Continuing Education in the Health Professions 30, no. 4 (2010): 237–245.

[21] Brownson, R. C., G. A. Colditz, and E. K. Proctore (eds). Dissemination and Implementation Research in Health: Translating Science to Practice. New York: Oxford University Press, 2012.

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2. Substance Abuse and Mental Health Services Administration. 2012. *Results from the 2012 National Survey on Drug Use and Health: Detailed Table*, Table 1.54A.a. Rockville, MD. http://www.samhsa.gov/data/NSDUH/2012SummNatFindDetTables/NationalFindings/NSDUHresults2012.htm. Accessed January 2014
3. Warner M, Chen LH, Makuc DM, Anderson RN, and Miniño AM. 2011. Drug Poisoning Deaths in the United States, 1980–2008, in U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *NCHS Data Brief*, *No 81*. December 2011. Hyattsville, MD. http://www.cdc.gov/nchs/data/databriefs/db81.pdf. Accessed on March 30, 2012.
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8. MedBiquitous Medical Education Metrics Definitions http://medbiq.org/mems/definitions. Accessed January 2014.
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10. Greiner, A., and Elisa Knebel. *Health Professions Education: a Bridge to Quality*. National Academy Press, 2003.
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20. Price, D. W., E. K. Miller, A. K. Rahm, N. E. Brace, and R. S. Larson. “Assessment of Barriers to Changing Practice as CME Outcomes.” *Journal of Continuing Education in the Health Professions* 30, no. 4 (2010): 237–245.
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Appendix A: Medical Education Metrics Definitions

Medical Education Metrics (MEMS 2.0) provides a standard XML format for CE outcomes data, including data related to FDA ER/LA Opioid Risk Evaluation and Mitigation Strategy (ER/LA Opioid REMS) education. One key component of evaluating the reach of ER/LA opioid REMS is evaluating the number of learners by category. One particular important category is the number of prescribers successfully completing REMS-compliant education.

MEMS 2.0 uses the following definitions:

FDA ER/LA Opioid REMS defined: ER/LA_opioid_prescriber: An individual clinician who is registered with the DEA to prescribe schedule 2 and/or 3 controlled substances and has written at least one ER/LA opioid script in the past year.

FDA ER/LA Opioid REMS defined: successfully_completing: Completing all components of an educational activity and meeting the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation.

FDA ER/LA Opioid REMS defined: prescribers_successfully_completing: FDA REMS defined ER/LA opioid prescribers that have completed all components of an educational activity and met the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation.

practice_type: A description of the clinician's practice by broad category (e.g. primary care). For a vocabulary of practice types related to the evaluation of pain management, see the Medical Education Metrics Vocabularies (http://medbiq.org/mems/vocabularies#practice_type).

schedule_2_or_3_registered_clinician: An individual clinician who is registered with the DEA to prescribe schedule 2 and/or 3 controlled substances.

schedule_2_or_3_registered_clinicians_successfully_completing: Schedule 2 or 3 registered clinicians that have completed all components of an educational activity and met the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation.

Appendix B: Overdose Deaths Related to ER/LA Opioid Analgesics and Understanding the Audience of ER/LA Opioid Prescribers

The contents of this Appendix is intended to provide background information on two topics of particular relevance to the REMS:

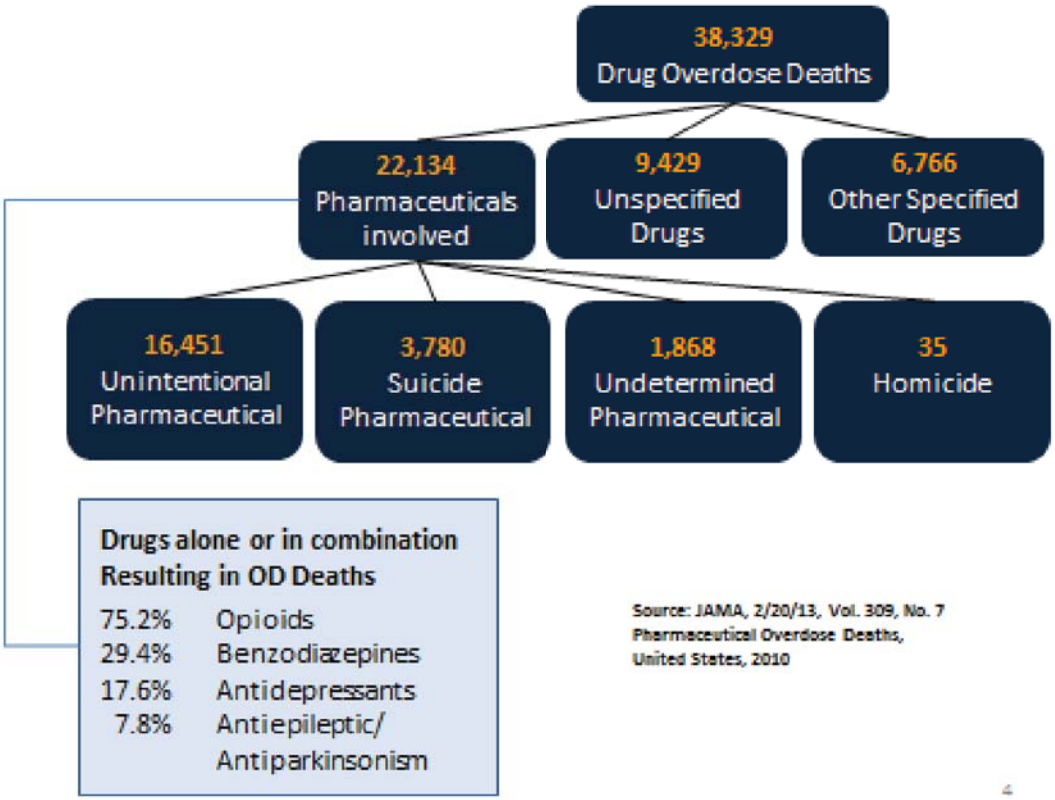
- Overdose deaths related to ER/LA opioid analgesics
- Demographic information on ER/LA opioid prescribers

What do we know about ER/LA opioid analgesics (opioid pain relievers (OPRs)) overdose deaths?

FDA REMS-compliant prescriber CE training, based on the FDA Blueprint, is largely motivated by the precipitous rise in prescription opioid medication abuse and overdose death during the past decade.

Figure 1 illustrates the total number of OPR deaths as a percentage of all drug overdose deaths in which pharmaceuticals were involved.

Figure 1. Breakdown of overdose deaths by type of drug, 2010 data from the National Vital Statistics System



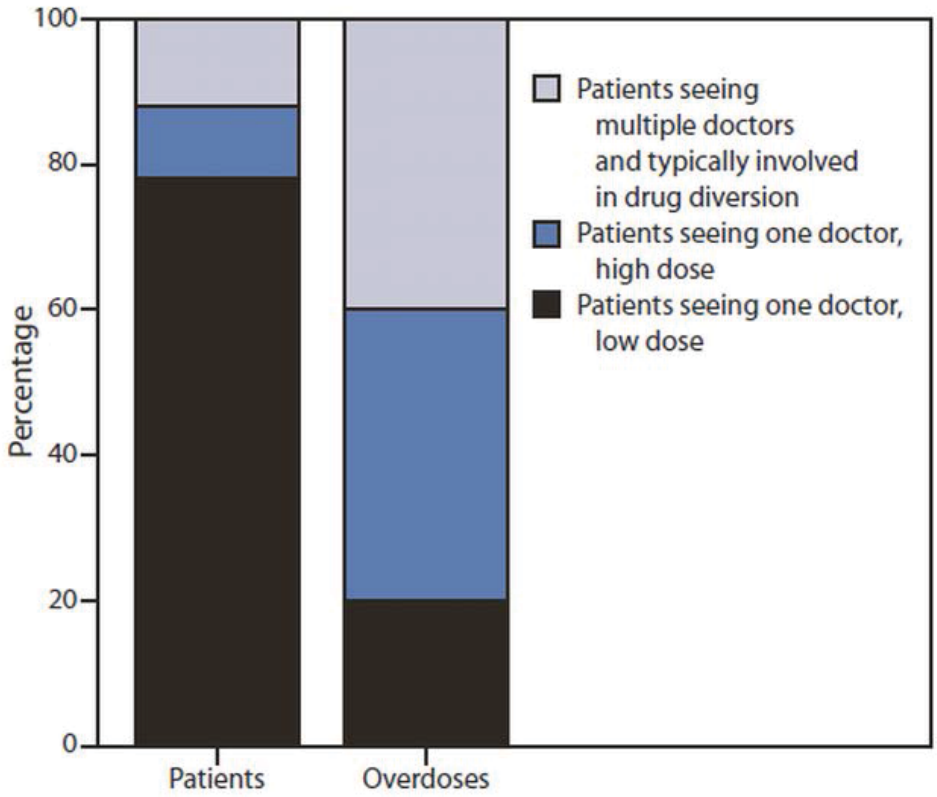
Key Findings on OPR overdose death:

- *Multiple prescription drugs* often play a role in OPR overdose death, the most common being benzodiazepines, antidepressants, antiepileptic and antiparkinsonism drugs, and antipsychotics and neuroleptics.
- Methadone accounts for only 2% of OPR prescriptions in the US but is involved in *more than 30% of overdose deaths* (*July 2012: Prescription Painkiller Overdoses: Use and Abuse of Methadone as a Painkiller).*
- Both immediate and extended-release formulations contribute to overdose death.

Populations most at risk for OPR overdose death:

- People who obtain multiple OPR prescriptions from multiple providers (e.g., doctor shoppers)
- People who take high daily dosages of OPR and those who misuse multiple abuse-prone prescription drugs
- About 60% of OPR overdose deaths are male, while 40% are female. But, OPR deaths increased fivefold between 1999 and 2010 for women, while the increase among men was 3.6 times.
- Low-income people and those living in rural areas: People on Medicaid are prescribed OPR at twice the rate of non-Medicaid patients and are at six times the risk of OPR overdose.
- People with mental illness and those with a history of substance abuse

Figure 2. Percentage of patients and prescription drug overdoses, by risk group—US



Hall et al. paper, JAMA 2008

This study by Hall et al. (JAMA 2008) was among the most rigorous attempts to understand OPR overdose death. The study investigated 295 decedents in West Virginia in 2006 since this state experienced the nation's largest increase in drug overdose death rates during 1999-2004. The drug overdose death rate in 2006 was 16.2.

Results:

- Opioid analgesics were taken by 93.2% of the decedents, of whom only 44% had ever been prescribed these drugs.
- 67.1% were male.
- 91.9% were aged 18-54.
- Pharmaceutical diversion occurred in 63.1% of deaths, and 21.4% were accompanied by doctor shopping.
- Diversion was highest among 18- to 24-year-olds and decreased across successive age groups.
- Having a controlled prescription from five or more doctors in the year prior to death was more common among women (30.9%) and decedents aged 35-44 (30.7%) compared with men (16.7%) and other age groups (18.2%).

- Methadone was responsible for more single-drug deaths and was involved in far more deaths than any other drug (40% vs. #2 hydrocodone 22.7%).
- 94.6% of decedents had indicators of substance abuse, including nonmedical routes of exposure and illicit contributory drugs particularly prevalent among drug diverters.
- Multiple contributory substances were involved in 79.3% of deaths.

What do we know about the target audience of ER/LA opioid prescribers?

Based on an analysis of prescribers who wrote *at least one* ER/LA opioid prescription in the 12 months ending March 2013, the total target audience is about 334,000.

Figure 3. Prescribers who wrote at least one ER/LA opioid prescription in the 12 months ending March 2013 by ZIP code

The map in Figure 3 indicates that prescribers of ER/LA opioid products are distributed throughout the US, with great concentrations occurring in large urban city areas as expected.

Source: IMS HEALTH Confidential and Proprietary; IMS Health Incorporated, IMS Xponent Plantrak

As shown in Figure 4, a follow-up analysis of the top twenty states based on highest number of ER/LA opioid prescribers was done.

Figure 4. ER/LA Opioid Prescribers by State—Top Twenty States

(b) (4)

Source: IMS HEALTH Confidential and Proprietary; IMS Health Incorporated, IMS Xponent Plantrak

As an alternative analysis, the following graph in Figure 5 divides total prescribers in a given state by the 2013 population census for that state.

Figure 5. ER/LA Opioid Prescribers by State divided by 2013 population census

(b) (4)

Further analysis of ER/LA opioid prescribers by *specialty group*, revealed:

(b) (4)

Figure 6. Percentage of total ER/LA opioid prescribers by specialty group

Source: IMS HEALTH Confidential and Proprietary; IMS Health Incorporated, IMS Xponent Plantrak

Note: IM=Internal Medicine, FP=Family Practice, GP=General Practitioner, NRP=Nurse Practitioners, and PHA=Physician Assistants

Appendix C - Patient Protocol and Survey, FDA Responses

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PROTOCOL

Extended Release (ER) / Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS): Patient Survey to Support Food and Drug Administration (FDA) Assessment Report 3

Protocol Version: 2, final

Protocol Date: 26 March 2014

Extended Release (ER) / Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS): Patient Survey to Support Food and Drug Administration (FDA) Assessment Report 3

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PROTOCOL SIGNATORY APPROVAL

Extended Release / Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS): Patient Survey to Support Food and Drug Administration (FDA) Assessment Report 3
Final Version 2

The following people have reviewed the final Protocol and give their approval.

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TABLE OF CONTENTS

1. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this Protocol.

Abbreviation or Special Term	Definition
CI	Confidence interval
CPT	Current Procedural Terminology
DAP	Data Analytics Plan
DSA	Data Sharing Agreement
ER	Extended release
FDA	Food and Drug Administration
GPI	Generic Product Identifier
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
HIRD[SM]	HealthCore Integrated Research Database[SM]
ICD-9-CM	International Classification of Diseases, Ninth Revision, Clinical Modification
IRB	Institutional Review Board
KAS	Knowledge Assessment Score
LA	Long-acting
LCR	List Completion Rate
MSA	Master Service Agreement
NDC	National Drug Code
OR	Odds ratio
ORC	ORC International, Inc.
PCD	Patient Counselling Document
PHI	Protected health information
REMS	Risk Evaluation and Mitigation Strategy
RFP	Request for Proposal
RPA	REMS Program Alliance
RPC	REMS Program Companies
SE	Safety Event
SD	Standard deviation

Abbreviation or Special Term	Definition
US	United States

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3. AMENDMENTS TO THE FINAL PROTOCOL

Version	Date dd/Mmm/yyyy	Author First initial. Last name	Protocol Section	Detail of Change
1	14 Jan 2014	D. Esposito	All	Final version 1
2	14 Mar 2014	D. Esposito	4	Modified synopsis to reflect edits throughout the study Protocol.
2	14 Mar 2014	D. Esposito	7	Edited the study design to show that the survey vendor did contact potential participants during the pre-test survey phase.
2	14 Mar 2014	D. Esposito	9	Clarifies that the final index drug will be defined based on self-report data from survey respondents. Clarifies inclusion and exclusion criteria to show whether they are claims or survey-based.
2	14 Mar 2014	D. Esposito	10	Clarifies that use of ER/LA opioid analgesics for detoxification is identified through claims only and that those patients unable to identify their ER/LA opioid analgesic will be excluded.
2	14 Mar 2014	D. Esposito	11	Modified outcomes related to the Medication Guide and patient counselling document (PCD) for clarity and survey consistency.

Version	Date dd/Mmm/yyyy	Author First initial. Last name	Protocol Section	Detail of Change
2	14 Mar 2014	D. Esposito	12	Final list of covariates identified was updated to align with the survey instrument.
2	14 Mar 2014	D. Esposito	13	Corrected an error stating that patients would be required to fill an ER/LA opioid analgesic within three months prior to survey.
2	14 Mar 2014	D. Esposito	14	Statistical methods were revised for clarity. New analyses to identify risk factors for a low KAS were incorporated.
2	14 Mar 2014	D. Esposito	Appendix A	Changed the pre-notification letter to state that the study is required by the Food and Drug Administration.
2	14 Mar 2014	D. Esposito	Appendix B	Removed/changed survey skip patterns at questions MG5, MG8 and PC3A.
2	14 Mar 2014	D. Esposito	Appendix B	Included a new question asking what type of healthcare provider first prescribed and ER/LA opioid.
2	14 Mar 2014	D. Esposito	Appendix B	Included a new question asking if patients understood the PCD.
2	14 Mar 2014	D. Esposito	All	Minor cosmetic edits were incorporated as needed.
2	24 Mar 2014	D. Esposito	2	Noted that Mark Baczowski (Mylan, Inc.) reviewed v1 of the Protocol only.

Version	Date dd/Mmm/yyyy	Author First initial. Last name	Protocol Section	Detail of Change
2	24 Mar 2014	D. Esposito	7	Only one dispensing of an ER/LA opioid analgesic is required.
2	24 Mar 2014	D. Esposito	9	Edited the inclusion and exclusion criteria as follows: (1) Require only one dispensing of an ER/LA opioid analgesic; (2) Do not require that patients are continuously eligible for their health plan during the most recent 12-month claims period and for at least six months prior to the index date; (1) Do not screen for current health plan eligibility at the start of the survey; and (4) Exclude patients that are current or former employees of HealthCore, ORC, FDA, or the RPC members.
2	24 Mar 2014	D. Esposito	11	Notes that the PCD may be received at any time in the last 12 months.
2	24 Mar 2014	D. Esposito	12	Adds duration of continuous health plan eligibility prior to the most recent dispensing of an ER/LA opioid analgesic.

Version	Date dd/Mmm/yyyy	Author First initial. Last name	Protocol Section	Detail of Change
2	24 Mar 2014	D. Esposito	13	Changed to past tense as the pre-test is complete and described in new Appendix E. Clarifies assumptions about sample size.
2	24 Mar 2014	D. Esposito	14	Incorporates additional stratification by number of ER/LA opioid dispensings and whether the patient received read and understood the Medication Guide and PCD. Removes survey targets by stratum.
2	24 Mar 2014	D. Esposito	15	Notes limitations that we can only survey currently eligible health plan members, and that we cannot survey caregivers of children using ER/LA opioid analgesics.
2	24 Mar 2014	D. Esposito	Appendix A	Clarifies that the FDA will not be aware of a given individual's participation.
2	24 Mar 2014	D. Esposito	Appendix C	Removes the screening question ensuring that patients are current health plan enrolees.
2	24 Mar 2014	D. Esposito	Appendix C	Excludes patients that are current or former employees of HealthCore, ORC, FDA, or the RPC members.
2	24 Mar 2014	D. Esposito	Appendix C	Asks whether the respondent received a PCD in the last 12 months. Clarifies timeframe for PCD questions throughout.

Version	Date dd/Mmm/yyyy	Author First initial. Last name	Protocol Section	Detail of Change
2	24 Mar 2014	D. Esposito	Appendix C	Clarifies text and skip patterns throughout.
2	26 Mar 2014	D. Esposito	13	Removes a stage of survey testing in which fielding is stopped and results analysed after the first night of calling is complete.

4. PROTOCOL SYNOPSIS

Background and Rationale

Extended release (ER) and long-acting (LA) opioid analgesics are approved for the management of chronic moderate-to-severe pain in the United States (US). The US Food and Drug Administration (FDA) approved a Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioid medications on 09 July 2012 (1). The purpose of this study is to assess patient knowledge of the safe use of these products following implementation of the REMS and to determine possible effects of the REMS, including impact on access to medication.

Objectives

The primary objectives of the patient survey are:

1. To determine whether patients received the Medication Guide and/or Patient Counseling Document (PCD) and from whom;
2. To determine whether patients read the Medication Guide and/or PCD;
3. To assess whether the patient understood the serious risks associated with the use of their ER/LA opioid analgesic;
4. To assess whether the patient knows what to do if they take too much drug;
5. To assess whether the patient understands the need to store the drug in a safe place;
6. To assess whether the patient knows they should not share the drug with anyone;
7. To assess whether the patient understands how to use the drug safely; and
8. To assess the impact of the ER/LA REMS on access to treatment.
    - Compared to before REMS, do patients perceive a change following REMS in physicians' prescribing of pain medication;
    - Compared to before REMS, do patients perceive a change following REMS in access to medications to treat pain; and
    - Compared to before REMS, do patients perceive a change following REMS in satisfaction with access to pain treatment.

Study Design

We will conduct a cross-sectional survey of commercially-insured patients who filled at least two prescriptions for ER/LA opioid analgesics within the most recent 12 months captured in the HealthCore Integrated Research Database^{SM} (HIRD^{SM}) data.

The survey will be conducted in two phases. The Phase I pre-test will test survey processes to identify and correct problems regarding the proposed methods and instrument prior to the initiation of the Phase II main survey. The sample size of the Phase I pre-test will be 21 completed surveys, approximately 5% of the targeted completed sample size for the Phase II main patient survey (N=400).

Population

The sampling frame for the Phase I and Phase II surveys will include adults who have filled at least one recent prescription (within the last 12 months) for ER/LA opioids in the HIRD^{SM}.

Exposures

The following three major ER/LA opioid analgesic groups of interest will be identified using administrative data:

- ER oral-dosage forms containing
  - Hydromorphone,
  - Hydrocodone,
  - Morphine,
  - Oxycodone,
  - Oxymorphone, or
  - Tapentadol;
- Fentanyl and buprenorphine-containing transdermal delivery systems; and
- Methadone tablets and solutions that are indicated for use as analgesics.

Outcomes

Patients will be asked whether they:

- Received the Medication Guide (described by interviewer or shown on the Internet) and/or PCD within the past 12 months;
- Read the Medication Guide and/or had a provider that referenced the PCD;
- Understood the Medication Guide and/or PCD;
- Understood the serious risks associated with the use of the most recent ER/LA opioid analgesic which was dispensed to them, as described in the respective core section of the Medication Guide or PCD;
- Understood how to use the drug safely;
- Understood what to do if they take too much drug;
- Understood the need to store the drug in a safe place; and
- Understood not to share the drug with anyone.

In order to assess the impact of the ER/LA REMS on access to treatment, survey items will also assess patient satisfaction with access to treatment. Further, we will query patients about how frequently their prescribing health care provider performed certain counseling and screening measures.

Analyses

To assess representativeness of the survey sample, we will describe and compare the demographic characteristics of patients who completed the survey with the demographic characteristics of patients who could not be contacted, who refused to participate in the study or who were excluded because they no longer met study criteria.

To assess the specific endpoints of the study, the percentage and number of patients, and 95% confidence interval (CI) will be reported for each of the specific endpoints. Univariate statistics (e.g., mean, median, standard deviation) will be calculated for continuous variables. A Knowledge Assessment Score (KAS) will be calculated from the responses to the items in the knowledge section. Univariate score descriptions (i.e., mean, SD, median, minimum and maximum) will be reported overall and by drug group; scores will also be reported as the percentage of patients scoring about a specific level, e.g., 70%. Bivariate analyses will be used to determine the unadjusted level of knowledge of the risks and safe use of ER/LA

opioid analgesics based on receipt and understanding of the Medication Guide and PCD. We will also assess risk factors for a KAS below 70%.

5. INTRODUCTION

5.1 BACKGROUND

Extended release (ER) and long-acting (LA) opioid analgesics are approved for the management of chronic moderate-to-severe pain in the United States (US). ER/LA opioid analgesics containing buprenorphine, fentanyl, hydromorphone, hydrocodone, methadone, morphine, oxycodone, oxymorphone, or tapentadol are indicated for the management of moderate-to-severe pain when a continuous, around-the-clock opioid analgesic is needed for an extended period of time. ER hydromorphone and transdermal fentanyl products are indicated for use in opioid-tolerant patients only. ER/LA opioid analgesics are not indicated for acute pain (2).

Although these medications are an important therapeutic option for many patients, serious adverse reactions include life-threatening respiratory depression, apnea, respiratory arrest, circulatory depression, hypotension, and death. Risk of abuse and misuse is highest in patients with psychiatric comorbidities and/or a history of substance abuse (3).

Concerns over inappropriate use have risen in recent years. According to the 2010 National Survey on Drug Use and Health, at least 35 million persons age 12 years or greater in the US have used these products for non-medical reasons, and 14,800 deaths were attributed to ER/LA opioid analgesics in 2008 (4). Further, substantial concerns about overdose, abuse, misuse, addiction, dependence, and serious consequences of inadvertent exposure have led to increased scrutiny (3).

5.2 STUDY RATIONALE

The US Food and Drug Administration (FDA) approved a Risk Evaluation and Mitigation Strategy (REMS) for ER/LA opioid medications on 09 July 2012 (1). The REMS includes class-wide safety labeling changes as well as educational efforts to include (1) Medication Guides, which are documents shared with patients at the point of medication dispensing to detail the risks of medication use and ensure that important safety information is disclosed; (2) Patient Counseling Documents (PCD) to facilitate discussions between patients and providers; and (3) additional prescriber training on all ER/LA opioid analgesics. Core educational messages are described in detail in the FDA Blueprint for physicians, including (1) understanding how to assess patients for treatment, (2) how to initiate therapy, modify dose, and discontinue use, (3) management of ongoing therapy, (4) safe use, including proper storage and disposal, and (5) product-specific drug information concerning safety.

The branded and generic drug products subject to this REMS include:

- ER oral-dosage forms containing
  - Hydromorphone,
  - Hydrocodone,
  - Morphine,
  - Oxycodone,
  - Oxymorphone, or
  - Tapentadol;

- Fentanyl and buprenorphine-containing transdermal delivery systems; and
- Methadone tablets and solutions that are indicated for use as analgesics.

The purpose of this study is to assess patient knowledge of the safe use of these products following implementation of the REMS and to determine whether access to medication and satisfaction with access to pain management has been impacted. To understand those core messages of the FDA Blueprint that can be assessed from the patient perspective, we will also assess patient perspectives on prescriber behaviors, including appropriate screening and counseling. These findings will support FDA Assessment Report 3 for the REMS.

6. STUDY OBJECTIVES

This patient survey will evaluate penetration of those core messages described in the FDA Blueprint that are evaluable from a patient perspective.

The primary objectives of the patient survey are:

1. To determine whether patients received the Medication Guide and/or PCD and from whom;
2. To determine whether patients read the Medication Guide and/or PCD;
3. To assess whether the patient understood the serious risks associated with the use of their ER/LA opioid analgesic;
4. To assess whether the patient knows what to do if they take too much drug;
5. To assess whether the patient understands the need to store the drug in a safe place;
6. To assess whether the patient knows they should not share the drug with anyone;
7. To assess whether the patient understands how to use the drug safely; and
8. To assess the impact of the ER/LA REMS on access to treatment.
    - Compared to before REMS, do patients perceive a change following REMS in physicians' prescribing of pain medication;
    - Compared to before REMS, do patients perceive a change following REMS in access to medications to treat pain; and
    - Compared to before REMS, do patients perceive a change following REMS in satisfaction with access to pain treatment.

7. STUDY DESIGN

We will conduct a cross-sectional survey of commercially-insured patients who filled at least one prescription for ER/LA opioid analgesics within the most recent 12 months captured in the HealthCore Integrated Research Database[SM] (HIRD[SM]).

The Phase I pre-test will test survey processes to identify and correct any issues regarding the proposed methods and instrument prior to the initiation of the Phase II main patient survey. The sample size of the Phase I pre-test study will be at least 21 completed surveys, approximately 5% of the targeted completed sample size for the Phase II main patient survey (N=400).

A telephone and web-based mixed survey administration was deemed the most appropriate survey methodology based on ER/LA opioid-using patient characteristics. This mixed approach will maximize the inclusion of a variety of demographic groups. Younger patients typically prefer to respond to Internet surveys, and older patients typically prefer a telephone approach.

Since HealthCore does not maintain its own call center, we partner with a survey vendor, ORC International, Inc. (ORC). ORC is a leading global research firm with offices across the US, Europe, and Asia Pacific. They have extensive qualitative and quantitative experience in the pharmaceutical industry and have interviewed physicians, other healthcare professionals, patients, caregivers, and providers (via Internet, phone, or in-person). Their analytical staff averages over 13 years of consumer research experience with extensive research design, statistical, and analytical expertise.

A pre-notification letter (see **Appendix A**) will be sent to all patients on the patient list, informing them that they have been selected for participation in this study. Patients who neither opt-out or opt-in will be called and recruited by interviewers over the telephone. The pre-notification letter will be used for the Phase 1 pre-test and the Phase II main patient survey.

Pre-notification letters will be sent by ORC to patients on the patient sample list. The following information is provided in the pre-notification letter:

- A brief description of the study;
- Informs patients that they are one of a number of health plan members that have been selected to participate in this study;
- States that the study is required by the FDA;
- Informs patients that study participation is voluntary, their confidentiality will be preserved, and only aggregated data will be reported;
- Provides an opt-out number that the patient can call to have their name removed from the sample list (for this and future studies);
- Provides an opt-in number that the patient can call to participate immediately; also, a web link will be provided if the patient wants to participate in the study by completing the survey on the Internet.

If patients do not respond to the pre-notification letter within approximately 10 days, ORC interviewers will call the patients and recruit them for the study. Patients who are called and give verbal consent to participate will complete the survey on the telephone unless the patient expressly mentions that they want to complete the survey on the Internet. In that case, the patient's e-mail address will be obtained and a link to the Internet survey will be provided.

8. DATA SOURCE

Both study phases will utilize administrative claims data from the HIRD[SM] to identify patients who filled prescriptions within the last 12 months for ER/LA opioid analgesics. These patients will constitute the source populations for the Phase I and Phase II surveys. The HIRD[SM] is currently a broad, clinically rich and geographically diverse spectrum of longitudinal claims data from health plan members in the Northeastern, Mid-Atlantic, Southeastern, Midwest, Central, and Western regions of the US. Patient enrollment, medical care (professional and facility claims), outpatient prescription drug use, laboratory test result data, and health care utilization may be tracked for patients in the database dating back to January 2006. The HealthCore Research Environment has the ability to link the claims data in the HIRD[SM] to other complementary data sources, including member inpatient and outpatient medical records, national vital records, cancer and vaccine registries (state-by-state), member and provider surveys, and point of care clinical data. As of November 2013, the database contains approximately 32.6 million lives with medical and pharmacy eligibility, of which 10.3 million are currently active. The HIRD[SM] is updated on a monthly basis. Eligible patients with ER/LA opioid pharmacy claims will be identified based on the most recent data update at the time of Institutional Review Board (IRB) approval.

9. STUDY POPULATION

The sampling frame for the Phase I and Phase II surveys will consist of currently active, commercially-insured, survey eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data.

The most recent pharmacy claim of any ER/LA opioid analgesic will be defined as the index date and the type of ER/LA opioid analgesic dispensed on the index date as the sample index drug for purposes of identifying members of the sampling frame. Patients will be asked about their most recent ER/LA opioid analgesic used at the time of the survey, and their response will define their survey index drug for subsequent analyses. If the sample index drug is methadone, it must be given for analgesic reasons.

Inclusion criteria

The following inclusion criteria will apply for both the Phase I pre-test and Phase II main patient survey. Subjects must meet all of the following inclusion criteria to be included in the patient list for the survey.

1. At least one pharmacy claim for an ER/LA opioid analgesic in the most recent 12-months of claims data.
2. Currently active, commercially-insured, survey eligible members with medical and pharmacy benefits.
3. At least 18 years of age as of the date of the most recent ER/LA opioid dispensing (the index date).
4. A non-missing telephone number and/or address.
5. Does not appear on the HealthCore "Do-not-call" list.

No history of substance abuse identified in the claims data.

Exclusion criteria

Patients that meet the inclusion criteria for the patient list as described above will be excluded based on the following criteria at the start of the survey.

1. Before the telephone survey can be administered, does not give verbal informed consent indicating that they have been informed of all pertinent aspects of the study and agree to participate; before the Internet survey can be completed, does not indicate that they have read about all pertinent aspects of the study and agree to participate.
2. They fail to validate their name and/or date of birth checks.
3. They state they did not fill a prescription for a specific ER/LA opioid analgesic within the past 12 months.
4. They are unable to understand the survey questions as designed (e.g., non-English speaking, etc.).
5. They are employed as a licensed physician.
6. They or their family member(s) are current or former employees of HealthCore, ORC, the FDA or members of the RPC.

10. EXPOSURE DEFINITION AND ASSESSMENT

ER/LA opioid analgesics will be identified in the HIRD[SM] by National Drug Code (NDC), which can be grouped using systems such as the Generic Product Identifier (GPI). These codes will be identified based on outpatient pharmacy drug dispensing claims. **Appendix B** lists the codes that will be included to define the following three major ER/LA opioid analgesic groups of interest:

- ER oral-dosage forms containing
  - Hydromorphone,
  - Hydrocodone,
  - Morphine,
  - Oxycodone,
  - Oxymorphone, or
  - Tapentadol;
- Fentanyl and buprenorphine-containing transdermal delivery systems; and
- Methadone tablets and solutions that are indicated for use as analgesics.

Patients whose methadone use is for detoxification treatment will be excluded from the study. Detoxification will be identified based on Healthcare Common Procedure Coding System (HCPCS) codes for substance abuse treatment and diagnoses indicating substance abuse/addiction that are recorded at any time during the patient's claims history. Survey respondents will not be asked about the reason for their ER/LA opioid use or treatment for substance abuse.

At the time of the survey, the patient will be asked to confirm the type of ER/LA opioid analgesic that they most recently used. Patients who cannot recall general ER/LA opioid analgesic exposure will be excluded. Patients who can only recall the general class will also be excluded. For patients whose most recently used ER/LA opioid analgesic reported at the time of the survey differs from their most recent pharmacy claim, their index survey drug will be defined by the patient's survey response.

11. OUTCOME DEFINITION AND ASSESSMENT

The survey will evaluate the effectiveness of the REMS in conveying important risk and safe use information about ER/LA opioid analgesics. The survey will also assess whether patients perceive an impact of the ER/LA REMS on access to treatment.

Patients will be asked whether they:

- Received the Medication Guide (described by interviewer or shown on the Internet) and/or PCD during the past 12 months;
- Read the Medication Guide and/or had a provider that referenced the PCD;
- Understood the Medication Guide and/or PCD;
- Understood the serious risks associated with the use of the most recent ER/LA opioid analgesic which was dispensed to them, as described in the respective core section of the Medication Guide or PCD;
- Understood how to use the drug safely;
- Understood what to do if they take too much drug;
- Understood the need to store the drug in a safe place; and
- Understood not to share the drug with anyone.

In order to assess the impact of the ER/LA REMS on access to treatment, survey items will also assess patient access to treatment and satisfaction with access to treatment. Further, we will query patients about whether their prescribing health care provider performed certain counseling and screening measures per the FDA Blueprint. In the Phase I pre-test survey, patients will also be given an opportunity to express opinions about the survey, including the descriptions of the Medication Guide and PCD, in an open-ended fashion. In addition, demographic questions will be asked to support analyses regarding variation in survey results in different demographic subgroups.

It is anticipated that the survey will average 20 minutes in length. The majority of the survey questions will be answered by all survey respondents and a small number will be specific to the type of ER/LA opioid analgesic prescribed. For example, transdermal patch users will be asked specific questions regarding the safe use of transdermal patches such as risks associated with heating patches; methadone users will be asked questions concerning increasing dose titration of methadone treatment; oral products users will be asked about such things as breaking, crushing, or chewing the medications.

Appendix C shows the survey questionnaire that will be used in the Phase II main survey and **Appendix A** shows the pre-notification letter that will be sent to all patients on the patient lists. Minor revisions were made to the questionnaire based on results of the Phase I pre-test survey.

12. COVARIATE DEFINITION AND ASSESSMENT

In addition to the main outcomes of interest, we will identify the following patient characteristics in the Phase I pre-test and the Phase II main patient surveys:

- Age;
- Gender;
- US region;
- Race/ethnicity;
- Marital status;
- Income level;
- Education level;
- Specific ER/LA opioid analgesic(s) used;
- New user of the index ER/LA opioid analgesic drug;
- Type of healthcare provider that prescribed the index ER/LA opioid analgesic drug;
- Time since last index ER/LA opioid analgesic prescription fill;
- Time since most recent visit to the healthcare provider who prescribed the index ER/LA opioid analgesic drug; and
- Time since healthcare provider first prescribed the index ER/LA opioid analgesic drug.

In order to assess the comparability of the patients surveyed with all ER/LA opioid analgesic users in the HIRD[SM], the following covariates will be identified from the claims data for all patients in the survey sampling frame for the Phase II main patient survey.

- Age;
- Gender;
- US region;
- Duration of continuous health plan eligibility prior to the most recent dispensing of an ER/LA opioid analgesic;
- Status as a new user of ER/LA opioid analgesics (i.e., whether the patient is continuously eligible for the health plan for at least six months prior to the first recorded dispensing of an ER/LA opioid analgesic);
- Duration of ER/LA opioid analgesic therapy during continuous health plan enrollment;
- Specific ER/LA opioid analgesic(s) used most recently before the survey;
- Number of previous dispensings of ER/LA opioid analgesics prior to the index date;
- Number of distinct drugs dispensed during the past six months prior to the index date; and
- Medical condition(s) for which ER/LA opioid analgesics are indicated.

13. CLINICAL DATA - SURVEY

13.1 PHASE I: PRE-TEST PATIENT SURVEY

The pre-test patient survey was a small scale preliminary study that was conducted to obtain data that supported the feasibility assessment and/or improvements to the design of the main study. The pre-test study allowed us to test the sampling design, survey methodology, determine patient understanding of the survey questions, and identify any other survey-related issues so that the quality and efficiency of the main survey could be improved.

The pre-test study assessed patients' understanding of the main patient survey questionnaire. ORC International, INC. (ORC) received a patient sample list that included the sample index drug type of each patient at their index date as well as contact information. Pre-notification letters were sent to all patients on the pre-test sample list. After patients consented to the survey and prior to the start of the survey, they were screened to ensure that they were still eligible for the study. Patients were excluded if they were no longer an active member of their health plan, failed the name and date of birth check, had not filled a prescription for an ER/LA opioid analgesic in the 12 months prior to the survey, or were a licensed physician.

The survey was designed to average no more than 20 minutes in length. Patients who completed the survey (telephone or Internet) received a $20 check to thank them for their time and participation. In addition to the questions that are included in the main patient survey, the pre-test survey included several additional questions related to the survey and survey process (see **Appendix C**).

The pre-test study consisted of 21 completed patient surveys (i.e., approximately 5% of the main survey targeted number of 400 completed surveys). The pre-test survey list included equal numbers of the three types of ER/LA opioid analgesics (i.e., transdermal patch, methadone, and oral products). All of the pre-test data, including responses to the post-survey questions asked of respondents, were used to identify the minor changes that were made to the survey processes or survey questions that resulted in a clearer, more comprehensive survey. Information gathered from the pre-test study, in addition to any regulatory comments, was used to update the proposed sampling methodology, survey processes, and survey prior to the start of the main patient survey. The pre-test data was discarded and not used for the main Phase II patient survey.

13.2 PHASE II: MAIN PATIENT SURVEY

The targeted sample size of 400 completed surveys for the main patient survey will be obtained over an approximate four-week interval. HealthCore will provide the list of eligible patients with index event claims to ORC. The survey index drug type of each patient at their index date will be provided to ORC, in addition to contact information. Pre-notification letters will be sent to patients on the list. After patients consent to the survey and prior to the start of the survey, they will be screened to ensure that they are still eligible for the study. Patients

will be excluded if they fail the name and date of birth check, have not filled a prescription for an ER/LA opioid analgesic in the 12 months prior to the survey, are a licensed physician, or are affiliated or have family members that are current or former employees of HealthCore, ORC, FDA, or members of the RPC.

The survey is designed to average approximately 20 minutes in duration. Patients who complete the survey (telephone or Internet) will receive a $20 check to thank them for their time and participation. ORC will conduct all survey-related activities, including printing and mailing the pre-notification letters, hosting the website, and contacting patients by telephone. All patients will hear or read an IRB-approved script that describes the purpose of the survey, emphasizes that participation is voluntary, and informs patients that although a de-identified survey data file may be shared with the study Sponsor, the data obtained from the surveys will only be presented in aggregated form for reporting purposes. ORC will follow their quality control procedures including pretesting the survey with hypothetical respondents to make sure the survey flow and skip patterns are correct, monitoring interviewer calls, and running data checks on completed surveys.

14. STATISTICAL METHODS AND SAMPLE SIZE

14.1 STATISTICAL METHODOLOGY

Descriptive statistics

The nature of the statistical analyses performed in this study is descriptive. Prior to assessing descriptive statistics on the survey data, an analysis will be done to compare the demographic characteristics of patients who completed the survey (respondents) with the demographic characteristics of those patients who did not complete the survey (all non-respondents), could not be contacted, who were excluded because they no longer met study inclusion criteria, or who refused to participate in the study. Demographic characteristics that can be determined from the claims data as described in Section 12 will be assessed and reported. We will also describe the number and percentage of patients that used specific ER/LA opioids in the sample list (Phase II main survey only) and among respondents.

For survey respondents, full demographic characteristics obtained from the survey (e.g., race, income, education level, etc.) and responses to questions about key messages from the Medication Guide and PCD will be shown overall and stratified as follows:

- By medication group (i.e., methadone, transdermal delivery systems, and oral products that are not methadone);
- By Medication Guide receipt/read/understood status;
- By PCD receipt/provider reference/understood status;
- By levels of the Knowledge Assessment Score (KAS) as defined below; and
- By number of ER/LA opioid analgesic dispensings recorded in the claims data prior to the index date (≤1 versus >1).

In order to assess the specific endpoints of the study, the percentage and number of patients, and 95% confidence intervals (CIs) will be reported for each of the following specific endpoints:

- Patients who received the Medication Guide and/or PCD during the past 12 months;
- Patients who read the Medication Guide and/or whose provider referenced the PCD; and
- Patients who understood the Medication Guide and/or PCD.

We will also describe patients that received, read, and understood both the Medication Guide and PCD as well as patients that did not receive, read, or understand either the Medication Guide or PCD.

Univariate statistics (e.g., mean, median, standard deviation, minimum, maximum) will be calculated for continuous variables, and the distribution of responses to survey questions will be determined to identify whether patients understood specific messages, such as:

- The serious risks associated with the use of the most recent ER/LA opioid analgesic which was dispensed to them;
- How to use the drug safely;
- What to do if they take too much drug;

- The need to store the drug in a safe place; and
- Not to share the drug with anyone.

A KAS will be calculated from the responses to the knowledge questions. The KAS will be defined as the proportion of knowledge questions that the respondent answered correctly. A mean knowledge score will be reported overall and by drug group. The percentage of patients above and below a threshold KAS (e.g., 70%) will also be reported.

Bivariate analyses will be used to determine the unadjusted level of knowledge, as defined by the KAS, of the risks and safe use of ER/LA opioid analgesics among patients who:

- Did and did not receive the Medication Guide and/or PCD;
- Did and did not read/reference the Medication Guide and/or PCD; or
- Did and did not understand the Medication Guide and/or PCD.

If sufficient data are available to support the analyses, we will identify potential factors associated with poor knowledge (i.e., a KAS below 70% or another threshold selected based on data distributions). We will use odds ratios (ORs) to evaluate candidate risk factors based on both univariate and multivariate logistic regression models.

Patients will also be asked questions concerning their satisfaction with access to pain management treatment. Responses to questions about physician behaviors when prescribing ER/LA opioid analgesics will also be reported (see **Appendix C** for the full survey).

A separate Data Analytics Plan (DAP) will provide further details concerning the planned analyses.

14.2 SAMPLE SIZE

HealthCore estimates the size of patient sample lists through the use of the List Completion Rate (LCR), a statistic developed by HealthCore. The LCR is the ratio of the number of completed surveys divided by the number of patient names on the sample list that was used by the survey vendor. It is a rate that is calculated at the completion of every survey study, along with cooperation, and refusal rates. Based on past survey experiences, HealthCore uses a conservative LCR of 5% for proposal and budgeting purposes. HealthCore has achieved LCRs ranging from 3% to 11%, depending on the therapeutic area and characteristics of the patient sample.

The drivers of the LCR include the following.

- Patient contact information is determined from WellPoint eligibility files. This information is often out-of-date. HealthCore estimates that about 30% of patients on a sample list will have an incorrect telephone number and/or address and contact is not possible.
- Another 30% of patients will not be contacted after the maximum number of allowable attempts specified in the survey protocol (usually five) has been made at

different times of the day and days of the week. HealthCore is very sensitive to member abrasion, thus limiting the number of times a patient may be called before the telephone number is retired.

- Of the 40% of patients who are contacted, 25% to 30% will opt-out through the pre-notification or refuse to participate when contacted on the telephone and <5% will agree to participate but will no longer meet the study inclusion criteria.
- The remaining 5% to 10% of patients will complete the survey.

These statistics are not unique to HealthCore; they are typical of sample lists including the contact information of other managed care organizations, Medicare, and Medicaid. Based on preliminary patient counts, HealthCore has determined that there will be sufficient sample to complete this study.

The pre-specified targeted number of completed surveys for the main patient survey is at least 400. At the time that we evaluated sample size, we anticipated that this would be approximately equally distributed by the three main types of ER/LA opioid analgesics: transdermal patch users (N=130); methadone users (N=130); oral products users (N=140).

In order to estimate the precision associated with these sample sizes, the following assumptions were made.

- The total number of completed surveys N is assumed to be 400 stratified into three groups, n_1, n_2, n_3 such that $n_1 = 130$, $n_2=130$, and $n_3=140$.
- The confidence level or risk level is assumed to be 95%. This means that in a normal distribution, approximately 95% of the sample values are within two standard errors of the true population mean and that 95 out of 100 samples will have the true population value within the range of precision.
- The degree of variability in the attributes being measured is estimated to be 0.5. We used this estimate because it represents the maximum variability and is often used in determining a more conservative (larger) sample size than if the true variability of the population attribute were used.
- The level of precision is defined as the range in which the true value of the population is assumed to fall. This means that if we find that 40% of patients received the Medication Guide then, with a precision rate of ±e%, we can conclude that between (40% minus e%) and (40% plus e%) of patients in our population received the Medication Guide. This is also true for the other endpoints; each of the endpoints, i.e., “received the Medication Guide”, “read the Medication Guide”, and “understand the Medication Guide”, have been powered to achieve a precision of ±e%.

Based on the above assumptions and using the following equation to estimate the precision, we found:

$$e = (Z^2pq / n)^{1/2} = (1.96^2 * 0.5 * 0.5 / 400)^{1/2} = \pm 5\%$$

where Z=1.96 is the value on the normal curve that corresponds to a 95% confidence level, p=0.5 (maximum variability), q=1-p=0.5, and N=400.

Based on the above calculation, the number of completed surveys proposed in the Request for Proposal (RFP), N=400 will yield a precision of ±5%. Similar calculations for the three

sub-groups indicate a precision of ±8% to ±9%. These precisions are adequate and we have sufficient sample to achieve them.

Pre-test study sample sizes are typically targeted at approximately 5% of the primary sample size. Based on 400 completed surveys for the main patient survey, this yields a pre-test study sample size of 21 completed surveys. This should be sufficient to assess whether there are problems with sampling or the survey (e.g., whether the survey questions are clear and understandable).

15. LIMITATIONS TO THE STUDY DESIGN

This study will utilize an administrative claims database to identify patients who are eligible to complete the survey and is subject to the limitations inherent in the use of such data. The database is representative of the commercially-insured population in the US; however, it is not representative of individuals without medical insurance or those with government-sponsored insurance such as Medicaid. Although all patients are required to have a pharmacy benefit, patients will be identified on the basis of submitted pharmacy claims; patients who choose not to use their pharmacy benefit will not be identified as being eligible for the survey unless there are submitted pharmacy claims.

Because the study population will be limited to adults with commercial insurance, representation of patients 65 years of age and older will be limited to those patients that receive medical and pharmacy benefits through continued coverage by an employer (or a spouse's employer). We are not able to survey parents or caregivers of children under the age of 18 using ER/LA opioid analgesics or those individuals that did not have current health plan benefits at the time that the patient list is generated. The age distribution of survey respondents may not ultimately represent the age distribution of the US population as the age distribution of the sampling frame will be driven by use of ER/LA opioid analgesics. We expect that this will be reflected in the respondents, and we will verify this through comparison of the respondents and sample list with respect to age (among other characteristics). Due to a relatively small target sample size within each of the three ER/LA opioid analgesic groups, we do not believe that the study will support meaningful subgroup analyses.

The large size of the HIRD^{SM} is a study strength in that it provides for a sufficient number of patients who meet eligibility criteria for the survey to achieve the targeted sample size of 400 completed surveys for the main patient survey with a precision of ±5%. We have used the HIRD^{SM} as the sampling frame for over 30 survey studies in the past three years; this has enabled us to extend the study designs we are able to achieve to include merging patients' survey data with their administrative claims data to study the health care research utilization and costs of these patients or incorporating data from patients' medical records with their survey data to asking the physicians of surveyed patients about their quality of life and beliefs, attitudes, or adherence behavior. Every type of data (e.g., administrative claims, medical records, patient/physician survey data) has their strengths and weaknesses. However, combining multiple types of data emphasize the strengths and decrease the weaknesses, such that the whole assessment is greater than any of its individual parts.

16. STUDY ETHICS

The current study is designed as an analysis based on medical and pharmacy claims data from a large insured population in the US. There is no active enrollment or active follow-up of study subjects. HealthCore, Inc. ("HealthCore") maintains Data Sharing Agreements (DSAs) and Business Associate Agreements with all covered entities who provide data to the HIRD[SM]. HealthCore's access, use, and disclosure of protected health information (PHI) are in compliance with the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule [45 CFR Part 160 and Subparts A and E of Part 164]. HealthCore does not access, use, or disclose identifiable PHI unless under a specific waiver of authorization (e.g., a HIPAA Waiver of Authorization from an IRB). HealthCore accesses the data in a manner that complies with federal and state laws and regulations, including those related to the privacy and security of individually identifiable health information.

As PHI must be accessed in order to survey patients, a HIPAA Waiver of Authorization will be applied for from an IRB prior to any PHI being identified.

At no time during or after the conduct of this study will HealthCore provide patient identifying information to Campbell Alliance, Ltd. ("Campbell Alliance") or the REMS Program Companies (RPC). Aggregated data will be reported to Campbell Alliance and the RPC Metrics Subteam (i.e., the scientific team representing the RPC). The de-identified patient survey data from Phase II will be transferred by HealthCore to Campbell Alliance, and will be shared by Campbell Alliance with the RPC Metrics Subteam.

17. SAFETY EVENT REPORTING

The term 'Safety Event' is defined as any information reported by a survey respondent that meets the criteria of an Adverse Event, Product Complaint, or Medical Information Request. During the course of the patient surveys, HealthCore may become aware of Safety Events. HealthCore will report spontaneously mentioned Safety Events associated with use of ER/LA opioid analgesics to the relevant RPC member(s) using the Safety Event Report Form shown in **Appendix D**.

18. STUDY DETAILS

18.1 FUNDING SOURCE

The study is funded through a study agreement with Campbell Alliance on behalf of the RPC, the manufacturers of ER/LA opioid analgesics included in the REMS.

18.2 REGULATORY REQUIREMENT

This study is required by the US FDA in support of Assessment Report 3 for the ER/LA opioid REMS approved on 09 July 2012.

18.3 DATA ANALYTICS PLAN REQUIREMENT

A separate DAP will be developed for the study. This will include further details of the planned analytic approach, full details of appropriate International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic, ICD-9-CM procedure, Current Procedural Terminology (CPT), HCPCS, NDC, and GPI codes to be used in the study, and table shells to further detail the analyses that will be presented.

18.4 STUDY DELIVERABLES AND COMMUNICATION OF RESULTS

The following deliverables will be created and shared with Campbell Alliance:

- Draft and final versions of the Protocol;
- A copy of the IRB approval letter;
- A status update (one-page memorandum) upon completion of pre-test survey fielding (Appendix E);
- Draft and final versions of the DAP;
- A status update (one-page memorandum) upon completion of survey vendor identification and training;
- A status update (one-page memorandum) upon completion of main survey fielding;
- Draft study tables;
- Draft and final versions of the patient survey section for FDA Assessment Report 3; and
- Draft and final versions of the Patient Survey Report.

Publications (i.e., presentation of study results at scientific meetings and preparation of a study manuscript) will be developed in accordance with the Master Service Agreement (MSA) effective 31 December 2013. HealthCore shall endeavor to publish the findings of the Services collaboratively with Client and/or REMS Program Alliance (RPA) Participants and accordingly have joint ownership with Client and RPA Participants of the copyright of any such publication. If Client or RPA Participants elects not to publish collaboratively with HealthCore and if Client and RPA Participant are in receipt of the de-identified Patient Survey data, then HealthCore may independently publish the findings of the Services under the applicable Work Order subject to the provisions of this Section 9 herein. If HealthCore

pursues independent publication, HealthCore will provide Client and RPA Participants with the full text of any proposed publication at least forty-five (45) days before it is submitted for publication or otherwise disclosed to allow Client and RPA Participants the opportunity to comment on such proposed publication. If any action by Client and/or one or more RPA Participants is needed to apply for or otherwise secure intellectual property rights of a discovery disclosed in HealthCore's independent publication, HealthCore shall, at Client and/or one or more RPA Participants' request, delay publication for up to ninety (90) days. Client and/or one or more RPA Participants, at their sole discretion, may publish the findings of the Services contained in the deliverables independently. If Client and/or one or more RPA Participants pursues independent publication, Client and/or one or more RPA Participants will provide HealthCore with the full text of any proposed publication at least forty-five (45) days before it is submitted for publication or otherwise disclosed to allow HealthCore the opportunity to comment on such proposed publication. If any action by HealthCore is needed to apply for or otherwise secure intellectual property rights of a discovery disclosed in the independent publication, Client and/or one or more RPA Participants, as applicable, shall, at HealthCore's request, delay publication for up to ninety (90) days

If any action by Client and/or one or more RPA Participants is taken to apply for or otherwise secure intellectual property rights of a discovery disclosed in the Publication, Client and/or one or more RPA Participants may request a delay of the publication for a reasonable period, not to exceed an additional ninety (90) days.

19. REFERENCES

(1) U.S. Food and Drug Administration. Risk Evaluation and Mitigation Strategy (REMS) for Extended-Release and Long-Acting Opioids. 10-25-2013.

(2) Trescot AM, Helm S, Hansen H, Benyamin R, Glaser SE, Adlaka R et al. Opioids in the management of chronic non-cancer pain: an update of American Society of the Interventional Pain Physicians' (ASIPP) Guidelines. *Pain Physician* 2008; 11(2 Suppl):S5-S62.

(3) Stanos S. Evolution of opioid risk management and review of the classwide REMS for extended-release/long-acting opioids. *Phys Sportsmed* 2012; 40(4):12-20.

(4) Manchikanti L, Helm S, Fellows B, Janata JW, Pampati V, Grider JS et al. Opioid epidemic in the United States. *Pain Physician* 2012; 15(3 Suppl):ES9-38.

(5) Brick J, Williams D. Explaining rising nonresponse rates in cross-sectional surveys. *Annals of the American Academy of Political and Social Science* 2013.

20. APPENDICES

APPENDIX A. PRE-NOTIFICATION LETTER

Phase I:

[HEALTH PLAN LOGO]

Date

Dear Member (ID#XXXXX):

You are invited to participate in a study conducted by ORC International, Inc. (ORC), a health survey research company, to understand what people know about safe use of some pain medications. ORC is conducting this study on behalf of HealthCore, Inc., a health outcomes research company that is a part of the family of companies that also includes [HEALTH PLAN NAME]. You are one of a number of [HEALTH PLAN NAME] members who has been chosen to participate in this study. *Only the member to whom this letter is addressed will be eligible to participate in this study*.

Participation in this study consists of completing a single, approximately 20-minute survey. You will receive a check in the amount of $20 after completing the survey to compensate you for your time. Only the first few participants will be included in this pilot test. If you are unable to access the survey at this time, you may qualify to participate in the future.

Your participation is voluntary, and you do not have to participate if you do not want to. If you participate, all of your answers to the questions that are asked will be kept confidential. [HEALTH PLAN NAME] will neither know whether you participate nor how you answer the survey questions. All identifying information will be removed from your data after you complete the survey. A de-identified data file will be prepared from the survey data of all respondents and used for analysis and may be shared with the study sponsor. No names, ID numbers, addresses, or other identifying information will be recorded in this data file. For reporting purposes, your answers will be combined with the answers from other respondents and will appear only as aggregated data. Participation will not impact your treatment or benefits in any way.

Your time and participation is very much appreciated. This study can only be successful with the generous help of people like you. We look forward to your participation in this study.

If you'd like to participate immediately, contact ORC at [INSERT CONTACT INFO] or go to [link to web survey]. If you have any questions or concerns about this survey, or do not want to be contacted, please call Amanda Rodriguez, HealthCore's Research Data Manager, at 877-905-7946 or arodriguez@healthcore.com.

Sincerely,

[TITLE]/Medical Director
[HEALTH PLAN NAME]

[HEALTHCORE REPRESENTATIVE]

Phase II:

[HEALTH PLAN LOGO]

Date

Dear Member (ID#XXXXX):

You are invited to participate in a study requested by the United States Food and Drug Administration (FDA) to understand what people know about safe use of some pain medications. ORC International, Inc. (ORC), a health survey research company, is conducting this study on behalf of HealthCore, Inc., a health outcomes research company that is a part of the family of companies that also includes [HEALTH PLAN NAME]. You are one of a number of [HEALTH PLAN NAME] members who has been chosen to participate in this study. *Only the member to whom this letter is addressed will be eligible to participate in this study*.

Participation in this study consists of completing a single, approximately 20-minute survey. You will receive a check in the amount of $20 after completing the survey to compensate you for your time.

Your participation is voluntary, and you do not have to participate. If you participate, all of your answers to the questions that are asked will be kept confidential. [HEALTH PLAN NAME] and the FDA will neither know whether you participate nor how you answer the survey questions. All identifying information will be removed from your data after you complete the survey. A de-identified data file will be prepared from the survey data of all respondents and used for analysis and may be shared with the study sponsor. No names, ID numbers, addresses, or other identifying information will be recorded in this data file. For reporting purposes, your answers will be combined with the answers from other respondents and will appear only as aggregated. Participation will not impact your treatment or benefits in any way.

Your time and participation is very much appreciated. This study can only be successful with the generous help of people like you. We look forward to your participation in this study.

If you'd like to participate immediately, contact ORC at [INSERT CONTACT INFO] or go to [link to web survey]. If you have any questions or concerns about this survey, or do not want to be contacted, please call Amanda Rodriguez, HealthCore's Research Data Manager, at 877-905-7946 or arodriguez@healthcore.com. Otherwise, an interviewer from ORC will call you in the next few days.

Sincerely,

[TITLE]/Medical Director
[HEALTH PLAN NAME]

[HEALTHCORE REPRESENTATIVE]

APPENDIX B. ER/LA OPIOID MEDICATIONS

- ER oral-dosage forms
  - Avinza® (GPI 651000552070x)
  - Embeda® (GPI 651000557002x)
  - Exalgo® (GPI 651000351075x, 6510003510A8x)
  - Kadian® (GPI 651000551070x*)
  - MS Contin® (GPI 651000551004x*, 651000551074*)
  - Nucynta® ER (GPI 651000911074x)
  - Opana® ER (GPI 651000801074x*, 6510008010A7x)
  - OxyContin® slow/extended release (GPI 651000751074x*, 6510007510A7x)
  - Morphine sulfate controlled/slow release tablets and capsules (GPI 651000551004x*, 651000551070x*, 651000551074*)
  - Oxycodone hydrochloride slow release tablets (GPI 651000751074x*)
  - Oxymorphone hydrochloride extended release tablets (GPI 651000801074x*)
  - Zohydro ER™ (GPI codes to be determined)
- Fentanyl and buprenorphine-containing transdermal delivery systems
  - Butrans® (GPI 652000100088x)
  - Duragesic® (GPI 651000250086x*)
  - Fentanyl transdermal system (GPI 651000250086x*)
- Methadone tablets and solutions
  - Dolophine® (GPI 651000501003x*, 651000501020x*)
  - Methadose™ (GPI 651000501003x*, 651000501013x*, 651000501073x*)
  - Methadone hydrochloride (GPI 6510005010x*)

*Some GPI codes are shared between generic and branded products.

APPENDIX C. PATIENT SURVEY

ER/LA OPIOID ANALGESIC REMS SURVEY
DRAFT 1
INTRODUCTION*/**/***

** Various error messages may appear during the online version of the survey that will provide further instructions to the respondent in situations such as attempting to skip a question, providing an answer that is outside of the acceptable range, or providing an answer that is not consistent with the type of question being asked (i.e., inserting a text answer when the question is expecting a numeric answer).*

*** If a respondent attempts to skip a question, the interviewer/online module will make a statement that reflects the importance of providing an answer and will repeat the question if possible. Otherwise, the interviewer/online module will continue to the next question. Similar techniques will be used for answers that are provided that are out of range or are not consistent with the type of question being asked. Further clarification or definition will be provided if the participant requests additional information.*

**** Some of the questions are designed to be administered primarily online or by an interviewer over the telephone. Interviewers may have to adjust the wording slightly for telephone administration. These changes will not affect the content of the survey or the survey response choices in any way; they will be conversational modifications only. If any of the programming directionals or other wording is found to be inaccurate at the time of programming the survey, adjustments will be made according to the intentions of the survey.*

(PHONE_INTRO) Hello, may I please speak with **[INSERT NAME FROM SAMPLE]**?

Yes, currently available/will get now	1	**CONTINUE**
Refused	2	**GO TO TERMINATE TEXT**
Respondent not available	3	**SCHEDULE CALL BACK APPT.**
No one by that name	4	**GO TO TERMINATE TEXT**

S1. Hello, my name is **[INSERT NAME]** and I am an interviewer with ORC International calling to ask you to participate in a study about certain pain medications.

This study is being conducted by HealthCore, a health outcomes research company that is a part of the family of companies including **[HEALTH PLAN NAME]**. The study is required by the Food and Drug Administration (FDA) to find out whether a new strategy for making sure these medications are used appropriately is working.

You are one of a number of **[HEALTH PLAN NAME]** members who have been chosen to participate. The specific purpose of the study is to better understand what patients know about the safe use, storage, and correct disposal of certain pain medications.

The study consists of completing a one-time survey. If you qualify and agree to participate, the survey will take approximately 20 minutes to complete, and, after completing it, you will receive a $20 check to compensate you for your time. Your participation is completely optional and voluntary. At any time during the survey, you may change your mind and decide to no longer participate. If this occurs, the interview will end and you will not be contacted again, by HealthCore or ORC International about this study, but the data collected up to that

point will be kept and may be used for reporting purposes. Your participation is important, however, because your answers will provide valuable information to help the FDA understand what people know about the safe use of some pain medications.

Your responses to all survey questions will remain confidential, and your health plan and employer will not be informed regarding your study participation. All identifying information will be removed from your data after you complete the survey. A de-identified data file will be prepared from the survey data of all respondents and used for analysis and may be shared with the study sponsor. No names, ID numbers, addresses, or other identifying information will be recorded in this data file. For reporting purposes, your answers will be combined with the answers from other respondents and will appear only as aggregated data. Any information provided by you may be used even if do not complete the entire survey. Based on what you have heard, do you agree to participate if you qualify?

(S1_AGREEMENT)	Yes	1	**GO TO NAME VERIFICATION PROCESS**
(S1_AGREEMENT)	No	2	**GO TO TERMINATE TEXT**

ADDITIONAL INSTRUCTIONS: PHONE SCRIPT

»PROGRAMMING NOTE: THIS STATEMENT WILL BE READ AFTER CONSENT (S1_AGREEMENT = 1 (YES)): *"Just so you know, this call may be monitored for quality assurance purposes."*

»PROGRAMMING NOTE: If a respondent attempts to skip a question, the interviewer will make a statement that reflects the importance of providing an answer and will repeat the question if possible. Otherwise, the interviewer will continue to the next question. Similar techniques will be used for answers that are provided that are out of range or are not consistent with the type of question being asked. Further clarification or definition will be provided if the participant requests additional information

ADDITIONAL INSTRUCTIONS: INTERNET ONLY

[INTERNET ONLY ADDITIONAL INSTRUCTIONS]
"Throughout the survey, you will always see a button at the bottom of the page (you may have to scroll down to see some of the longer pages). The 'Next Page' button accepts your answer and advances to the next page.
Do not use your browser's forward or back buttons.
If you encounter any problems, please click here and reference study number XXX and User ID XXXXX or call us toll-free at 1-800-729-6774 from 9am to 5pm EDT Monday through Friday and ask for XXX.
If you would like to finish this survey at a later time please click here to save your information and that will allow you come back to complete the survey at a more convenient time."
Various error messages may appear during the online version of the survey that will provide further instructions to the respondent in situations such as attempting to skip a question, providing an answer that is outside of the acceptable range or providing an answer that is not consistent with the type of question being asked (i.e., inserting a text answer when the question is expecting a numeric answer).

NAME AND DATE OF BIRTH VERIFICATION PROCESS

The next questions are to confirm that you are eligible to participate in the study.

S2. **(NAME_VER)** What is your full legal name?

INTERVIEWER: DOES THE NAME ENTERED MATCH THE NAME ON THE SAMPLE?

Yes	1	**GO TO BIRTH_VER**
No	0	**GO TO TERMINATE TEXT**

***»INTERVIEWER NOTE**: RESPONDENT'S NAME WILL APPEAR ON SCREEN. MAKE SURE FIRST AND LAST NAME MATCH. IF NOT **GO TO TERMINATE TEXT**.*

S3. In what year were you born?

In what month were you born?

And on what day were you born?

(BIRTH_VER) Just to verify, your date of birth is **[INSERT FULL BIRTHDATE RECORDED ABOVE]**. Is that correct?

Yes	1	**GO TO HEALTH PLAN SCREENING**
No	0	**GO TO TERMINATE TEXT**

***»PROGRAMMING NOTE:** VERIFY THAT THE DATE GIVEN MATCHES THE DATE IN THE SAMPLE AND **GO TO HEALTH PLAN SCREENING**. IF IT DOES NOT, REPEAT THE BIRTHDATE VERIFICATION SECTION ONCE; IF IT STILL DOESN'T MATCH, **GO TO TERMINATE TEXT**.*

TERMINATE TEXT

Thank you for your time. You will not be contacted by HealthCore or ORC International about this study again.

EMPLOYMENT SCREENING

S4a. Are you or any of your immediate family members (that is, your spouse and/or children) current or former employees of any of the following companies?

ORC International	1	**TERMINATE & GO TO DISQUALIFY TEXT S4**
HealthCore	2	**TERMINATE & GO TO DISQUALIFY TEXT S4**
The Food and Drug Administration or FDA	3	**TERMINATE & GO TO DISQUALIFY TEXT S4**
A pharmaceutical company or drug manufacturer	4	**CONTINUE (to S4b)**
None of these or not sure	5	**CONTINUE (to S5)**
Refused (DO NOT READ OR SHOW ON SCREEN)	9	**TERMINATE & GO TO DISQUALIFY TEXT S4**

S4b. Which pharmaceutical company? (DO NOT READ, BUT ASK FOR RESPONSE AND CHECK WHETHER IT MATCHES BELOW. FOR THE ONLINE SURVEY, SHOW RESPONSES AND ALLOW PATIENTS TO SELECT ALL THAT APPLY)

Actavis Elizabeth	1	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Alpharma Pharmaceuticals	2	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Aveva Drug Delivery Systems	3	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Apotex	4	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Endo Pharmaceuticals	5	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Impax Laboratories	6	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Janssen Pharmaceuticals	7	**TERMINATE & GO TO DISQUALIFY TEXT S4**
King Pharmaceuticals	8	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Mallinckrodt	9	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Mylan Pharmaceuticals or Technologies	10	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Noven Pharmaceuticals	11	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Par Pharmaceuticals	12	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Pfizer	13	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Purdue Pharma	14	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Ranbaxy Laboratories Limited	15	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Rhodes Pharmaceuticals	16	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Roxanne Laboratories	17	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Sandoz	18	**TERMINATE & GO TO DISQUALIFY TEXT S4**
The PharmaNetwork	19	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Upsher-Smith Laboratories	20	**TERMINATE & GO TO DISQUALIFY TEXT S4**
VistaPharm	21	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Watson Laboratories	22	**TERMINATE & GO TO DISQUALIFY TEXT S4**
Zogenix	23	**TERMINATE & GO TO DISQUALIFY TEXT S4**
None of these or not sure	24	**CONTINUE (to S5)**
Refused (DO NOT READ OR SHOW ON SCREEN)	99	**TERMINATE & GO TO**

DISQUALIFY TEXT S4

DISQUALIFY TEXT S4

We're sorry but you don't qualify for this particular study because you or a family member are a current or past employee of ORC International, HealthCore, the FDA, or a selected pharmaceutical company. Thank you for your time. The information you have provided will not be used and you will not be contacted again about this study by HealthCore or ORC International.

PHYSICIAN SCREENING

S5.	Are you a licensed physician?		
	Yes	1	**TERMINATE & GO TO DISQUALIFY TEXT S5**
	No	2	**CONTINUE (to S8)**
	Refused (DO NOT READ OR SHOW ON SCREEN)	9	**TERMINATE & GO TO DISQUALIFY TEXT S5**

DISQUALIFY TEXT S5

We're sorry but you don't qualify for this particular study because you are a licensed physician. Thank you for your time. The information you have provided will not be used and you will not be contacted again about this study by HealthCore or ORC International.

MODE
PHONE OR WEB SURVEY (only used if respondent requests to complete survey online)

If you prefer to complete the survey on the Internet, I will need to obtain your e-mail address in order to send you the link and password for completing the web survey.
You will have (Phase I) three (3) days / (Phase II) two (2) weeks from today to complete the survey. Which would you prefer – telephone or Internet? Remember, the survey will take about 20 minutes of your time to complete.

S6. I apologize that we do not have your e-mail address on file. Can you please tell me your e-mail address so that I can send you the link and password to the study?

ENTER EMAIL ADDRESS: _____

S7: [***PROGRAMMING NOTE:*** *IF PHONE: TYPE IN AND READ FOR CONFIRMATION*
"Just to confirm, your email address is _____]

Yes	1	**CONTINUE**
No	2	**GO BACK TO S6**
Refused (DO NOT READ OR SHOW ON SCREEN)	9	**TERMINATE & GO TO DISQUALIFY TEXT S7**

Thank you. I will send you the link and password to the web survey. Please keep in mind that you will have (Phase I) three (3) days / (Phase II) two (2) weeks to complete the survey. The e-mail will be coming from **[TO BE ADDED BY ORC]**. You may want to write this e-mail address down and add it to your contact list so that it doesn't go to your SPAM folder. Please call us back at **[TO BE ADDED BY ORC]** if you have any questions or decide you would like to take the survey by phone.

Once you receive the e-mail, please complete the survey by **[INSERT** (Phase I) **THREE (3) DAYS** / (Phase II) **TWO (2) WEEK DEADLINE DATE]**. Have a nice day. Good bye!

DISQUALIFY TEXT S7

We're sorry but unless you give or confirm your email address, you do not qualify for this study. Thank you for your time. The information you have provided will not be used and you will not be contacted by HealthCore or ORC International about this study again.

ER/LA OPIOID ANALGESIC REMS SCREENING QUESTION S8

S8. Have you filled a prescription for a controlled release or CR, extended release or ER, slow release, or long-acting or LA opioid pain medication (meaning a tablet or capsule, patch, or methadone oral solution or concentrate to be used less than four times per day) at your pharmacy within the last 12 months to treat your pain?

Yes	1	**CONTINUE**
No	2	**TERMINATE & GO TO DISQUALIFY TEXT S8**
Not Sure	3	**TERMINATE & GO TO DISQUALIFY TEXT S8**
Refused (DO NOT SHOW ON SCREEN)	9	**TERMINATE & GO TO DISQUALIFY TEXT S8**

DISQUALIFY TEXT S8

We're sorry but you do not qualify for this study because you did not fill a prescription for a long-acting opioid pain medication within the last 12 months. Thank you for your time. The information you have provided will not be used and you will not be contacted by HealthCore or ORC International about this study again.

ER/LA OPIOID ANALGESIC REMS SCREENING QUESTION S9

S9. Was the prescription for:

Patch	1	**GO TO QUESTION S9A SET COHORT = PATCH**
Methadone	2	**GO TO QUESTION S9B SET COHORT =**
METHADONE		
Oral drugs that are not methadone	3	**GO TO QUESTION S9C SET COHORT = TAB_CAP**
Patch AND Methadone	4	**GO TO QUESTION S9B SET COHORT =**
METHADONE		

Patch AND oral drugs (not methadone)	5	**GO TO QUESTION S9A** **SET COHORT = PATCH**
Methadone AND oral drugs (not methadone)	6	**GO TO QUESTION S9B** **SET COHORT =**
METHADONE All of the above	7	**GO TO QUESTION S9B** **SET COHORT =**
METHADONE		
Not Sure	8	**TERMINATE & GO TO DISQUALIFY TEXT S9**
Refused (DO NOT SHOW ON SCREEN)	9	**TERMINATE & GO TO DISQUALIFY TEXT S9**

S9a. Was the most recent patch prescription for :

Butrans	1	**GO TO START OF SURVEY**
Duragesic	2	**GO TO START OF SURVEY**
Fentanyl, generic	3	**GO TO START OF SURVEY**
Patch, multiple types	4	**GO TO START OF SURVEY**
Not Sure	5	**TERMINATE & GO TO DISQUALIFY TEXT S9**
Refused (DO NOT SHOW ON SCREEN)	9	**TERMINATE & GO TO DISQUALIFY TEXT S9**

S9b. Was the most recent methadone prescription for:

Dolophine	1	**GO TO START OF SURVEY**
Methadose	2	**GO TO START OF SURVEY**
Methadone, generic	3	**GO TO START OF SURVEY**
Methadone, multiple types	4	**GO TO START OF SURVEY**
Not Sure	5	**TERMINATE & GO TO DISQUALIFY TEXT S9**
Refused (DO NOT SHOW ON SCREEN)	9	**TERMINATE & GO TO DISQUALIFY TEXT S9**

S9c. Was the most recent oral drug (not methadone) prescription for:

Avinza	1	**GO TO START OF SURVEY**
Embeda	2	**GO TO START OF SURVEY**
Exalgo	3	**GO TO START OF SURVEY**
Kadian	4	**GO TO START OF SURVEY**
MS Contin	5	**GO TO START OF SURVEY**
Nucynta extended release or ER	6	**GO TO START OF SURVEY**
Opana extended release or ER	7	**GO TO START OF SURVEY**
OxyContin slow or extended release or ER	8	**GO TO START OF SURVEY**
Zohydro extended release or ER	9	**GO TO START OF SURVEY**
Morphine controlled or slow release, generic	10	**GO TO START OF SURVEY**
Oxycodone slow release, generic	11	**GO TO START OF SURVEY**
Oxymorphone extended release, ER; generic	12	**GO TO START OF SURVEY**
Extended-release or ER opioids, multiple	13	**GO TO START OF SURVEY**
Not Sure	44	**TERMINATE & GO TO**

Refused (DO NOT SHOW ON SCREEN)	99	**DISQUALIFY TEXT S9 TERMINATE & GO TO DISQUALIFY TEXT S9**

[THROUGHOUT SURVEY, INSERT THE DRUG NAME INDICATED IN S9A, S9B, or S9C where [OPIOID] is indicated]

DISQUALIFY TEXT S9

We're sorry but you do not qualify for this study. Thank you for your time. The information you have provided will not be used and you will not be contacted by HealthCore or ORC International about this study again.

START OF SURVEY
ER/LA OPIOID ANALGESIC KNOWLEDGE ASSESSMENT

Great, now that you have qualified, we are going to start by asking you some questions about [OPIOID].

KA1. Based upon what you know about [OPIOID], please [INTERNET: indicate/PHONE: tell me] whether you agree or disagree with the following statements. Would you say you "strongly disagree," "disagree," "neither agree nor disagree," "agree" or "strongly agree" that…

	[RANDOMIZE ORDER OF STATEMENTS]	Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
a.	Taking or using too much [OPIOID], also called overdose, may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death.	1	2	3	4	5
b.	It's okay to stop taking or using [OPIOID] without talking to your healthcare provider.	1	2	3	4	5
c.	If the dose you are taking or using doesn't control the pain, it is okay to take or use more medicine without talking to your healthcare provider.	1	2	3	4	5
d.	[OPIOID] can make you dizzy, lightheaded or sleepy.	1	2	3	4	5
e.	It's okay to drink alcohol while taking or using [OPIOID].	1	2	3	4	5
f.	You should store [OPIOID] in a medicine cabinet with other medications in the household.	1	2	3	4	5

g.	You should get emergency medical help if you take or use too much or overdose on [OPIOID], even if you feel fine.	1	2	3	4	5
h.	You should get emergency medical help if you experience side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain or swelling of your face, tongue or throat, after taking or using [OPIOID].	1	2	3	4	5
i.	It is okay for you to give [OPIOID] to other people who have the same condition as you have.	1	2	3	4	5
j.	After you stop taking or using [OPIOID], it is okay to throw any unused medicine in the trash.	1	2	3	4	5
k.	It's not necessary to read the attached Medication Guide every time you fill your [OPIOID] prescription.	1	2	3	4	5
l.	You don't have to tell your healthcare provider about all the other medications you use.	1	2	3	4	5
m.	You don't have to tell your healthcare provider if you have a history of abuse of street or prescription drugs, alcohol addiction, or mental health problems.	1	2	3	4	5
n.	Selling or giving away your [OPIOID] is against the law.	1	2	3	4	5
o.	If a child takes or uses your [OPIOID], they could die.	1	2	3	4	5
p.	You don't have to tell your healthcare provider about over-the-counter medicines, vitamins, and dietary supplements.	1	2	3	4	5
q.	It's okay to drink caffeine while using [OPIOID].	1	2	3	4	5

[(KA1-r) ONLY FOR PATIENTS WITH COHORT = TAB_CAP]

r.	If you have trouble swallowing your medication, you should split or crush the pill.	1	2	3	4	5
s.	If you miss a dose of [OPIOID], you can take more when it is time for your next dose.	1	2	3	4	5

[(KA1-s) THROUGH (KA1-u) ONLY FOR PATIENTS WITH COHORT = PATCH]

t.	You need to tell your healthcare provider if you have a fever.	1	2	3	4	5
u.	If you still have pain, you should try using a hot tub or sauna while using [OPIOID].	1	2	3	4	5
v.	It is okay to cut your patch in half if you want to use less medicine.	1	2	3	4	5

ER/LA OPIOID ANALGESIC MEDICATION GUIDE QUESTIONS

We would now like to ask you some questions about the last time you filled a prescription for [OPIOID] from the pharmacy.

MG1. When was the last time you or your caregiver filled this prescription?

Less than 1 month ago	1
1 month to less than 2 months ago	2
2 months to less than 3 months ago	3
3 months to less than 6 months ago	4
6 months to less than 9 months ago	5
9 months to less than 12 months ago	6
12 months or more ago	7
Not Sure	8
Refused (DO NOT SHOW ON SCREEN)	9

MG2. Was this the first time that you used [OPIOID] or had you used [OPIOID] before?

First use	1
Used before	2
Not Sure	3
Refused (DO NOT READ OR SHOW ON SCREEN)	9

Now I'm going to describe something called the "Medication Guide" for your drug.

[MEDICATION GUIDE DESCRIPTION}

The Medication Guide consists of one or more pages that are computer-generated or a **1-page, 1-sided** document with plain black writing that would have been stapled to the outside of the bag or placed inside the bag that was given to you with your last prescription. It has the words "Medication Guide" written at the top of the page with the name of your opioid analgesic drug and its pronunciation below. The document highlights the drug's risks and safe use. Two examples of sections of the document are "Important information about the drug" and [for COHORT = TAB_CAP or METHADONE] "Who should not take the drug." / [for COHORT = PATCH] "Who should not use the drug."

MG3. Did you or your caregiver receive the Medication Guide for [OPIOID] from your pharmacist or someone at the pharmacy with your last prescription fill?

Yes	1
No	2
Not sure	3
Refused (DO NOT READ OR SHOW ON SCREEN)	9

MG4. Have you or your caregiver received the Medication Guide for [OPIOID] from your pharmacist or someone at the pharmacy in the last 12 months?

Yes	1
No	2

Not sure	3
Refused (DO NOT READ OR SHOW ON SCREEN)	9

MG5. Did you or your caregiver get the Medication Guide for [OPIOID] from any source besides your pharmacist or someone at the pharmacy in the last 12 months?

Yes	1	GO TO MG6
No	2	GO TO MG7
Not sure	3	GO TO MG7
Refused (DO NOT READ OR SHOW ON SCREEN)	9	GO TO MG7

MG6. We would like to know where you or your caregiver got the Medication Guide for your [OPIOID]. Did you or your caregiver get the Medication Guide from … *(Select one response per row)*

	Yes	No	Refused (DO NOT READ OR SHOW ON SCREEN)
a. Your healthcare provider's office or clinic	1	2	9
b. The Internet	1	2	9
c. Another healthcare professional	1	2	9
d. Family or friends	1	2	9
e. Somewhere else	1	2	9

MG7. Would you say you have… (READ LIST)

Never read any of the Medication Guide	1
Read some of the Medication Guide at least once	2
Read all of the Medication Guide at least once	3
Read all of the Medication Guide with each pharmacy fill	4
Refused (DO NOT READ OR SHOW ON SCREEN)	9

MG8. Did anyone offer to explain the Medication Guide to you in the last 12 months?

Yes	1	GO TO MG9
No	2	GO TO Programming note before MG11
Not sure	3	GO TO Programming note before MG11
Refused (DO NOT READ OR SHOW ON SCREEN)	9	GO TO Programming note before MG11

MG9. Who offered to explain the Medication Guide? Was it … *(Select one response per row)*

	Yes	No	Refused (NO NOT READ OR SHOW ON SCREEN)
a. Your pharmacist or someone at the pharmacy	1	2	9
b. Your healthcare provider or someone in the healthcare provider's office/clinic	1	2	9
c. A member of your family or a friend	1	2	9
d. A caregiver other than a member of your family or a friend	1	2	9
e. Someone else	1	2	9

MG10. Did you accept the offer to have the Medication Guide explained to you?

Yes	1
No	2
Not sure	3
Refused (DO NOT READ OR SHOW ON SCREEN)	9

»PROGRAMMING NOTE: If respondent answers No (2) or Refused (9) to MG3, MG4, MG5, MG7, AND MG8, skip questions MG11 and MG12 and GO TO PC1.

MG11. How useful did you find the information in the Medication Guide? Was it . . . (READ LIST)

Not useful at all	1
Not very useful	2
Somewhat useful	3
Very useful	4
Refused (DO NOT READ OR SHOW ON SCREEN)	9

MG12. How well did you understand the information in the Medication Guide? Would you say . . . (READ LIST)

I did not understand it at all	1
I understood less than half of the information	2
I understood about half of the information	3
I understood most of the information	4
I understood all of the information	5
Refused (DO NOT READ OR SHOW ON SCREEN)	9

ER/LA OPIOID ANALGESIC PATIENT COUNSELING DOCUMENT (PCD) QUESTIONS

Now we want to know more about the healthcare provider who prescribed [OPIOID].

PC1. How long ago was your most recent visit to the healthcare provider who prescribed [OPIOID]?

Less than 1 month ago	1
1 month to less than 2 months ago	2
2 months to less than 3 months ago	3
3 months to less than 6 months ago	4
6 months to less than 9 months ago	5
9 months to less than 12 months ago	6
12 months or more ago	7
Not Sure	8
Refused (DO NOT READ OR SHOW ON SCREEN)	9

PC2a. How long ago did your healthcare provider first prescribe [OPIOID]?

Less than 1 month ago	1
1 month to less than 2 months ago	2
2 months to less than 3 months ago	3
3 months to less than 6 months ago	4
6 months to less than 9 months ago	5
9 months to less than 12 months ago	6
12 months or more ago	7
Not Sure	8
Refused (DO NOT READ OR SHOW ON SCREEN)	9

PC2b. What kind of healthcare provider first prescribed [OPIOID]?

Pain specialist	1
Primary care physician, general practitioner, internal medicine specialist, or family practice physician	2
Other type of specialist	3
Nurse Practitioner or Physician Assistant	4
Not Sure	5
Refused (DO NOT READ OR SHOW ON SCREEN)	9

Now I am going to describe something called the Patient Counseling Document or PCD for your drug.

[PCD DESCRIPTION]

The PCD is a **1-page** document with two columns that says "PATIENT COUNSELING DOCUMENT ON EXTENDED-RELEASE / LONG-ACTING OPIOID ANALGESICS" at the top. The first column describes the DOs and DON'Ts of ER/LA Opioid Analgesics and the second column provides space for your healthcare provider to write additional information to help you use your [OPIOID] safely.

PC3a. When your healthcare provider prescribed your current [OPIOID] medicine the first time, did he/she give you or your caregiver a Patient Counseling Document or PCD?

Yes	1
No	2
Not sure	3
Refused (DO NOT READ OR SHOW ON SCREEN)	9

PC3b. Did your healthcare provider give you or your caregiver a Patient Counseling Document or PCD for [OPIOID] in the last 12 months?

Yes	1

No	2
Not sure	3
Refused (DO NOT READ OR SHOW ON SCREEN)	9

PC3c. When your healthcare provider prescribed [OPIOID] in the last 12 months, did he/she ever refer to or talk to you or your caregiver about a Patient Counseling Document or PCD?

Yes	1
No	2
Not sure	3
Refused (DO NOT READ OR SHOW ON SCREEN)	9

»PROGRAMMING NOTE: If respondent answers No (2) or Refused (9) to PC3A, PC3B, AND PC3C, skip question PC3D and GO TO PC4.

PC3d. How well did you understand the information discussed from the Patient Counseling Document or PCD? Would you say… (READ LIST)

I did not understand it at all	1
I understood less than half of the information	2
I understood about half of the information	3
I understood most of the information	4
I understood all of the information	5
Refused (DO NOT READ OR SHOW ON SCREEN)	9

PC4. When your healthcare provider prescribed [OPIOID] in the last 12 months, did he/she ever discuss with you or your caregiver why he/she chose [OPIOID], including the benefits and risks associated with opioid therapy, and important safety information related to this type of medication?

Yes	1
No	2
Not sure	3
Refused (DO NOT READ OR SHOW ON SCREEN)	9

PC5. When your healthcare provider prescribed [OPIOID] in the last 12 months, did he/she ever discuss with you or your caregiver how to safely discontinue [OPIOID}?

Yes	1
No	2
Not sure	3
Refused (DO NOT READ OR SHOW ON SCREEN)	9

PC6. When your healthcare provider prescribed [OPIOID] in the last 12 months, did he/she ever discuss with you or your caregiver what you should do if you miss a dose of [OPIOID]?

Yes	1
No	2
Not sure	3
Refused (DO NOT READ OR SHOW ON SCREEN)	9

PC7. When your healthcare provider prescribed [OPIOID] in the last 12 months, did he/she ever complete a Patient Prescriber Agreement also known as the PPA or patient contract with you or your caregiver? A PPA is an agreement with your healthcare provider that you or your caregiver sign. It reviews goals for using your medicine, and specifies provider responsibilities, patient responsibilities, and any special information such as information about getting more medication and risks.

Yes	1
No	2
Not sure	3
Refused (DO NOT READ OR SHOW ON SCREEN)	9

ER/LA OPIOID ANALGESIC ACCESS QUESTIONS

We would now like to ask you some questions about your experiences with obtaining ER/LA opioid analgesic medicines.

AT1. Based upon your experience using ER/LA opioid analgesic medicines, please [INTERNET: indicate/PHONE: tell me] whether you agree or disagree with the following statements. Would you say you "strongly disagree," "disagree," "neither agree nor disagree," "agree" or "strongly agree" that…

	[RANDOMIZE ORDER OF STATEMENTS]	Strongly Disagree	Disagree	Neither Agree Nor Disagree	Agree	Strongly Agree
a.	I can get a prescription for [OPIOID] from my healthcare provider when I need it for my pain.	1	2	3	4	5
b.	I am satisfied with my ability to get a prescription for [OPIOID].	1	2	3	4	5
c.	My healthcare provider asked me about my medical history when prescribing [OPIOID].	1	2	3	4	5
d.	My healthcare provider talked to me about how much medication to take or use when s/he prescribed [OPIOID].	1	2	3	4	5
e.	My healthcare provider talked to me about what to do with extra medication when s/he prescribed [OPIOID].	1	2	3	4	5
f.	I am satisfied with my access to [OPIOID].	1	2	3	4	5
g.	I have to go to my healthcare provider too often when I need more [OPIOID].	1	2	3	4	5
h.	I am satisfied with my ability to get [OPIOID] from	1	2	3	4	5

a pharmacy.

AT2. We would like to know how often your healthcare provider did the following activities in the past 12 months when you visited him/her. Please answer "always", "regularly", "sometimes", "rarely", "never" or "I don't know."

	[RANDOMIZE ORDER OF STATEMENTS]	Always	Regularly	Sometimes	Rarely	Never	I don't know
a.	Used the Patient Counseling Document or PCD on Extended-Release/Long-Acting Opioids for discussions with me.	1	2	3	4	5	6
b.	Cautioned me about important risks associated with [OPIOID], including overdose or taking or using too much.	1	2	3	4	5	6
c.	Discussed with me how to safely discontinue [OPIOID] if I no longer need it.	1	2	3	4	5	6
d.	Counseled me on the most common side effects from using [OPIOID].	1	2	3	4	5	6
e.	Instructed me about the importance and how to safely dispose of any unused opioid drugs, including [OPIOID].	1	2	3	4	5	6
f.	Instructed me about keeping [OPIOID] safe and away from children.	1	2	3	4	5	6
g.	Instructed me not to share my [OPIOID] with anyone else.	1	2	3	4	5	6

DEMOGRAPHIC INFORMATION

Finally, we would like to know more about you.

D1. (IF PHONE: Mark gender without asking, unless confirmation of gender is needed.) Are you …

Male	1
Female	2
Refused (DO NOT READ OR SHOW ON SCREEN)	9

D2. How old are you?

_____ YEARS
[RANGE 18-120]
998 = Don't know/Not sure
999 = Refused (DO NOT READ OR SHOW ON SCREEN)

D3. Do you consider yourself to be Hispanic or Latino?

Yes	1
No	2
Refused (DO NOT READ OR SHOW ON SCREEN)	9

D4. What race do you consider yourself to be? (INTERNET: Please choose one response) (PHONE: READ LIST)

White or Caucasian	1
Black or African American	2
Asian or Pacific Islander	3
American Indian or Alaska Native	4
Mixed racial background	5
Some other race	6
Refused (DO NOT READ OR SHOW ON SCREEN)	9

D5. What is your current marital status? Would you say you are…

Single, never married	1
Married/Living with partner	2
Separated/Divorced	3
Widowed	4
Other marital status	5
Refused (DO NOT READ OR SHOW ON SCREEN)	9

D6. What is the highest level of education you have completed or the highest degree you have received? (INTERNET: Please choose one response) (PHONE: READ LIST)

Less than high school	1
Some high school, but no degree or GED	2
High school or equivalent such as a GED	3
Some college, but no degree	4
Two-year degree (community or technical)	5
College graduate	6
Graduate school	7
Other	8
Don't know	9
Refused (DO NOT READ OR SHOW ON SCREEN)	99

D7. Which of the following categories best describes your household's total income this past year (2013) before taxes? (INTERNET: Please choose one response) (PHONE: READ LIST)

Less than $25,000	1
$25,000 - $49,999	2
$50,000 - $74,999	3
$75,000 - $99,999	4
$100,000 or more	5
Don't know	6
Refused (DO NOT READ OR SHOW ON SCREEN)	9

(PHASE 1 ONLY) SURVEY FEEDBACK QUESTIONS

We would now like to ask you some questions about your experience with this survey.

SF1. Based upon your experience with this survey, please [INTERNET: indicate/PHONE: tell me] whether there were any questions in this survey that you found confusing or had difficulty understanding or answering?

YES 1 **GO TO SF2**
NO 0 **GO TO SF3**

SF2. What did you find confusing or have difficulty answering in this survey?

ENTER RESPONSE: _____

SF3. Were the Medication Guide, and Patient Counseling Document or PCD described clearly?

YES 1 **GO TO SF5**
NO 0 **GO TO SF4**

SF4. What did you find confusing in the explanation of the Medication Guide, or Patient Counseling Document or PCD?

ENTER RESPONSE: _____

SF5. By which term(s) do you refer to your [OPIOID]? Do you say… *(Select one response per row)*

	Yes	No	Refused (NO NOT READ OR SHOW ON SCREEN)
a. Extended release	1	2	9
b. ER	1	2	9
c. Controlled release	1	2	9
d. Long-acting	1	2	9
e. LA	1	2	9
f. Slow release	1	2	9

SF6. If you use a different term to describe your [OPIOID], what is it?

ENTER RESPONSE: _____

SF7. What, if any, suggestions do you have for improving the survey?

ENTER RESPONSE: _____

SF8. Do you have any additional comments?

ENTER RESPONSE: _____

END OF SURVEY

SURVEY CLOSING

Thank you very much for your participation in this study. As a thank you for your contribution to this research study, we will be sending you a check for $20 to compensate you for your time.

PHONE SURVEY CLOSING

(PHONE_CLOSE)
INTERVIEWER:
I will be transferring you to my supervisor to collect your contact information. Please hold while I transfer the call?.

INTERVIEWER:

- ☑ MARK INTERVIEW AS COMPLETE - TRANSFERING TO INCENTIVE SURVEY
- ☑ PLACE THE CALL ON HOLD
- ☑ VACATE THE INTERVIEWER STATION
- ☑ ALERT SUPERVISOR OF COMPLETE

SUPERVISOR:

- ☑ TAKE SEAT AT INTERVIEWER STATION
- ☑ COLLECT INCENTIVE INFORMATION

SUPERVISOR: Thank you for holding. My name is (INSERT NAME) and I will be collecting your name and address information in order to send you the check for $20.

SUPERVISOR:
I1. Just to confirm, can you please say and spell your first and last name?

NAME: (INCENT_NAME) _____

I2. Can you please say and spell your full street address?

STREET ADDRESS: (INCENT_STREET) _____

I3. Can you please spell your city?

CITY: (INCENT_CITY) _____

I4. And, what state do you live in?

STATE: (INCENT_STATE) _____

I5. Finally, what is your zip-code?

ZIP CODE: (INCENT_ZIP) _____

Thank you, just to confirm, I have (REPEAT ALL INFORMATION UNTIL CORRECT).

NAME:(INCENT_NAME) _____

STREET ADDRESS:(INCENT_STREET) _____

CITY:(INCENT_CITY) _____

STATE:(INCENT_STATE) _____

ZIP CODE:(INCENT_ZIP) _____

WARNING TEXT IF THEY DO NOT PROVIDE NAME AND ADDRESS
You have not given your name and address information, if you want to continue without answering please hit "Next Page". If you do not provide your complete name and address we will be unable to send you the payment. Would you like to receive the payment?

Yes	1	COLLECT INFORMATION
No	2	End call and mark as Refused Incentive

[ACCEPTED HONORARIA]
You should receive your check in the four to six weeks. If you do not, please call 1-800-729-6774 and refer to the (INSERT STUDY NAME) study. Again, thank you very much for your help!

ONLINE SURVEY CLOSING

[Internet: Please fill in your name and mailing address in the spaces below so that we can send you the $20 check we promised as our way of showing our thanks for your participation. You will receive the check for $20 by mail within the next four to six weeks. If you do not, please call **XXX** and refer to **XXX STUDY**.

Your participation in the study provides valuable information to help the FDA understand what people know about the safe use of some pain medications. Again, thank you very much!]

NAME: _____
STREET ADDRESS 1: _____
STREET ADDRESS 2: _____
CITY: _____
STATE: _____
ZIP CODE: _____

»PROGRAMMING NOTE: *WARNING TEXTS WILL APPEAR IF THEY DO NOT PROVIDE NAME AND ADDRESS OR IF THERE ARE INVALID ANSWERS ENTERED IN STATE/ZIP FIELDS.*

»PROGRAMMING NOTE: *THESE ADDITIONAL INSTRUCTIONS WILL APPEAR ON THE ONLINE CLOSING SCREEN: In order to receive the $20 payment for your time, please enter information in all fields and then click on the "Next Page" button below to submit your responses.*

If you prefer not to disclose this information, simply click the "Next Page" button. However, if you do not provide your complete name and address we will be unable to send you the payment.

END

APPENDIX D. SAFETY EVENT REPORT FORM

Safety Event (SE) Reporting Instructions

- Only spontaneously reported AE events mentioned in association with an extended release (ER) / long-acting (LA) opioid analgesic product will be reported. Please see "Product information" for a list of reportable products.
- No further information will be probed for and only what was stated during the course of the normal survey process will be documented.
- Vendor to send to Amanda Rodriguez (HealthCore, Inc.) within one (1) business day of discovery of AE.
- Email form to arodriguez@healthcore.com or fax to 302-230-2020.

Data always to be reported

Patient information

- Initials _____
- Gender _____
- Age _____

Product information

Drug name (circle name)

- Avinza®
- Butrans®
- Duragesic®
- Dolophine®
- Embeda®
- Exalgo®
- Fentanyl transdermal system (generic)
- Kadian®
- Methadose™
- Methadone hydrochloride (generic)
- Morphine sulfate controlled/slow release tablets and capsules (generic)
- MS Contin®
- Nucynta® ER
- Opana® ER
- OxyContin® slow/extended release
- Oxycodone hydrochloride slow release tablets (generic)
- Oxymorphone hydrochloride extended release tablets (generic)
- Zohydro ER™

Reporter information

- Vendor contact information (address/phone number)

Adverse Event information

- Description:

_____
_____
_____
_____
_____

Data to be reported if mentioned spontaneously during the survey. DO NOT PROBE!

Product information

- Dose _____
- Time of administration _____
- Indication _____

Adverse Event information

- Date of occurrence _____
- Additional Outcome details:

_____
_____

APPENDIX E. PRE-TEST PATIENT SURVEY RESULTS

14 March 2014

"Extended Release (ER) / Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS): Patient Survey to Support Food and Drug Administration (FDA) Assessment Report 3"

Memorandum: Patient survey pre-test results

At this time, we have completed the Phase I pre-test patient survey as described in the study Protocol titled "Extended Release (ER) / Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS): Patient Survey to Support Food and Drug Administration (FDA) Assessment Report 3" (final version 1, 14 January 2014). This memorandum describes key results and recommended modifications to the Phase II main patient survey arising from this exercise.

Pre-test survey process and results

Using administrative data in the HIRD[SM], we identified 39,237 patients that had at least two distinct pharmacy claims for any ER/LA opioid analgesic between 01 November 2012 and 31 October 2013. Of these, 12,478 met all preliminary screening criteria.

Pre-notification letters were sent to 642 individuals selected as candidates for inclusion in the pre-test survey with the goal of obtaining 21 completed surveys. Because we did not reach the number of completed surveys in the targeted timeframe, we revised the Protocol to allow our survey vendor (ORC) to contact patients by telephone as part of the pre-test survey process. Of the 642 patients included in the initial list, 21 completed the survey, 5 started but chose not to finish, 23 did not meet in-survey screening criteria, 94 refused to participate and 180 had invalid contact information. An additional 319 candidates were not contacted by phone as the target number of completed surveys had been reached. The median survey length, including the introduction, closing, and additional pre-test feedback questions was less than 25 minutes.

The mean age of the 21 survey respondents was 49.6 years and 76% were female. All were Caucasian, 52% were married/living with a partner and 76% had at least some college education. In total, six used only oral drugs that were not methadone, four used patch products and no methadone (two using patch only and two using both patch and oral drugs), and 11 used methadone (six using methadone only, three using methadone and non-methadone oral products, and two using methadone, non-methadone oral drugs, and patch). Only two patients were new users of ER/LA opioid analgesics, and 86% had last filled a prescription less than two months prior to the survey.

All 21 respondents reported that they had received the Medication Guide in the past 12 months, and 20 (95%) reported receiving it with their most recent ER/LA opioid dispensing.

Due to an error in survey skip patterns that have been corrected in the main survey questionnaire, questions about whether patients read and understood the Medication Guide were asked of only two participants. There were five respondents that recalled receiving a PCD.

Pre-test survey respondents showed strong understanding of the key messages from the Medication Guide and PCD. The mean Knowledge Assessment Score (KAS; i.e., proportion of correctly answered questions about safe use, storage, and disposal of ER/LA opioid analgesics with possible score values ranging from 0% to 100%) was 89.7% ± 8.4%, and 95% of pre-test respondents had a KAS ≥70%.

All pre-test respondents correctly identified that overdose may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death; they must seek emergency medical care in the presence of key side effects; alcohol should not be used while taking these medications; these medications cannot be shared; and a child could die from using these medications. The questions that respondent most often answered incorrectly were not to store ER/LA opioid analgesics in the medicine cabinet with other medications in the household (62% correct), the Medication Guide should be read at each ER/LA opioid prescription fill (71% correct), and the negative control question of whether caffeine can be used with these medications (52% correct). Most questions concerning satisfaction with access to treatment had a favorable response.

As part of the pre-test survey, we asked for feedback and recommendations to improve the survey; six respondents (29%) found at least one survey question confusing or difficult to understand. Most noted survey wording but could not recall specific problematic questions. One respondent referred specifically to questions about satisfaction with access to treatment. Pre-specified terms chosen to indicate ER/LA opioid analgesics rather than immediate release equivalents (e.g., “extended release,” “controlled release”, “long-acting”, etc.) were well understood. Other recommendations included identifying whether patients were under the care of a pain specialist and clarifying that the survey is required by the FDA.

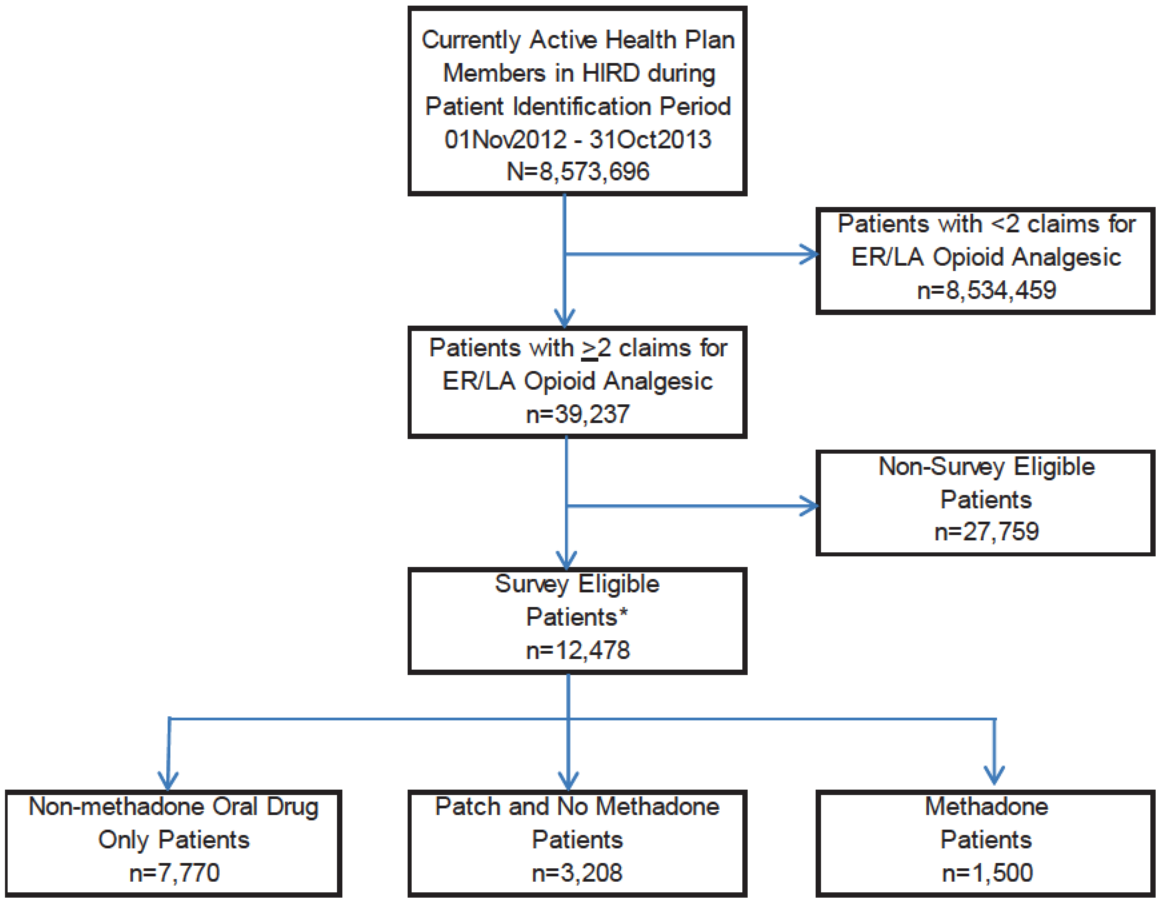
Recommendations

On the basis of an analysis of the pre-test processes and data, recommended modifications to the survey processes and/or patient survey questionnaire are:

- Revise the pre-notification letter to state that the survey is required by the FDA.
- Make the following changes to survey skip patterns:
    - Ask all patients whether they read and understood the Medication Guide;
    - Do not ask patients stating that no one offered to explain the Medication Guide whether they accepted the offer to have the Medication Guide explained; and
    - Ask all patients whether their healthcare provider referred to a PCD.
- Include a new question asking patients whether they understood the PCD.
- Include a new question asking what type of physician prescribed the ER/LA opioid analgesic.

Full results from the patient survey pre-test are shown in the following figure and tables.

Figure 1: Patient Sample List Selection, Phase I Pre-test Patient Survey



*Survey eligible = Age ≥18 years; continuous eligibility during entire study period with >6 months continuous eligibility prior to most recent claims for any ER/LA opioid analgesic; no claims for methadone and substance abuse or addiction; currently active member of commercial health plan; not on HealthCore Do-Not-Call list; non-missing address/telephone number

Table 1. Demographic Characteristics Among Survey Respondents, Phase I Pre-test Patient Survey		
	N	*(%)*
Total number of respondents	**21**	**(28.6)**
Age in years, *mean ± STD* [D2]		49.6 ± 9.9
18 to 34	2	(9.5)
35 to 49	7	(33.3)
50 to 64	11	(52.4)
65+	1	(4.8)
Gender [D1]		
Female [D1=2]	16	(76.2)
Male	5	(23.8)
US region [3] [I4]		
Northeast	1	(4.8)
South	5	(23.8)
Midwest	8	(38.1)
West	7	(33.3)
Hispanic or Latino [D3]	6	(28.6)
Race/ethnicity [D4]		
White or Caucasian	21	(100.0)
Other	0	(0.0)
Marital status [D5]		
Single, never married	5	(23.8)
Married/Living with partner	11	(52.4)
Separated/Divorced/Widowed	5	(23.8)
Other marital status	0	(0.0)
Income level, US dollars [D7]		
Less than $25,000	1	(4.8)
$25,000 to $49,999	3	(14.3)
$50,000 to $74,999	5	(23.8)
$75,000 to $99,999	6	(28.6)
$100,000 or more	4	(19.0)
Don't know/refused	1	(4.8)
Education level [D6]		
Less than high school	0	(0.0)
Some high school, but no degree or GED	0	(0.0)
High school or equivalent such as a GED	5	(23.8)
Some college, but no degree	4	(19.0)
Two-year degree (community or technical)	4	(19.0)
College graduate	5	(23.8)
Graduate school	3	(14.3)

Specific ER/LA opioid analgesic(s) used [S9]		
Oral drugs that are not methadone only	**6**	**(28.6)**
Patch and no methadone	**4**	**(19.0)**
Patch only	2	(9.5)
Patch and oral drug(s) that are not methadone	2	(9.5)
Methadone	**11**	**(52.4)**
Methadone only	6	(28.6)
Methadone and oral drug(s) that are not methadone	3	(14.3)
Methadone and patch	0	(0.0)
Methadone, oral drug(s) that are not methadone, and patch	2	(9.5)
New user [MG2]		
First use	2	(9.5)
Used before	19	(90.5)
Time since last prescription [MG1]		
Less than one month ago	14	(66.7)
One month to less than two months ago	4	(19.0)
Two months to less than three months ago	1	(4.8)
Three months to less than six months ago	1	(4.8)
Six months to less than nine months ago	1	(4.8)
Nine or more months ago	0	(0.0)

ER, extended release; GED, General Education Degree; LA, long-acting; STD, standard deviation; US, United States. Corresponding survey question numbers are indicated in brackets.

Table 2. Respondents who Received and/or Read the Medication Guide, Phase I Pre-test Patient Survey		
	N	*(%)*
Total number of respondents	**21**	
Received MG from pharmacist with last ER/LA opioid analgesic prescription fill [MG3]	20	(95.2)
Received MG from pharmacist in the last 12 months [MG4]	21	(100.0)
Received MG from non-pharmacist in the last 12 months [MG5]	2	(9.5)
Read MG * [MG7]		
Never read any	0	(0.0)
Read some, at least once	0	(0.0)
Read all, at least once	1	(4.8)
Read all, with each pharmacy fill	1	(4.8)
Offer to explain MG [MG8]	2	(9.5)
Person offering to explain MG [MG9]		
Pharmacist or someone at the pharmacy	2	(9.5)
Healthcare provider or someone in the healthcare provider's office/clinic	1	(4.8)
Accepted offer to explain MG [MG10]	0	(0.0)
Usefulness of the information in the MG [MG11]		
Not useful at all	1	(4.8)
Not very useful	0	(0.0)
Somewhat useful	1	(4.8)
Very useful	0	(0.0)
Understanding of the information in the MG [MG12]		
Did not understand it at all	0	(0.0)
Understood some of the information	0	(0.0)
Understood about half of the information	0	(0.0)
Understood most of the information	1	(4.8)
Understood all of the information	1	(4.8)

ER, extended release; MG, Medication Guide; LA, long-acting. Corresponding survey question numbers are indicated in brackets.
* Due to an error in the pre-test survey skip pattern, only respondents with a non-pharmacist source that provided the Medication Guide in the past 12 months (N = 2) were asked questions in the blue shaded region.

Table 3. Respondents who Received and/or Referenced the Patient Counseling Document, by ER/LA Opioid Analgesic Type, Phase I Pre-test Patient Survey		
	N	*(%)*
Total number of respondents	**21**	
Most recent visit to the healthcare provider who prescribed the most recent ER/LA opioid analgesic [PC1]		
Less than one month ago	9	(42.9)
One month to less than two months ago	4	(19.0)
Two months to less than three months ago	7	(33.3)
Three months to less than six months ago	1	(4.8)
Six or more months ago	0	(0.0)
Time since healthcare provider first prescribed the most recent ER/LA opioid analgesic [PC2]		
Less than six months ago	0	(0.0)
Six months to less than nine months ago	1	(4.8)
Nine months to less than 12 months ago	0	(0.0)
12 months or more ago	19	(90.5)
Received PCD from healthcare provider when first prescribed the current ER/LA opioid analgesic [PC3A]		
Yes	5	(23.8)
No	4	(19.0)
Not sure	12	(57.1)
Healthcare provider referred to or discussed PCD when prescribing the current ER/LA opioid analgesic * [PC3B]		
Yes	1	(4.8)
No	11	(52.4)
Not sure	4	(19.0)
Healthcare provider discussed opioid choice, including the benefits and risks associated with opioid therapy, and important safety information when first prescribing the current ER/LA opioid analgesic [PC4]	18	(85.7)
Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic when it was first prescribed [PC5]	12	(57.1)
Healthcare provider discussed what to do if a dose was missed of the current ER/LA opioid analgesic when it was first prescribed [PC6]	14	(66.7)
Healthcare provider completed a Patient Prescriber Agreement (PPA) or patient contract when the current ER/LA opioid analgesic was first prescribed [PC7]	11	(52.4)

ER, extended release; LA, long-acting; PCD, Patient Counseling Document; PPA, Patient Prescriber Agreement. Corresponding survey question numbers are indicated in brackets.
* Due to an error in the pre-test survey skip pattern, only respondents that stated that they had received a PCD from their healthcare provider when first prescribed the current ER/LA opioid analgesic (N = 16) were asked whether their healthcare provider referenced or discussed the PCD (the blue shaded region).

Table 4. Respondent Knowledge Assessment, Phase I Pre-test Patient Survey		
	N	*(%)*
Total number of respondents	**21**	
Whether the patient understands the serious risks associated with the use of their ER/LA opioid analgesic		
Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death.		
Answered correctly [KA1a=4,5]	21	(100.0)
Answered incorrectly [KA1a=1,2]	0	(0.0)
Didn't know [KA1a=3]	0	(0.0)
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.		
Answered correctly [KA1d=4,5]	19	(90.5)
Answered incorrectly [KA1d=1,2]	2	(9.5)
Didn't know [KA1d=3]	0	(0.0)
Whether the patient knows what to do if they take too much drug		
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine.		
Answered correctly [KA1g=4,5]	20	(95.2)
Answered incorrectly [KA1g=1,2]	0	(0.0)
Didn't know [KA1g=3]	1	(4.8)
Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics.		
Answered correctly [KA1h=4,5]	21	(100.0)
Answered incorrectly [KA1h=1,2]	0	(0.0)
Didn't know [KA1h=3]	0	(0.0)
Whether the patient understands the need to store the drug in a safe place		
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household.		
Answered correctly [KA1f=1,2]	13	(61.9)
Answered incorrectly [KA1f=4,5]	6	(28.6)
Didn't know [KA1f=3]	2	(9.5)
Do not throw any unused ER/LA opioid analgesic in the trash.		
Answered correctly [KA1j=1,2]	18	(85.7)
Answered incorrectly [KA1j=4,5]	2	(9.5)
Didn't know [KA1j=3]	1	(4.8)
A child could die if they take or use the respondent's ER/LA opioid analgesics.		
Answered correctly [KA1o=4,5]	21	(100.0)

Answered incorrectly [KA1o=1,2]	0	(0.0)
Didn't know [KA1o=3]	0	(0.0)
Whether the patient knows they should not share the drug with anyone		
Do not give ER/LA opioid analgesics to other people who have the same condition as you.		
Answered correctly [KA1i=1,2]	21	(100.0)
Answered incorrectly [KA1i=4,5]	0	(0.0)
Didn't know [KA1i=3]	0	(0.0)
Selling or giving away ER/LA opioid analgesics is against the law.		
Answered correctly [KA1n=4,5]	20	(95.2)
Answered incorrectly [KA1n=1,2]	1	(4.8)
Didn't know [KA1n=3]	0	(0.0)
Whether the patient understands how to use the drug safely		
Talk to a healthcare provider prior to stopping ER/LA opioid analgesics.		
Answered correctly [KA1b=1,2]	20	(95.2)
Answered incorrectly [KA1b=4,5]	1	(4.8)
Didn't know [KA1b=3]	0	(0.0)
Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control the pain.		
Answered correctly [KA1c=1,2]	19	(90.5)
Answered incorrectly [KA1c=4,5]	1	(4.8)
Didn't know [KA1c=3]	1	(4.8)
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics.		
Answered correctly [KA1e=1,2]	21	(100.0)
Answered incorrectly [KA1e=4,5]	0	(0.0)
Didn't know [KA1e=3]	0	(0.0)
Read the attached MG every time an ER/LA opioid prescription is filled.		
Answered correctly [KA1k=1,2]	15	(71.4)
Answered incorrectly [KA1k=4,5]	5	(23.8)
Didn't know [KA1k=3]	1	(4.8)
Inform healthcare provider about all the other medications being used.		
Answered correctly [KA1l=1,2]	20	(95.2)
Answered incorrectly [KA1l=4,5]	1	(4.8)
Didn't know [KA1l=3]	0	(0.0)
Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems.		
Answered correctly [KA1m=1,2]	19	(90.5)
Answered incorrectly [KA1m=4,5]	1	(4.8)

Didn't know [KA1m=3]	1	(4.8)
Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplements.		
Answered correctly [KA1p=1,2]	20	(95.2)
Answered incorrectly [KA1p=4,5]	1	(4.8)
Didn't know [KA1p=3]	0	(0.0)
Do not drink caffeine while using ER/LA opioid analgesics.		
Answered correctly [KA1q=4,5]	11	(52.4)
Answered incorrectly [KA1q=1,2]	2	(9.5)
Didn't know [KA1q=3]	8	(38.1)
Survey questions only asked of non-methadone oral drugs only respondents (N = 6)		
ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication.		
Answered correctly [KA1r=1,2]	6	(100.0)
Answered incorrectly [KA1r=4,5]	0	(0.0)
Didn't know [KA1r=3]	0	(0.0)
Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed.		
Answered correctly [KA1s=1,2]	5	(83.3)
Answered incorrectly [KA1s=4,5]	1	(16.7)
Didn't know [KA1s=3]	0	(0.0)
Survey questions only asked of patch and no methadone respondents (N = 4)		
Inform healthcare provider of any fever.		
Answered correctly [KA1t=4,5]	4	(100.0)
Answered incorrectly [KA1t=1,2]	0	(0.0)
Didn't know [KA1t=3]	0	(0.0)
Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists.		
Answered correctly [KA1u=1,2]	4	(100.0)
Answered incorrectly [KA1u=4,5]	0	(0.0)
Didn't know [KA1u=3]	0	(0.0)
Do not cut ER/LA opioid analgesic patches in half to use less medicine.		
Answered correctly [KA1v=1,2]	4	(100.0)
Answered incorrectly [KA1v=4,5]	0	(0.0)
Didn't know [KA1v=3]	0	(0.0)

ER, extended release; LA, long-acting. Corresponding survey question numbers are indicated in brackets.

Table 5. Respondent Knowledge Assessment Score, Phase I Pre-test Patient Survey		
	N	*(%)*
Total number of respondents	**21**	
Knowledge Assessment Score (KAS), *mean ± STD*	89.7 ± 8.4	
Knowledge Assessment Score (KAS), *median*	94.1	
Knowledge Assessment Score (KAS), *minimum*	68.4	
Knowledge Assessment Score (KAS), *maximum*	100.0	
KAS threshold		
>= 70%	20	(95.2)
< 70%	1	(4.8)

ER, extended release; KAS, Knowledge Assessment Score; LA, long-acting; STD, standard deviation.

Table 6. Respondent Satisfaction with Access to ER/LA Opioid Analgesic Treatment, Phase I Pre-test Patient Survey		
	N	*(%)*
Total number of respondents	**21**	
Able to get a prescription for ER/LA opioid analgesics through my healthcare provider when needed.		
Agreed [AT1a=4,5]	18	(85.7)
Disagreed [AT1a=1,2]	1	(4.8)
Neither agreed nor disagreed [AT1a=3]	2	(9.5)
Satisfied with ability to get a prescription for ER/LA opioid analgesics.		
Agreed [AT1b=4,5]	16	(76.2)
Disagreed [AT1b=1,2]	3	(14.3)
Neither agreed nor disagreed [AT1b=3]	2	(9.5)
Healthcare provider asked about medical history when prescribing ER/LA opioid analgesics.		
Agreed [AT1c=4,5]	21	(100.0)
Disagreed [AT1c=1,2]	0	(0.0)
Neither agreed nor disagreed [AT1c=3]	0	(0.0)
Healthcare provider talked about how much medication to take or use when ER/LA opioid analgesics were prescribed.		
Agreed [AT1d=4,5]	21	(100.0)
Disagreed [AT1d=1,2]	0	(0.0)
Neither agreed nor disagreed [AT1d=3]	0	(0.0)
Healthcare provider talked about what to do with extra medication when ER/LA opioid analgesics were prescribed.		
Agreed [AT1e=4,5]	10	(47.6)
Disagreed [AT1e=1,2]	7	(33.3)
Neither agreed nor disagreed [AT1e=3]	4	(19.0)
Satisfied with access to ER/LA opioid analgesics.		
Agreed [AT1f=4,5]	19	(90.5)
Disagreed [AT1f=1,2]	2	(9.5)
Neither agreed nor disagreed [AT1f=3]	0	(0.0)
Does not have to go to healthcare provider too often when more ER/LA opioid analgesics are needed.		
Agreed [AT1g=1,2]	6	(28.6)
Disagreed [AT1g=4,5]	14	(66.7)
Neither agreed nor disagreed [AT1g=3]	1	(4.8)
Satisfied with ability to get ER/LA opioid analgesics from a pharmacy.		
Agreed [AT1h=4,5]	20	(95.2)
Disagreed [AT1h=1,2]	1	(4.8)
Neither agreed nor disagreed [AT1h=3]	0	(0.0)

ER, extended release; LA, long-acting. Corresponding survey question numbers are indicated in brackets.

Table 7. Respondent-reported Healthcare Provider Activities in the Past 12 Months, Phase I Pre-test Patient Survey

	All survey respondents	
	N	*(%)*
Total number of respondents	**21**	
Used the PCD on ER/LA Opioids for discussions.		
Always [AT2a=1]	2	(9.5)
Regularly [AT2a=2]	1	(4.8)
Sometimes [AT2a=3]	0	(0.0)
Rarely [AT2a=4]	5	(23.8)
Never [AT2a=5]	7	(33.3)
Didn't know [AT2a=6]	6	(28.6)
Cautioned about important risks associated with ER/LA opioid analgesics, including overdose or taking or using too much.		
Always [AT2b=1]	4	(19.0)
Regularly [AT2b=2]	5	(23.8)
Sometimes [AT2b=3]	4	(19.0)
Rarely [AT2b=4]	4	(19.0)
Never [AT2b=5]	3	(14.3)
Didn't know [AT2b=6]	1	(4.8)
Discussed how to safely discontinue ER/LA opioid analgesics if they are no longer needed.		
Always [AT2c=1]	5	(23.8)
Regularly [AT2c=2]	3	(14.3)
Sometimes [AT2c=3]	1	(4.8)
Rarely [AT2c=4]	7	(33.3)
Never [AT2c=5]	5	(23.8)
Didn't know [AT2c=6]	0	(0.0)
Counseled on the most common side effects from using ER/LA opioid analgesics.		
Always [AT2d=1]	3	(14.3)
Regularly [AT2d=2]	5	(23.8)
Sometimes [AT2d=3]	7	(33.3)
Rarely [AT2d=4]	5	(23.8)
Never [AT2d=5]	1	(4.8)
Didn't know [AT2d=6]	0	(0.0)
Instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics.		
Always [AT2e=1]	3	(14.3)

Regularly [AT2e=2]	3	(14.3)
Sometimes [AT2e=3]	3	(14.3)
Rarely [AT2e=4]	4	(19.0)
Never [AT2e=5]	7	(33.3)
Didn't know [AT2e=6]	1	(4.8)
Instructed about keeping ER/LA opioid analgesics safe and away from children.		
Always [AT2f=1]	5	(23.8)
Regularly [AT2f=2]	3	(14.3)
Sometimes [AT2f=3]	3	(14.3)
Rarely [AT2f=4]	7	(33.3)
Never [AT2f=5]	2	(9.5)
Didn't know [AT2f=6]	1	(4.8)
Instructed not to share ER/LA opioid analgesics with anyone else.		
Always [AT2g=1]	6	(28.6)
Regularly [AT2g=2]	3	(14.3)
Sometimes [AT2g=3]	1	(4.8)
Rarely [AT2g=4]	8	(38.1)
Never [AT2g=5]	2	(9.5)
Didn't know [AT2g=6]	1	(4.8)

ER, extended release; LA, long-acting; PCD, Patient Counseling Document. Corresponding survey question numbers are indicated in brackets.

Appendix XX: Changes to the Patient Survey Protocol Following FDA Submission

On January 22, 2014, a protocol entitled "Extended Release (ER) / Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS): Patient Survey to Support Food and Drug Administration (FDA) Assessment Report 3" was submitted to the FDA for review. Following receipt of FDA comments and completion of the pre-test survey, the following protocol changes were implemented.

Table A1: Protocol Changes Requested by the FDA

PROTOCOL SECTION(S)	CHANGE REQUESTED	DESCRIPTION OF CHANGE
7. Study Design 9. Study Population 14. Statistical Methods	*Patients who have filled at least one prescription for ER/LA opioid analgesics within the most recent 12 months should be allowed to participate in the survey.*	We required only one dispensing of an ER/LA opioid analgesic rather than at least two prescriptions as an eligibility criterion for the survey patient list. We had initially proposed requiring at least two prescriptions in order to ensure that these patients were chronic medication users, however we expanded the candidate pool as requested. Based on the distribution of ER/LA opioid analgesic medication use in the sample list, we anticipated that approximately 35% of patients will have received only one prescription, and recognized the possibility that these patients may not have used the ER/LA opioid that was prescribed for them given the single dispensing. As such, stratified analyses were added comparing patients with only one recorded dispensing of an ER/LA opioid analgesic versus those that had more than one dispensing.
9. Study Population 12. Covariate Definition and Ascertainment 15. Limitations	*The requirement that patients are continuously eligible for their health plan during the most recent 12-month claims period and for at least 6 months prior to the index date (the most recent pharmacy claim for an ER/LA opioid analgesic) is not necessary. Patients should be eligible to participate as long as they are identified as having filled at least one prescription for ER/LA opioid analgesics within the most recent 12 months of claims data, regardless of the status of their memberships with the health plans. Provide justification for this requirement if it will be applied in the survey.*	We removed the requirements that patients are continuously eligible for their health plan during the most recent 12-month claims period and have at least six months of health plan eligibility prior to their most recent claims dispensing. We described duration of health plan eligibility prior to the most recent claims dispensing to better understand our ascertainment of the baseline demographic and clinical characteristics presented for respondents and non-respondents. Per our agreements with WellPoint, HealthCore can only use health plan members currently active at the time that the patient list is identified for survey purposes. As such, we were unable to remove the requirement that patients be currently active in an eligible health plan in order to qualify for the patient list.

9. Study Population Appendix B (Patient Survey)	*The exclusion criterion that patients who are no longer currently active members of their health plan at the time of the survey will be excluded is not appropriate. Since the survey does not need to collect future events or information, it is unnecessary to require that patients have to be currently active members of their health plans at the time of the survey. Provide justification for this requirement if it will be applied in the survey.* *Remove the proposed question S4: "Do you still have medical insurance with a health plan? Terminate if no". Patients who are not current member of a certain health plan should be still eligible to participate in the survey.*	We eliminated the survey screening requirement that patients have current health plan eligibility at the time of survey. This screening question was therefore removed.
9. Study Population Appendix B (Patient Survey)	*Exclude patients who have or whose immediate family members have ever worked for the sponsors of any ER/LA opioid analgesics, HealthCore, ORC International, Inc., or the FDA from participating in the surveys to minimize potential bias of survey results.*	We excluded patients who had or whose immediate family members had ever worked for HealthCore, the third party survey vendor, the FDA, or any RPC members. Applicable screening questions were added to the survey (S4A, S4B).
13. Clinical Data - Survey 14. Statistical Methods and Sample Size	*You are proposing to use a stratified sample with three strata (oral product users, patch users and methadone users). Please justify the choice of these strata and the weights used in sample size for each group in the sample, e.g. oral products users / patch users / methadone users. We are concerned that sample size for certain groups would under-represent or over-represent that group in the whole population. In a stratified sample, we recommend the precision of the estimate in the overall population be adjusted to account for sampling weights in this design.*	We removed the stratified approach and collected 400 surveys without requiring a fairly equal distribution across users of transdermal delivery systems, methadone, and other oral products.

Appendix B (Patient Survey)	*Modify the skipping logic for question MG8: "Did anyone offer to explain the MG to you in the last 12 months?" If "Yes", go to MG9. If "No", "Not sure", or refused in MG8, and "Never read any of the MG" is selected in MG7, go to PC1.* *Add skipping logic for MG10 so that if "Never read any of the MG" is selected in MG7, and "Yes" selected in MG8, and "No", "Not sure", or refused in MG10, go to PC1.*	We applied the requested skip patterns, noting that patients were still asked if they understood the Medication Guide and PCD if they were unsure of whether they received or read/had a provider that referenced the respective Medication Guide or PCD document. We modified skip patterns at questions MG5, MG8, and PC3A and added programming notes after MG10 and PC3c.
Appendix B (Patient Survey)	*Change the proposed question AT1a to: "I am able to get a prescription for opioid through my healthcare provider when I need it for my pain".*	The recommended language was inserted. Questions concerning access to treatment were reviewed and revised for clarity.

Table A2: FDA Comments Not Resulting in Protocol Changes

CHANGE REQUESTED	RESPONSE
Besides patients, caregivers for those patients who cannot complete the survey or those who are under 18 years of age, should be allowed to participate in the survey for assessment of their awareness and understanding of the serious risks associated with ER/LA opioid analgesics and compliance with the safe use requirements.	We were unable to implement the requested change. For purposes of collecting data from caregivers, HealthCore is required to ensure that the caregiver is a valid personal representative of the member, who can consent on behalf of the member. HealthCore does not have access to these records. Thus, was not possible to obtain a valid authorization and consent to participate from a third party for the purpose of this survey. In the case of minors, because our eligibility data comes from the health plan, only the information concerning the primary beneficiary is available to HealthCore. Often, this may not be the responsible parent or custodial parent and again, there is a consent issue. In addition, for purposes of including minors and/or their caregivers in research, we were required by the IRB to obtain written consent by the custodial parent and written assent by minors (ages 14 through 17 years) before proceeding with any data gathering. Participation rates were expected to be low and potentially non-representative.
Remove the proposed questions S6 and S7 which collect patients' e-mail address so patients can complete the survey on the internet. Instead, provide the link to the that survey and password in the pre-notification letter in addition to the opt-in phone number.	We agreed that the pre-notification letter should include a survey link and password. In the original Protocol and survey process, the link to the survey was included in the pre-notification letter, and patients that opt-in were able to access it either online or by phone. The reason that we additionally collected email addresses in questions S6 and S7 was that some patients contacted by phone may spontaneously request to complete the survey online. Because we did not already have email addresses available, we obtained them so that we could send a hyperlink to those individuals that

	asked to complete the survey online and chose to provide an email address. Given that many patients may have misplaced the mailed letter by the time they were contacted by phone and could not therefore be redirected to the pre-notification document, this was a useful approach.
Provide a list of ER/LA opioid analgesic products (ideally with names and pictures) with the proposed question S8 to help patients recognized whether they have filled such prescriptions.	After careful consideration, we concluded that the original approach achieves the main goals of this recommendation. We provided a list of ER/LA opioid analgesic products in the subsequent question, S9, after identifying whether patients used oral, patch or methadone products. This limited the need to read a long list of medications that were not applicable to a given patient group. We did not include pictures. The majority of respondents completed the survey by phone, and showing the products to only a small subset of respondents may have introduced differences. Also, generic products have a variety of appearances, and a picture of an unfamiliar, related product may have caused confusion had the recommendation been implemented.
Show a blurred version of Medication Guide (MG) along with the description of 11 MG after the proposed question MG2.	We did not incorporate this recommendation. We anticipated that the majority of respondents would complete the survey by phone without visual support. Because of this, only a small proportion of respondents would have seen the images. Of note, 100% of pre-test survey respondents felt that the Medication Guide description was clear.
Show a blurred version of PCD along with the description of PCD after the proposed question PC2.	We did not incorporate this recommendation. We anticipated that the majority of respondents would complete the survey by phone without visual support. Because of this, only a small proportion of respondents would have seen the images. Of note, 100% of pre-test survey respondents felt that the PCD description was clear.
Please explain why such low of 5% responder rate was observed in HealthCore database. We are concerned about how responders will represent whole population.	In prior surveys done by HealthCore, the proportion of patients who complete a survey of those patients who are contacted has ranged between 25 and 40%. The 5% rate is the list response rate (LCR) that is defined as the estimated percentage of completed surveys expected from a patient sample list. It is a metric, developed by HealthCore, used to estimate patient list size and number of completed surveys for budgeting and proposal purposes. It was developed because the patient list data HealthCore uses is often out-of-date. The patient contact information comes from the health plan eligibility files. These data are collected at the time the member enrolls in the health plan but are seldom, if at all, updated. Based on HealthCore's prior survey experience, it has been found that approximately 30% of the contact information on a patient list is incorrect/out-of-date and the patient cannot be contacted. In addition, another 30% of patients cannot be contacted after the maximum of 5 contact attempts (made at different times of the day and days of the week) has been reached. The maximum of 5 attempts is low compared to many the number of contact attempts allowed by many survey research organizations and it does limit the number of patients that can be reached. However, because member disturbance and abrasion is a primary

	concern, the maximum number of contact attempts has been set low and is a number that is indicated in the protocol and approved by the IRB. This means that approximately 60% of the patients on a patient list cannot be contacted. Of the approximately 40% of patients that are contacted, refusals account for 20-30%, exclusions because the patient no longer qualifies for the survey are <5%, and the remaining 5-10% patients complete the survey. Again, because of concern for member abrasion, refusal conversion is not allowed. So, in summary, for every 100 patient names on a survey sample list, approximately 60 will not be contacted either because their contact information is out-of-date or the maximum number of contact attempts has been reached, and of the 40 that can be contacted, 5-10 will complete the survey and the remaining will either refuse to participate or no longer meet survey eligibility criteria. A better metric to use is the cooperation rate which is the percentage of patients who complete a survey of those patients who are contacted. Cooperation rates ranging from 25-40% have been obtained in prior surveys.

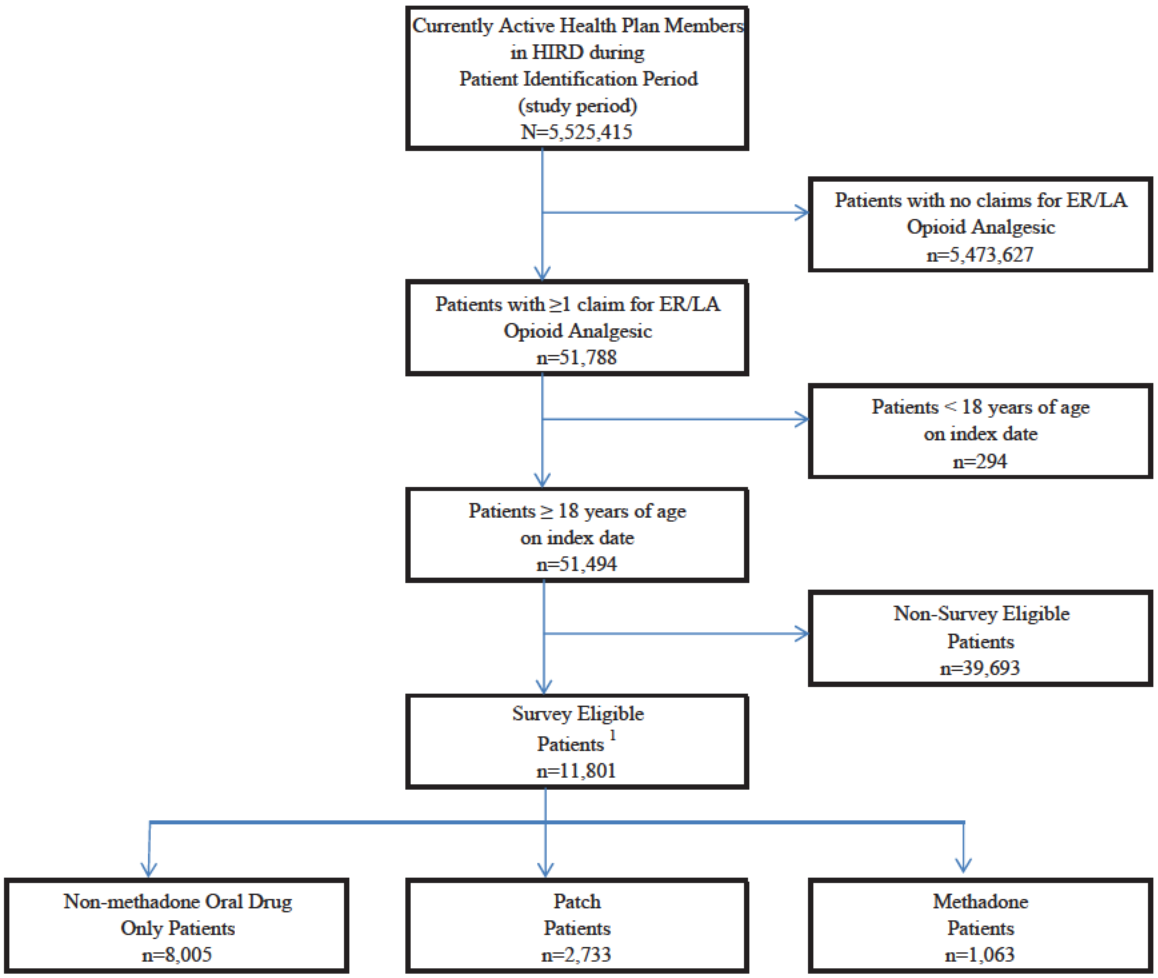
Table A3: Protocol Changes Not Requested by the FDA

PROTOCOL SECTION(S)	DESCRIPTION OF CHANGE	REASON FOR CHANGE
7. Study Design	Edited the study design to show that the survey vendor did contact potential participants during the pre-test patient survey.	During the pre-test, we determined that enrollment would not proceed within the required timeline without using the same vendor outbound dialing approach that was planned for the main survey. As such, we added this outbound dialing approach to the pre-test survey.
7. Study Design	Removed a stage of survey testing in which fielding is stopped and results analyzed after the first night of calling is complete.	Although interim survey results were reviewed for consistency, surveying was not stopped after the first night.
11. Outcome Definition and Assessment	Modified outcomes related to the Medication Guide and PCD for clarity and survey consistency.	This change aligned the survey, protocol and study objectives.
14. Statistical Methods and Sample Size	Statistical methods were revised for clarity. New analyses to identify risk factors for a low KAS were incorporated, and stratification by characteristics of interest was incorporated.	These changes were implemented to ensure alignment of the study objectives, Protocol and DAP.
Appendix B (Patient Survey)	Throughout the patient survey, we reviewed and edited wording and skip patterns for clarity and consistency.	We identified and corrected an incorrect skip pattern in the pre-test patient survey for PC3A to ensure that all applicable patients were asked about their understanding of the PCD.
Appendix B (Patient Survey)	New questions were added concerning (1) the type of healthcare provider that first	These questions were added to support desired analyses as described in Section 14.

	prescribed an ER/LA opioid analgesic (PC2B), and (2) whether the patient understood the PCD (PC3D).	
All	Minor clarifications and edits were incorporated for clarity and consistency. Discrepancies between protocol descriptions and survey questions were resolved.	

TABLE OF CONTENTS, PATIENT SURVEY

FIGURE 1: PATIENT SAMPLE LIST SELECTION



ER, extended release; KAS, Knowledge Assessment Score; LA, long-acting.

1. Survey eligible patients are defined as age≥18 years; no claims for methadone and substance abuse or addiction; currently active member of commercial health plan at the time of index date; not on HealthCore Do-Not-Call list; non-missing address/telephone number, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013. All results are aggregated and de-identified.

Patients are eligible if they use more than one drug type, but will be assigned in the following mutually exclusive hierarchy: methadone (patients received any methadone tablet or solution indicated for analgesic use, regardless of concurrent ER oral-dosage form or transdermal delivery system); patch and no methadone (patients received any fentanyl and buprenorphine-containing transdermal delivery system type of ER/LA opioid analgesic AND no methadone tablet or solution indicated for analgesic use, regardless of concurrent ER oral-dosage); and non-methadone oral drug only (patients received only an ER oral-dosage form of ER/LA opioid analgesic containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol).

TABLE 1. DEMOGRAPHIC CHARACTERISTICS, BY RESPONDENT STATUS [1]

	Survey respondents		All survey non-respondents [2]		Survey non-respondents who were not contacted [3]		Survey non-respondents who refused to participate	
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*
	413	**(3)**	**11,388**	**(97)**	**9,878**	**(87)**	**1,239**	**(11)**
Age in years, *mean (STD)*	*51.0 (11.18)*		*49.5 (11.55)*		*49.3 (11.45)*		*51.2 (12.11)*	
18 to 34	47	(11)	1,448	(13)	1,271	(13)	142	(11)
35 to 49	107	(26)	3,456	(30)	3,075	(31)	307	(25)
50 to 64	241	(58)	6,031	(53)	5,170	(52)	711	(57)
65+	18	(4)	453	(4)	362	(4)	79	(6)
Gender								
Female	255	(62)	5,962	(52)	5,181	(52)	623	(50)
Male	158	(38)	5,426	(48)	4,697	(48)	616	(50)
US Census region of residence[5]								
Northeast	72	(17)	1,821	(16)	1,592	(16)	182	(15)
South	128	(31)	3,502	(31)	3,065	(31)	353	(28)
Midwest	33	(8)	803	(7)	676	(7)	93	(8)
West	175	(42)	5,102	(45)	4,397	(45)	601	(49)
Unknown	5	(1)	160	(1)	148	(2)	10	(1)
Specific ER/LA opioid analgesic(s) used most recently before the survey[6]								
Oral drugs that are not methadone only	267	(65)	7 738	(68)	6 680	(68)	866	(70)
Patch and no methadone	108	(26)	2,625	(23)	2,277	(23)	293	(24)
Patch only	106	(26)	2,584	(23)	2,240	(23)	290	(23)
Patch and oral drug(s) that are not methadone	< 5	(< 1)	41	(< 1)	37	(< 1)	< 5	(< 1)
Methadone	38	(9)	1 025	(9)	921	(9)	80	(6)
Methadone only	35	(8)	982	(9)	885	(9)	73	(6)
Methadone and oral drug(s) that are not methadone	< 5	(< 1)	30	(< 1)	25	(< 1)	5	(< 1)
Methadone and patch	0	(0)	13	(< 1)	11	(< 1)	< 5	(< 1)
Methadone oral drug(s) that are not methadone and patch	0	(0)	0	(0)	0	(0)	0	(0)
Duration of continuous health plan eligibility prior to the most recent dispensing of an ER/LA opioid analgesic, mean (STD)	*14.3 (4.37)*		*13.6 (4.65)*		*13.6 (4.64)*		*13.4 (4.70)*	
Duration of ER/LA opioid analgesic(s) used most recently before the survey, month *mean (STD)*	*7.6 (7.10)*		*6.6 (6.97)*		*6.7 (6.97)*		*6.3 (6.99)*	
Number of previous dispensings of ER/LA opioid analgesics prior to the index dat *mean (STD)*	*9.0 (8.96)*		*7.7 (8.97)*		*7.8 (8.96)*		*7.4 (9.32)*	
Number of distinct drugs dispensed during the past six months prior to the index dat *mean (STD)*	*9.4 (5.59)*		*8.3 (5.30)*		*8.3 (5.29)*		*8.3 (5.26)*	
Medical condition(s) for which ER/LA opioid analgesics are indicated[7]								
Amputation in the lower limbs or extremities	< 5	(< 1)	31	(< 1)	27	(< 1)	< 5	(< 1)
Arthritis, arthropathies, osteoarthritis, and musculoskeletal pain	368	(89)	9,987	(88)	8,665	(88)	1,089	(88)
Chronic pain	171	(41)	3,806	(33)	3,334	(34)	398	(32)
Fibromyalgia	123	(30)	2,465	(22)	2,156	(22)	273	(22)
Malignancy	65	(16)	1,692	(15)	1,467	(15)	185	(15)
Multiple sclerosis	8	(2)	124	(1)	113	(1)	8	(1)
Neuropathic pain	113	(27)	2,543	(22)	2,221	(22)	270	(22)
Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers	7	(2)	266	(2)	221	(2)	38	(3)
Stroke	24	(6)	451	(4)	388	(4)	51	(4)
Other	31	(8)	714	(6)	615	(6)	84	(7)
Unspecified abdominal pain	127	(31)	2,779	(24)	2,417	(24)	311	(25)
None of the above	14	(3)	608	(5)	525	(5)	66	(5)

DNC, Do Not Call; ER, extended release; GED, General Education Degree; LA, long-acting; STD, standard deviation; US, United States

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified.

2.All survey non-respondents include survey non-respondents who were not contacted, survey non-respondents who refused to participate, and survey respondents (n=271) who only partially completed the survey, who failed survey screening or who failed survey criteria.

3.Survey non-respondents who were not contacted include non-contact patients (1) who were contacted the maximum five attempts or (2) never contacted, or patients with invalid/bad contact information such as (3) a non-working telephone number, or (4) no one by that name at the provided telephone number.

4. Survey non-respondents who refused to participate include patients (1) who were contacted but refused, (2) who were contacted but did not agree to participate, (3) who were contacted but requested to be added to or were already on the D Not Contact (DNC) list.

5. US Census regions of residence based on claims data at the time of index date Northeast (ME, NH, VT, MA, RI, CT, NY, PA, NJ); South (DE, MD, DC, VA, WV, NC, SC, GA, FL, KY, TN, MS, AL, OK, TX, AR, LA); Midwest (WI, MI, IL, IN, OH, MO, ND, SD, NE, KS, MN, IA); West (ID, MT, WY, NV, UT, CO, AZ, NM, AK, WA, OR, CA, HI).

6. ER/LA opioid analgesics Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use).

7. Medical condition(s) for which ER/LA opioid analgesics are indicated, as defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis, ICD-9-CM procedure, and Current Procedural Terminology (CPT) codes Amputation in the lower limbs or extremities (ICD-9-CM procedure 84.1x; CPT codes 27880 through 27889, 28800 through 28825); Arthritis, arthropathies, osteoarthritis, and musculoskeletal pain (ICD-9-CM diagnosis 710.x through 729.x [excluding 729.1x, fibromyalgia]); Chronic pain, including central pain syndrome and generalized pain (ICD-9-CM diagnosis 338.0x, 338.2x, 338.4x, 780.96); Fibromyalgia, including myalgia and myositis, unspecified (ICD-9-CM diagnosis 729.1x); Malignancy (ICD-9-CM diagnosis 140.x through 209.x); Multiple sclerosis (ICD-9-CM diagnosis 340.x; Neuropathic pain, including herpes zoster with other nervous system complication, diabete with neurological manifestations or polyneuropathy in diabetes, spinal cord disease not otherwise specified, peripheral autonomic neuropathy in disorders classified elsewhere, reflex sympathetic dystrophy, multiple sclerosis, unspecified demyelinating disease of central nervous system, trigeminal nerve disorders, facial nerve disorders, nerve root and plexus disorders, mononeuritis (of lower limb, multiplex, lower limb, and unspecified site), hereditary and idiopathic peripher l neuropathy, chronic inflammatory demyelinating polyneuritis, neuralgia, neuritis, and radiculitis, injury to facial nerve, spinal cord injury without evidence of spinal bone injury, injury to brachial plexus, injury to cutaneous sensory or digital nerve of upper limb or other specified nerve(s) of shoulder girdle and upper limb (ICD-9-CM diagnosis 053.1x, 250.6x, 336.9x, 337.1x, 337.2x, 340.x, 341.9x, 350.x, 351.x, 353.x, 354.x, 355.x, 356.x, 357.2x, 357.81, 729.2x, 951.4x, 952.x, 953.4x, 955.5x through 955.7x); Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers, including atherosclerosis of native arteries or bypass graft of the extremities and peripheral angiopathy in diseases classified elsewhere (ICD-9-CM diagnosis 440.2x, 440.3x, 443.81, 443.9x); Stroke, including occlusion and stenosis of precerebral and cerebral arteries and cerebrovascular disease (acute but ill-defined, other and ill-defined, or late effects o) (ICD-9-CM diagnosis 433.x through 434.x, 436.x through 438.x); Other, including pain disorders related to psychological factors (ICD-9-CM diagnosis 307.8x), temporomandibular joint-pain-dysfunction syndrome (ICD-9-CM diagnosis 524.60), chronic pancreatitis (ICD-9-CM diagnosis 577.1x), pathologic hip fracture (ICD-9-CM diagnosis 733.14), chronic fatigue syndrome (ICD-9-CM diagnosis 780.71), and open or closed hip fracture (ICD-9-CM diagnosis 820.8x, 820.9x); and Unspecified abdominal pain (ICD-9-CM diagnosis 789.0x).

TABLE 2A. DEMOGRAPHIC CHARACTERISTICS AMONG SURVEY RESPONDENTS, BY ER/LA OPIOID ANALGESIC TYPE [1]

	All survey respondents		Survey respondents, by ER/LA opioid analgesic type[2]					
			Non-methadone oral drugs only		Patch		Methadone	
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*
Total number of respondents	**413**		**266**	**(64)**	**102**	**(25)**	**45**	**(11)**
Age in years,*mean (STD)*	*51.0 (11.18)*		*51.0 (11.20)*		*51.1 (11.42)*		*50.9 (10.71)*	
18 to 34	47	(11)	35	(13)	9	(9)	< 5	(< 11)
35 to 49	107	(26)	63	(24)	28	(27)	16	(36)
50 to 64	241	(58)	159	(60)	58	(57)	24	(53)
65	18	(4)	9	(3)	7	(7)	< 5	(< 11)
Gender								
Female	255	(62)	164	(62)	58	(57)	33	(73)
Male	158	(38)	102	(38)	44	(43)	12	(27)
US Census region of residence[3]								
Northeast	72	(17)	52	(20)	16	(16)	< 5	(< 11)
South	128	(31)	70	(26)	39	(38)	19	(42)
Midwest	33	(8)	22	(8)	7	(7)	< 5	(< 11)
West	175	(42)	119	(45)	38	(37)	18	(40)
Unknown	5	(1)	< 5	(< 2)	< 5	(< 5)	0	(0)
Hispanic or Latino ethnicity	10	(2)	7	(3)	< 5	(< 5)	0	(0)
Race								
White or Caucasian	383	(93)	243	(91)	97	(95)	43	(96)
Black or African American	11	(3)	9	(3)	< 5	(< 5)	< 5	(< 11)
Mixed racial background	10	(2)	7	(3)	< 5	(< 5)	0	(0)
Other	9	(2)	7	(3)	< 5	(< 5)	< 5	(< 11)
Marital status								
Single, never married	60	(15)	44	(17)	11	(11)	5	(11)
Married/Living with partner	292	(71)	186	(70)	77	(75)	29	(64)
Other marital status	61	(15)	36	(14)	14	(14)	11	(24)
Income level, US dollars								
Less than $25,000	48	(12)	30	(11)	10	(10)	8	(18)
$25,000 to $49,999	99	(24)	67	(25)	19	(19)	13	(29)
$50,000 to $74,999	82	(20)	49	(18)	21	(21)	12	(27)
$75,000 to $99,999	49	(12)	33	(12)	11	(11)	5	(11)
$100,000 or more	112	(27)	71	(27)	35	(34)	6	(13)
Don't know	23	(6)	16	(6)	6	(6)	< 5	(< 11)
Education level								
Less than/Some high school, but no degree or GED	12	(3)	8	(3)	< 5	(< 5)	< 5	(< 11)
High school or equivalent such as a GED	58	(14)	40	(15)	13	(13)	5	(11)
Some college, but no degree	80	(19)	43	(16)	23	(23)	14	(31)
Two-year degree (community or technical)	49	(12)	34	(13)	10	(10)	5	(11)
College graduate	132	(32)	82	(31)	37	(36)	13	(29)
Graduate school	75	(18)	56	(21)	15	(15)	< 5	(< 11)
Other	7	(2)	< 5	(< 2)	< 5	(< 5)	< 5	(< 11)
Specific ER/LA opioid analgesic(s) use[2]								
Oral drugs that are not methadone only	266	(64)	266	(100)		NA		NA
Patch and no methadone	102	(25)			102	(100)		
Patch only	35	(8)		NA	35	(34)		NA
Patch and oral drug(s) that are not methadone	67	(16)		NA	67	(66)		NA
Methadone	45	(11)					45	(11)
Methadone only	22	(5)		NA		NA	22	(49)
Methadone and oral drug(s) that are not methadone	18	(4)		NA		NA	18	(40)
Methadone and patch	< 5	(< 1)		NA		NA	< 5	(< 11)
Methadone oral drug(s) that are not methadone and patch	< 5	(< 1)		NA		NA	< 5	(< 11)
New user								
First use	69	(17)	45	(17)	21	(21)	< 5	(< 11)
Used before	342	(83)	219	(82)	81	(79)	42	(93)
Not sure	< 5	(< 1)	< 5	(< 2)	0	(0)	0	(0)
Time since last prescription								
Less than one month ago	221	(54)	132	(50)	60	(59)	29	(64)
One month to less than two months ago	54	(13)	37	(14)	13	(13)	< 5	(< 11)
Two months to less than three months ago	15	(4)	7	(3)	< 5	(< 5)	6	(13)
Three months to less than six months ago	42	(10)	30	(11)	9	(9)	< 5	(< 11)
Six months to less than nine months ago	37	(9)	30	(11)	6	(6)	< 5	(< 11)
Nine months to less than 12 months ago	29	(7)	24	(9)	< 5	(< 5)	< 5	(< 11)
12 months or more ago	11	(3)	< 5	(< 2)	7	(7)	0	(0)
Not sure	< 5	(< 1)	< 5	(< 2)	< 5	(< 5)	< 5	(< 11)
Time since most recent visit to the healthcare provider who prescribed ER/LA opioid analgesic								
Less than one month ago	208	(50)	133	(50)	46	(45)	29	(64)
One month to less than two months ago	76	(18)	51	(19)	19	(19)	6	(13)
Two months to less than three months ago	36	(9)	16	(6)	15	(15)	5	(11)
Three months to less than six months ago	44	(11)	32	(12)	10	(10)	< 5	(< 11)
Six months to less than nine months ago	25	(6)	16	(6)	8	(8)	< 5	(< 11)
Nine months to less than 12 months ago	11	(3)	10	(4)	0	(0)	< 5	(< 11)
12 months or more ago	11	(3)	6	(2)	< 5	(< 5)	< 5	(< 11)
Not sure	< 5	(< 1)	< 5	(< 2)	0	(0)	0	(0)
Time since healthcare provider first prescribed ER/LA opioid analgesic								
Less than one month ago	17	(4)	15	(6)	< 5	(< 5)	< 5	(< 11)
One month to less than two months ago	10	(2)	8	(3)	< 5	(< 5)	< 5	(< 11)
Two months to less than three months ago	6	(1)	< 5	(< 2)	< 5	(< 5)	< 5	(< 11)
Three months to less than six months ago	43	(10)	28	(11)	9	(9)	6	(13)
Six months to less than nine months ago	57	(14)	36	(14)	18	(18)	< 5	(< 11)
Nine months to less than 12 months ago	54	(13)	38	(14)	15	(15)	< 5	(< 11)
12 months or more ago	221	(54)	134	(50)	56	(55)	31	(69)
Not sure	5	(1)	< 5	(< 2)	< 5	(< 5)	< 5	(< 11)
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic drug								
Pain specialist	179	(43)	97	(36)	52	(51)	30	(67)
Primary care physician, general practitioner, internal medicine specialist, or family practice physician	100	(24)	65	(24)	25	(25)	10	(22)
Other type of specialist	126	(31)	100	(38)	22	(22)	< 5	(< 11)
Nurse Practitioner or Physician Assistant	< 5	(< 1)	< 5	(< 2)	< 5	(< 5)	< 5	(< 11)
Not sure	< 5	(< 1)	< 5	(< 2)	< 5	(< 5)	0	(0)

ER, extended release; GED, General Education Degree; LA, long-acting; STD, standard deviation; US, United States

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified.

2. ER/LA opioid analgesic: Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use).

3. US Census regions of residence based on claims data at the time of index date: Northeast (ME, NH, VT, MA, RI, CT, NY, PA, NJ); South (DE, MD, DC, VA, WV, NC, SC, GA, FL, KY, TN, MS, AL, OK, TX, AR, LA); Midwest (WI, MI, IL, IN, OH, MO, ND, SD, NE, KS, MN, IA); West (ID, MT, WY, NV, UT, CO, AZ, NM, AK, WA, OR, CA, HI).

TABLE 2B. DEMOGRAPHIC CHARACTERISTICS AMONG SURVEY RESPONDENTS, BY MEDICATION GUIDE RECEIPT/READ/COMPREHENSION STATUS [1]

	Received Medication Guide [2]					Read Medication Guide [3]					Understood Medication Guide [4]				
	Yes		No		p-value [5]	Yes		No		p-value [5]	Yes		No		p-value [5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**389**	**(94)**	**24**	**(6)**		**399**	**(97)**	**14**	**(3)**		**399**	**(98)**	**10**	**(2)**	
(95% confidence interval)	**(351 - 430)**		**(15 - 36)**			**(361 - 440)**		**(8 - 23)**			**(361 - 440)**		**(5 - 18)**		
Age in years, *mean (STD)*	*51.2 (11.14)*		*47.6 (11.45)*		0.288	*51.1 (11.11)*		*47.9 (13.04)*		0.746	*51.2 (11.03)*		*46.4 (14.69)*		0.491
18 to 34	44	(11)	< 5	(< 21)		45	(11)	< 5	(< 36)		44	(11)	< 5	(< 50)	
35 to 49	98	(25)	9	(38)		102	(26)	5	(36)		102	(26)	< 5	(< 50)	
50 to 64	229	(59)	12	(50)		234	(59)	7	(50)		236	(59)	< 5	(< 50)	
65	18	(5)	0	(0)		18	(5)	0	(0)		17	(4)	< 5	(< 50)	
Gender					0.609					0.842					0.036
Female	239	(61)	16	(67)		246	(62)	9	(64)		250	(63)	< 5	(< 50)	
Male	150	(39)	8	(33)		153	(38)	5	(36)		149	(37)	7	(70)	
US Census region of residence [6]					0.585					0.353	68	(17)	< 5	(< 50)	0.086
Northeast	67	(17)	5	(21)		68	(17)	< 5	(< 36)						
South	122	(31)	6	(25)		126	(32)	< 5	(< 36)		126	(32)	< 5	(< 50)	
Midwest	32	(8)	< 5	(< 21)		33	(8)	0	(0)		32	(8)	< 5	(< 50)	
West	164	(42)	11	(46)		167	(42)	8	(57)		169	(42)	5	(50)	
Unknown	< 5	(< 1)	< 5	(< 21)		5	(1)	0	(0)		< 5	(< 1)	< 5	(< 50)	
Hispanic or Latino ethnicity	10	(3)	0	(0)	0.427	10	(3)	0	(0)	0.549	9	(2)	< 5	(< 50)	0.117
Race					0.147					0.844					0.337
White or Caucasian	362	(93)	21	(88)		370	(93)	13	(93)		370	(93)	9	(90)	
Black or African American	10	(3)	< 5	(< 21)		11	(3)	0	(0)		11	(3)	0	(0)	
Mixed racial background	9	(2)	< 5	(< 21)		9	(2)	< 5	(< 36)		10	(3)	0	(0)	
Other	8	(2)	< 5	(< 21)		9	(2)	0	(0)		8	(2)	< 5	(< 50)	
Marital status					0.051					0.055					0.745
Single, never married	56	(14)	< 5	(< 21)		58	(15)	< 5	(< 36)		57	(14)	< 5	(< 50)	
Married/Living with partner	279	(72)	13	(54)		285	(71)	7	(50)		283	(71)	6	(60)	
Other marital status	54	(14)	7	(29)		56	(14)	5	(36)		59	(15)	< 5	(< 50)	
Income level, US dollars					0.667					0.837					0.458
Less than $25,000	43	(11)	5	(21)		47	(12)	< 5	(< 36)		45	(11)	< 5	(< 50)	
$25,000 to $49,999	95	(24)	< 5	(< 21)		95	(24)	< 5	(< 36)		96	(24)	< 5	(< 50)	
$50,000 to $74,999	78	(20)	< 5	(< 21)		81	(20)	< 5	(< 36)		81	(20)	< 5	(< 50)	
$75,000 to $99,999	47	(12)	< 5	(< 21)		47	(12)	< 5	(< 36)		48	(12)	< 5	(< 50)	
$100,000 or more	105	(27)	7	(29)		107	(27)	5	(36)		107	(27)	< 5	(< 50)	
Don't know	21	(5)	< 5	(< 21)		22	(6)	< 5	(< 36)		22	(6)	< 5	(< 50)	
Education level					0.397					0.873					0.808
Less than/Some high school, but no degree or GED	12	(3)	0	(0)		12	(3)	0	(0)		12	(3)	0	(0)	
High school or equivalent such as a GED	56	(14)	< 5	(< 21)		57	(14)	< 5	(< 36)		55	(14)	< 5	(< 50)	
Some college, but no degree	73	(19)	7	(29)		78	(20)	< 5	(< 36)		76	(19)	< 5	(< 50)	
Two-year degree (community or technical)	46	(12)	< 5	(< 21)		46	(12)	< 5	(< 36)		47	(12)	< 5	(< 50)	
College graduate	121	(31)	11	(46)		126	(32)	6	(43)		129	(32)	< 5	(< 50)	
Graduate school	74	(19)	< 5	(< 21)		73	(18)	< 5	(< 36)		73	(18)	< 5	(< 50)	
Other	7	(2)	0	(0)		7	(2)	0	(0)		7	(2)	0	(0)	
Specific ER/LA opioid analgesic(s) used [7]					0.791					0.736					0.551
Oral drugs that are not methadone only	251	(65)	15	(63)		256	(64)	10	(71)		258	(65)	5	(50)	
Patch and no methadone	97	(25)	5	(21)		100	(25)	< 5	(< 36)		97	(24)	5	(50)	
Patch only	32	(8)	< 5	(< 21)		33	(8)	< 5	(< 36)		34	(9)	< 5	(< 50)	
Patch and oral drug(s) that are not methadone	65	(17)	< 5	(< 21)		67	(17)	0	(0)		63	(16)	< 5	(< 50)	
Methadone	41	(11)	< 5	(< 21)		43	(11)	< 5	(< 36)		44	(11)	0	(0)	
Methadone only	20	(5)	< 5	(< 21)		21	(5)	< 5	(< 36)		22	(6)	0	(0)	
Methadone and oral drug(s) that are not methadone	16	(4)	< 5	(< 21)		17	(4)	< 5	(< 36)		17	(4)	0	(0)	
Methadone and patch	< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)	
Methadone oral drug(s) that are not methadone and patch	< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)	
New user					0.006					0.149					0.001
First use	62	(16)	7	(29)		64	(16)	5	(36)		61	(15)	6	(60)	
Used before	326	(84)	16	(67)		333	(83)	9	(64)		336	(84)	< 5	(< 50)	
Not sure	< 5	(< 1)	< 5	(< 21)		< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)	
Time since last prescription					<0.001					0.039					0.008
Less than one month ago	214	(55)	7	(29)		216	(54)	5	(36)		218	(55)	< 5	(< 50)	
One month to less than two months ago	52	(13)	< 5	(< 21)		53	(13)	< 5	(< 36)		53	(13)	< 5	(< 50)	
Two months to less than three months ago	14	(4)	< 5	(< 21)		15	(4)	0	(0)		15	(4)	0	(0)	
Three months to less than six months ago	38	(10)	< 5	(< 21)		41	(10)	< 5	(< 36)		39	(10)	< 5	(< 50)	
Six months to less than nine months ago	33	(8)	< 5	(< 21)		34	(9)	< 5	(< 36)		35	(9)	< 5	(< 50)	
Nine months to less than 12 months ago	27	(7)	< 5	(< 21)		26	(7)	< 5	(< 36)		27	(7)	< 5	(< 50)	
12 months or more ago	10	(3)	< 5	(< 21)		11	(3)	0	(0)		10	(3)	< 5	(< 50)	
Not sure	< 5	(< 1)	< 5	(< 21)		< 5	(< 1)	< 5	(< 36)		< 5	(< 1)	< 5	(< 50)	
Time since most recent visit to the healthcare provider who prescribed ER/LA opioid analgesi					0.015					0.008					0.026
Less than one month ago	201	(52)	7	(29)		204	(51)	< 5	(< 36)		206	(52)	< 5	(< 50)	
One month to less than two months ago	73	(19)	< 5	(< 21)		74	(19)	< 5	(< 36)		74	(19)	< 5	(< 50)	
Two months to less than three months ago	33	(8)	< 5	(< 21)		33	(8)	< 5	(< 36)		31	(8)	< 5	(< 50)	
Three months to less than six months ago	41	(11)	< 5	(< 21)		44	(11)	0	(0)		41	(10)	< 5	(< 50)	
Six months to less than nine months ago	22	(6)	< 5	(< 21)		22	(6)	< 5	(< 36)		23	(6)	< 5	(< 50)	
Nine months to less than 12 months ago	9	(2)	< 5	(< 21)		9	(2)	< 5	(< 36)		11	(3)	0	(0)	
12 months or more ago	8	(2)	< 5	(< 21)		11	(3)	0	(0)		11	(3)	0	(0)	
Not sure	< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)	
Time since healthcare provider first prescribed ER/LA opioid analgesi					0.070					0.198					<0.001
Less than one month ago	14	(4)	< 5	(< 21)		15	(4)	< 5	(< 36)		17	(4)	0	(0)	
One month to less than two months ago	10	(3)	0	(0)		10	(3)	0	(0)		10	(3)	0	(0)	
Two months to less than three months ago	5	(1)	< 5	(< 21)		5	(1)	< 5	(< 36)		5	(1)	0	(0)	
Three months to less than six months ago	42	(11)	< 5	(< 21)		43	(11)	0	(0)		39	(10)	< 5	(< 50)	
Six months to less than nine months ago	50	(13)	7	(29)		54	(14)	< 5	(< 36)		54	(14)	< 5	(< 50)	
Nine months to less than 12 months ago	51	(13)	< 5	(< 21)		52	(13)	< 5	(< 36)		52	(13)	< 5	(< 50)	
12 months or more ago	212	(55)	9	(38)		215	(54)	6	(43)		219	(55)	< 5	(< 50)	
Not sure	5	(1)	0	(0)		5	(1)	0	(0)		< 5	(< 1)	< 5	(< 50)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic dru					0.165					0.004					0.008
Pain specialist	167	(43)	12	(50)		176	(44)	< 5	(< 36)		175	(44)	< 5	(< 50)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physicia	96	(25)	< 5	(< 21)		98	(25)	< 5	(< 36)		99	(25)	< 5	(< 50)	
Other type of specialist	120	(31)	6	(25)		119	(30)	7	(50)		118	(30)	6	(60)	
Nurse Practitioner or Physician Assistan	< 5	(< 1)	< 5	(< 21)		< 5	(< 1)	< 5	(< 36)		< 5	(< 1)	0	(0)	
Not sure	< 5	(< 1)	< 5	(< 21)		< 5	(< 1)	< 5	(< 36)		< 5	(< 1)	< 5	(< 50)	

ER, extended release; GED, General Education Degree; LA, long-acting; MG, Medication Guide; STD, standard deviation; US, United State

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified.

2. Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months.

3. Read some or all of the Medication Guide at least once. Respondents who did not receive the Medication Guide from any of the specified sources were still asked whether they read the Medication Guide.

4. Understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide. Respondents who did not receive and did not read the Medication Guide were not asked their comprehension of the Medication Guide.

5. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood with those who did not receive/read/understood the MG, respectively.

6. US Census regions of residence based on claims data at the time of index date: Northeast (ME, NH, VT, MA, RI, CT, NY, PA, NJ); South (DE, MD, DC, VA, WV, NC, SC, GA, FL, KY, TN, MS, AL, OK, TX, AR, LA); Midwest (WI, MI, IL, IN, OH, MO, ND, SD, NE, KS, MN, IA); West (ID, MT, WY, NV, UT, CO, AZ, NM, AK, WA, OR, CA, HI).

7. ER/LA opioid analgesics: Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use).

TABLE 2C. DEMOGRAPHIC CHARACTERISTICS AMONG SURVEY RESPONDENTS, BY PATIENT COUNSELING DOCUMENT RECEIPT/REFERENCED/COMPREHENSION STATUS [1]

	Received PCD [2]					Referenced PCD [3]					Understood PCD [4]				
	Yes		No		p-value [5]	Yes		No		p-value [5]	Yes		No		p-value [5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**175**	**(42)**	**238**	**(58)**		**109**	**(26)**	**304**	**(74)**		**244**	**(90)**	**28**	**(10)**	
(95% confidence interval)	**(150 - 203)**		**(209 - 270)**			**(90 - 131)**		**(271 - 340)**			**(214 - 277)**		**(19 - 40)**		
Age in years, *mean (STD)*	*51.3 (11.38)*		*50.8 (11.05)*		0.724	*50.9 (11.00)*		*51.1 (11.26)*		0.937	*51.4 (11.12)*		*44.0 (11.55)*		0.080
18 to 34	20	(11)	27	(11)		12	(11)	35	(12)		26	(11)	6	(21)	
35 to 49	41	(23)	66	(28)		29	(27)	78	(26)		62	(25)	11	(39)	
50 to 64	106	(61)	135	(57)		64	(59)	177	(58)		145	(9)	11	(39)	
65	8	(5)	10	(4)		< 5	(< 5)	14	(5)		11	(5)	0	(0)	
Gender					0.532					0.395					0.360
Female	105	(60)	150	(63)		71	(65)	184	(61)		144	(59)	14	(50)	
Male	70	(40)	88	(37)		38	(35)	120	(39)		100	(41)	14	(50)	
US Census region of residence [6]					0.708					0.187					0.439
Northeast	35	(20)	37	(16)		17	(16)	55	(18)		42	(17)	5	(18)	
South	6	(32)	72	(30)		44	(40)	84	(28)		81	(33)	7	(25)	
Midwest	12	(7)	21	(9)		7	(6)	26	(9)		18	(7)	< 5	(< 18)	
West	70	(40)	105	(44)		40	(37)	135	(44)		101	(41)	11	(39)	
Unknown	< 5	(< 3)	< 5	(< 2)		< 5	(< 5)	< 5	(< 2)		< 5	(< 2)	< 5	(< 18)	
Hispanic or Latino ethnicity	6	(3)	< 5	(< 2)	0.254	< 5	(< 5)	9	(3)	0.234	7	(3)	0	(0)	0.364
Race					0.390					0.213					0.853
White or Caucasian	159	(91)	224	(94)		100	(92)	283	(93)		223	(91)	27	(96)	
Black or African American	8	(5)	< 5	(< 2)		6	(6)	5	(2)		10	(4)	< 5	(< 18)	
Mixed racial background	< 5	(< 3)	6	(3)		< 5	(< 5)	9	(3)		6	(2)	0	(0)	
Other	< 5	(< 3)	5	(2)		< 5	(< 5)	7	(2)		5	(2)	0	(0)	
Marital status					0.895					0.900					0.623
Single, never married	28	(16)	32	(13)		17	(16)	43	(14)		37	(15)	< 5	(< 18)	
Married/Living with partner	119	(68)	173	(73)		74	(68)	218	(72)		169	(69)	23	(82)	
Other marital status	28	(16)	33	(14)		18	(17)	43	(14)		38	(16)	< 5	(< 18)	
Income level, US dollars					0.076					0.848					0.905
Less than $25,000	26	(15)	22	(9)		14	(13)	34	(11)		34	(14)	< 5	(< 18)	
$25,000 to $49,999	39	(22)	60	(25)		25	(23)	74	(24)		59	(24)	6	(21)	
$50,000 to $74,999	28	(16)	54	(23)		24	(22)	58	(19)		43	(18)	6	(21)	
$75,000 to $99,999	27	(15)	22	(9)		15	(14)	34	(11)		28	(11)	< 5	(< 18)	
$100,000 or more	48	(27)	64	(27)		25	(23)	87	(29)		68	(28)	8	(29)	
Don't know	7	(4)	16	(7)		6	(6)	17	(6)		12	(5)	< 5	(< 18)	
Education level					0.908					0.086					0.405
Less than/Some high school, but no degree or GED	5	(3)	7	(3)		< 5	(< 5)	9	(3)		7	(3)	< 5	(< 18)	
High school or equivalent such as a GED	28	(16)	30	(13)		14	(13)	44	(14)		36	(15)	5	(18)	
Some college, but no degree	38	(22)	42	(18)		29	(27)	51	(17)		50	(20)	6	(21)	
Two-year degree (community or technical)	20	(11)	29	(12)		13	(12)	36	(12)		29	(12)	6	(21)	
College graduate	51	(29)	81	(34)		32	(29)	100	(33)		73	(30)	7	(25)	
Graduate school	30	(17)	45	(19)		17	(16)	58	(19)		45	(18)	< 5	(< 18)	
Other	< 5	(< 3)	< 5	(< 2)		< 5	(< 5)	6	(2)		< 5	(< 2)	0	(0)	
Specific ER/LA opioid analgesic(s) used [7]					0.658					0.413					0.953
Oral drugs that are not methadone only	112	(64)	154	(65)		69	(63)	197	(65)		156	(64)	17	(61)	
Patch and no methadone	40	(23)	62	(26)		27	(25)	75	(25)		59	(24)	8	(29)	
Patch only	13	(7)	22	(9)		11	(10)	24	(8)		20	(8)	< 5	(< 18)	
Patch and oral drug(s) that are not methadone	27	(15)	40	(17)		16	(15)	51	(17)		39	(16)	5	(18)	
Methadone	23	(13)	22	(9)		13	(12)	32	(11)		29	(12)	< 5	(< 18)	
Methadone only	10	(6)	12	(5)		6	(6)	16	(5)		14	(6)	< 5	(< 18)	
Methadone and oral drug(s) that are not methadone	9	(5)	9	(4)		< 5	(< 5)	14	(5)		10	(4)	< 5	(< 18)	
Methadone and patch	< 5	(< 3)	< 5	(< 2)		< 5	(< 5)	< 5	(< 2)		< 5	(< 2)	0	(0)	
Methadone oral drug(s) that are not methadone and patch	< 5	(< 3)	0	(0)		0	(0)	< 5	(< 2)		< 5	(< 2)	0	(0)	
New user					0.170					0.305					0.109
First use	24	(14)	45	(19)		14	(13)	55	(18)		36	(15)	6	(21)	
Used before	151	(86)	191	(80)		95	(87)	247	(81)		207	(8)	21	(75)	
Not sure	0	(0)	< 5	(< 2)		0	(0)	< 5	(< 2)		< 5	(< 2)	< 5	(< 18)	
Time since last prescription					0.131					0.402					0.099
Less than one month ago	105	(60)	116	(49)		63	(58)	158	(52)		141	(58)	8	(29)	
One month to less than two months ago	25	(14)	29	(12)		17	(16)	37	(12)		34	(14)	5	(18)	
Two months to less than three months ago	8	(5)	7	(3)		< 5	(< 5)	11	(4)		9	(4)	< 5	(< 18)	
Three months to less than six months ago	13	(7)	29	(12)		10	(9)	32	(11)		18	(7)	6	(21)	
Six months to less than nine months ago	11	(6)	26	(11)		8	(7)	29	(10)		19	(8)	< 5	(< 18)	
Nine months to less than 12 months ago	9	(5)	20	(8)		7	(6)	22	(7)		16	(7)	< 5	(< 18)	
12 months or more ago	< 5	(< 3)	8	(3)		0	(0)	11	(4)		6	(2)	< 5	(< 18)	
Not sure	< 5	(< 3)	< 5	(< 2)		0	(0)	< 5	(< 2)		< 5	(< 2)	0	(0)	
Time since most recent visit to the healthcare provider who prescribed ER/LA opioid analgesic					0.068					0.201					0.137
Less than one month ago	101	(58)	107	(45)		68	(62)	140	(46)		131	(54)	12	(43)	
One month to less than two months ago	30	(17)	46	(19)		17	(16)	59	(19)		41	(17)	< 5	(< 18)	
Two months to less than three months ago	11	(6)	25	(11)		6	(6)	30	(10)		15	(6)	5	(18)	
Three months to less than six months ago	13	(7)	31	(13)		8	(7)	36	(12)		24	(10)	< 5	(< 18)	
Six months to less than nine months ago	8	(5)	17	(7)		5	(5)	20	(7)		15	(6)	< 5	(< 18)	
Nine months to less than 12 months ago	< 5	(< 3)	7	(3)		< 5	(< 5)	8	(3)		7	(3)	< 5	(< 18)	
12 months or more ago	6	(3)	5	(2)		< 5	(< 5)	9	(3)		9	(4)	0	(0)	
Not sure	< 5	(< 3)	0	(0)		0	(0)	< 5	(< 2)		< 5	(< 2)	0	(0)	
Time since healthcare provider first prescribed ER/LA opioid analgesic					0.032					0.065					0.147
Less than one month ago	9	(5)	8	(3)		7	(6)	10	(3)		11	(5)	0	(0)	
One month to less than two months ago	7	(4)	< 5	(< 2)		6	(6)	< 5	(< 2)		8	(3)	0	(0)	
Two months to less than three months ago	< 5	(< 3)	< 5	(< 2)		0	(0)	6	(2)		< 5	(< 2)	0	(0)	
Three months to less than six months ago	18	(10)	25	(11)		14	(13)	29	(10)		24	(10)	7	(25)	
Six months to less than nine months ago	15	(9)	42	(18)		10	(9)	47	(15)		28	(11)	6	(21)	
Nine months to less than 12 months ago	17	(10)	37	(16)		15	(14)	39	(13)		29	(12)	< 5	(< 18)	
12 months or more ago	104	(59)	117	(49)		56	(51)	165	(54)		138	(57)	12	(43)	
Not sure	< 5	(< 3)	< 5	(< 2)		< 5	(< 5)	< 5	(< 2)		< 5	(< 2)	0	(0)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic drug					0.052					0.682					0.055
Pain specialist	82	(47)	97	(41)		51	(47)	128	(42)		109	(45)	15	(54)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physician	47	(27)	53	(22)		27	(25)	73	(24)		61	(25)	< 5	(< 18)	
Other type of specialist	46	(26)	80	(34)		30	(28)	96	(32)		73	(30)	10	(36)	
Nurse Practitioner or Physician Assistant	0	(0)	< 5	(< 2)		0	(0)	< 5	(< 2)		0	(0)	0	(0)	
Not sure	0	(0)	< 5	(< 2)		< 5	(< 5)	< 5	(< 2)		< 5	(< 2)	< 5	(< 18)	

ER, extended release; GED, General Education Degree; LA, long-acting; PCD, Patient Counseling Document; STD, standard deviation; US, United States

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified.

2. Healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months.

3. Healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months.

4. Understood PCD, as self-reported by the respondent that they understood at least some, half, most, or all of the information discussed from the PCD. Respondents who did not receive and did not have a provider who referenced the PCD were not asked their comprehension of the PCD.

5. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/referenced/understood with those who did not receive/referenced/understood the PCD, respectively.

6. US Census regions of residence based on claims data at the time of index date: Northeast (ME, NH, VT, MA, RI, CT, NY, PA, NJ); South (DE, MD, DC, VA, WV, NC, SC, GA, FL, KY, TN, MS, AL, OK, TX, AR, LA); Midwest (WI, MI, IL, IN, OH, MO, ND, SD, NE, KS, MN, IA); West (ID, MT, WY, NV, UT, CO, AZ, NM, AK, WA, OR, CA, HI).

7. ER/LA opioid analgesics: Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use).

TABLE 2D. DEMOGRAPHIC CHARACTERISTICS AMONG SURVEY RESPONDENTS, BY RECEIPT/READ/UNDERSTOOD STATUS OF BOTH OR NEITHER MEDICATION GUIDE AND PATIENT COUNSELING DOCUMENT [1]

	Received/Read/Understood Medication Guide and PCD [2]					Did Not Receive/Read/Understand Medication Guide or PCD [3]				
	Yes		No		p-value [4]	Yes		No		p-value [4]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**94**	**(23)**	**319**	**(77)**		**5**	**(1)**	**408**	**(99)**	
(95% confidence interval)	**(76 - 115)**		**(285 - 356)**			**(2 - 12)**		**(369 - 450)**		
Age in years, *mean (STD)*	*50.8 (10.87)*		*51.1 (11.28)*		0.945	*41.2 (12.77)*		*51.1 (11.12)*		0.276
18 to 34	10	(11)	37	(12)		< 5	(< 100)	46	(11)	
35 to 49	26	(28)	81	(25)		< 5	(< 100)	104	(25)	
50 to 64	55	(59)	186	(58)		< 5	(< 100)	240	(59)	
65+	< 5	(< 5)	15	(5)		0	(0)	18	(4)	
Gender					0.475					0.314
Female	61	(65)	194	(61)		< 5	(< 100)	253	(62)	
Male	33	(35)	125	(39)		< 5	(< 100)	155	(38)	
US Census region of residence [5]					0.190					0.164
Northeast	17	(18)	55	(17)		< 5	(< 100)	69	(17)	
South	38	(40)	90	(28)		< 5	(< 100)	127	(31)	
Midwest	7	(7)	26	(8)		0	(0)	33	(8)	
West	31	(33)	144	(45)		< 5	(< 100)	174	(43)	
Unknown	< 5	(< 5)	< 5	(< 2)		0	(0)	5	(1)	
Hispanic or Latino ethnicity	< 5	(< 5)	9	(3)	0.330	0	(0)	10	(2)	0.723
Race					0.142					0.995
White or Caucasian	86	(91)	297	(93)		5	(100)	378	(93)	
Black or African American	6	(6)	5	(2)		0	(0)	11	(3)	
Mixed racial background	< 5	(< 5)	9	(3)		0	(0)	10	(2)	
Other	< 5	(< 5)	8	(3)		0	(0)	9	(2)	
Marital status					0.795					0.948
Single, never married	16	(17)	44	(14)		< 5	(< 100)	59	(14)	
Married/Living with partner	65	(69)	227	(71)		< 5	(< 100)	289	(71)	
Other marital status	13	(14)	48	(15)		< 5	(< 100)	60	(15)	
Income level, US dollars					0.973					0.412
Less than $25,000	13	(14)	35	(11)		0	(0)	48	(12)	
$25,000 to $49,999	23	(24)	76	(24)		< 5	(< 100)	97	(24)	
$50,000 to $74,999	19	(20)	63	(20)		0	(0)	82	(20)	
$75,000 to $99,999	11	(12)	38	(12)		0	(0)	49	(12)	
$100,000 or more	23	(24)	89	(28)		< 5	(< 100)	109	(27)	
Don't know	5	(5)	18	(6)		0	(0)	23	(6)	
Education level					0.510					0.921
Less than/Some high school, but no degree or GED	< 5	(< 5)	10	(3)		0	(0)	12	(3)	
High school or equivalent such as a GED	13	(14)	45	(14)		0	(0)	58	(14)	
Some college, but no degree	25	(27)	55	(17)		< 5	(< 100)	78	(19)	
Two-year degree (community or technical)	10	(11)	39	(12)		< 5	(< 100)	48	(12)	
College graduate	29	(31)	103	(32)		< 5	(< 100)	131	(32)	
Graduate school	14	(15)	61	(19)		< 5	(< 100)	74	(18)	
Other	< 5	(< 5)	6	(2)		0	(0)	7	(2)	
Specific ER/LA opioid analgesic(s) used [6]					0.232					0.570
Oral drugs that are not methadone only	60	(64)	206	(65)		< 5	(< 100)	263	(64)	
Patch and no methadone	24	(26)	78	(25)		< 5	(< 100)	101	(25)	
Patch only	9	(10)	26	(8)		< 5	(< 100)	34	(8)	
Patch and oral drug(s) that are not methadone	15	(16)	52	(16)		0	(0)	67	(16)	
Methadone	10	(11)	35	(11)		< 5	(< 100)	44	(11)	
Methadone only	5	(5)	17	(5)		0	(0)	22	(5)	
Methadone and oral drug(s) that are not methadone	< 5	(< 5)	16	(5)		< 5	(< 100)	17	(4)	
Methadone and patch	< 5	(< 5)	< 5	(< 2)		0	(0)	< 5	(< 1)	
Methadone oral drug(s) that are not methadone and patch	0	(0)	< 5	(< 2)		0	(0)	< 5	(< 1)	
New user					0.507					0.370
First use	13	(14)	56	(18)		< 5	(< 100)	67	(16)	
Used before	81	(86)	261	(82)		< 5	(< 100)	339	(83)	
Not sure	0	(0)	< 5	(< 2)		0	(0)	< 5	(< 1)	
Time since last prescription					0.297					0.002
Less than one month ago	55	(59)	166	(52)		< 5	(< 100)	220	(54)	
One month to less than two months ago	15	(16)	39	(12)		0	(0)	54	(13)	
Two months to less than three months ago	< 5	(< 5)	12	(4)		0	(0)	15	(4)	
Three months to less than six months ago	10	(11)	32	(10)		< 5	(< 100)	41	(10)	
Six months to less than nine months ago	8	(9)	29	(9)		< 5	(< 100)	36	(9)	
Nine months to less than 12 months ago	< 5	(< 5)	26	(8)		< 5	(< 100)	28	(7)	
12 months or more ago	0	(0)	11	(3)		0	(0)	11	(3)	
Not sure	0	(0)	< 5	(< 2)		< 5	(< 100)	< 5	(< 1)	
Time since most recent visit to the healthcare provider who prescribed ER/LA opioid analgesic					0.265					0.009
Less than one month ago	58	(62)	150	(47)		0	(0)	208	(51)	
One month to less than two months ago	17	(18)	59	(19)		< 5	(< 100)	75	(18)	
Two months to less than three months ago	5	(5)	31	(10)		< 5	(< 100)	34	(8)	
Three months to less than six months ago	8	(9)	36	(11)		0	(0)	44	(11)	
Six months to less than nine months ago	< 5	(< 5)	21	(7)		< 5	(< 100)	23	(6)	
Nine months to less than 12 months ago	< 5	(< 5)	10	(3)		0	(0)	11	(3)	
12 months or more ago	< 5	(< 5)	10	(3)		0	(0)	11	(3)	
Not sure	0	(0)	< 5	(< 2)		0	(0)	< 5	(< 1)	
Time since healthcare provider first prescribed ER/LA opioid analgesic					0.023					0.020
Less than one month ago	7	(7)	10	(3)		0	(0)	17	(4)	
One month to less than two months ago	6	(6)	< 5	(< 2)		0	(0)	10	(2)	
Two months to less than three months ago	0	(0)	6	(2)		< 5	(< 100)	5	(1)	
Three months to less than six months ago	13	(14)	30	(9)		0	(0)	43	(11)	
Six months to less than nine months ago	10	(11)	47	(15)		< 5	(< 100)	55	(13)	
Nine months to less than 12 months ago	13	(14)	41	(13)		< 5	(< 100)	53	(13)	
12 months or more ago	44	(47)	177	(55)		< 5	(< 100)	220	(54)	
Not sure	< 5	(< 5)	< 5	(< 2)		0	(0)	5	(1)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic drug					0.588					<0.001
Pain specialist	44	(47)	135	(42)		< 5	(< 100)	177	(43)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physician	23	(24)	77	(24)		0	(0)	100	(25)	
Other type of specialist	27	(29)	99	(31)		< 5	(< 100)	124	(30)	
Nurse Practitioner or Physician Assistant	0	(0)	< 5	(< 2)		0	(0)	< 5	(< 1)	
Not sure	0	(0)	< 5	(< 2)		< 5	(< 100)	< 5	(< 1)	

ER, extended release; GED, General Education Degree; LA, long-acting; MG, Medication Guide; PCD, Patient Counseling Document; STD, standard deviation; US, United States

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified.

2. Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; read some or all of the Medication Guide at least once; understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide; healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months; healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months; and understood PCD, as self-reported by the respondent that they understood about half, most, or all of the information discussed from the PCD.

3. Did not receive Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; never read any of the Medication Guide; did not understand the Medication Guide, as self-reported by the respondent that they did not understand at all or understood less than half of the information in the Medication Guide; healthcare provider did not give PCD when ER/LA opioid analgesic was prescribed the first time nor in the last 12 months; healthcare provider did not refer to or speak about PCD when current ER/LA opioid analgesic was prescribed; and did not understood the PCD, as self-reported by the respondent that they did not understand at all or understood less than half of the information discussed from the PCD.

4. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood both or neither MG and PCD with those who did not receive/read/understood both or neither MG and PCD, respectively.

5. US Census regions of residence based on claims data at the time of index date Northeast (ME, NH, VT, MA, RI, CT, NY, PA, NJ); South (DE, MD, DC, VA, WV, NC, SC, GA, FL, KY, TN, MS, AL, OK, TX, AR, LA); Midwest (WI, MI, IL, IN, OH, MO, ND, SD, NE, KS, MN, IA); West (ID, MT, WY, NV, UT, CO, AZ, NM, AK, WA, OR, CA, HI).

6. ER/LA opioid analgesics Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadon (any methadone tablet or solution indicated for analgesic use).

TABLE 2E. DEMOGRAPHIC CHARACTERISTICS AMONG SURVEY RESPONDENTS, BY RECEIPT OF MORE THAN ONE ER/LA OPIOID ANALGESIC PRIOR TO INDEX DATE [1]

	More than one ER/LA opioid analgesic dispensing [2]				
	Yes		No		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**315**	**(76)**	**98**	**(24)**	
(95% confidence interval)	**(281 - 352)**		**(80 - 119)**		
Age in years, *mean (STD)*	*51.3 (10.67)*		*50.1 (12.69)*		0.063
18 to 34	30	(10)	17	(17)	
35 to 49	85	(27)	22	(22)	
50 to 64	187	(59)	54	(55)	
65+	13	(4)	5	(5)	
Gender					0.406
Female	191	(61)	64	(65)	
Male	124	(39)	34	(35)	
US Census region of residence					0.063
Northeast	51	(16)	21	(21)	
South	105	(33)	23	(23)	
Midwest	22	(7)	11	(11)	
West	135	(43)	40	(41)	
Unknown	< 5	(< 2)	< 5	(< 5)	
Hispanic or Latino ethnicity	8	(3)	< 5	(< 5)	0.779
Race					0.344
White or Caucasian	290	(92)	93	(95)	
Black or African American	10	(3)	< 5	(< 5)	
Mixed racial background	9	(3)	< 5	(< 5)	
Other	6	(2)	< 5	(< 5)	
Marital status					0.321
Single, never married	43	(14)	17	(17)	
Married/Living with partner	230	(73)	62	(63)	
Other marital status	42	(13)	19	(19)	
Income level, US dollars					0.293
Less than $25,000	37	(12)	11	(11)	
$25,000 to $49,999	79	(25)	20	(20)	
$50,000 to $74,999	62	(20)	20	(20)	
$75,000 to $99,999	42	(13)	7	(7)	
$100,000 or more	80	(25)	32	(33)	
Don't know	15	(5)	8	(8)	
Education level					0.222
Less than/Some high school, but no degree or GED	11	(3)	< 5	(< 5)	
High school or equivalent such as a GED	49	(16)	9	(9)	
Some college, but no degree	65	(21)	15	(15)	
Two-year degree (community or technical)	38	(12)	11	(11)	
College graduate	97	(31)	35	(36)	
Graduate school	50	(16)	25	(26)	
Other	5	(2)	< 5	(< 5)	
Specific ER/LA opioid analgesic(s) used [5]					0.005
Oral drugs that are not methadone only	187	(59)	79	(81)	
Patch and no methadone	85	(27)	17	(17)	
Patch only	27	(9)	8	(8)	
Patch and oral drug(s) that are not methadone	58	(18)	9	(9)	
Methadone	43	(14)	< 5	(< 5)	
Methadone only	21	(7)	< 5	(< 5)	
Methadone and oral drug(s) that are not methadone	17	(5)	< 5	(< 5)	
Methadone and patch	< 5	(< 2)	0	(0)	
Methadone oral drug(s) that are not methadone and patch	< 5	(< 2)	0	(0)	
New user					<0.001
First use	30	(10)	39	(40)	
Used before	285	(90)	57	(58)	
Not sure	0	(0)	< 5	(< 5)	
Time since last prescription					<0.001
Less than one month ago	207	(66)	14	(14)	
One month to less than two months ago	43	(14)	11	(11)	
Two months to less than three months ago	9	(3)	6	(6)	
Three months to less than six months ago	24	(8)	18	(18)	
Six months to less than nine months ago	9	(3)	28	(29)	
Nine months to less than 12 months ago	12	(4)	17	(17)	
12 months or more ago	9	(3)	< 5	(< 5)	
Not sure	< 5	(< 2)	< 5	(< 5)	
Time since most recent visit to the healthcare provider who prescribed ER/LA opioid analgesic					<0.001
Less than one month ago	177	(56)	31	(32)	
One month to less than two months ago	61	(19)	15	(15)	
Two months to less than three months ago	25	(8)	11	(11)	
Three months to less than six months ago	24	(8)	20	(20)	
Six months to less than nine months ago	10	(3)	15	(15)	
Nine months to less than 12 months ago	7	(2)	< 5	(< 5)	
12 months or more ago	9	(3)	< 5	(< 5)	
Not sure	< 5	(< 2)	0	(0)	
Time since healthcare provider first prescribed ER/LA opioid analgesic					<0.001
Less than one month ago	13	(4)	< 5	(< 5)	
One month to less than two months ago	7	(2)	< 5	(< 5)	
Two months to less than three months ago	6	(2)	0	(0)	
Three months to less than six months ago	23	(7)	20	(20)	
Six months to less than nine months ago	25	(8)	32	(33)	
Nine months to less than 12 months ago	34	(11)	20	(20)	
12 months or more ago	204	(65)	17	(17)	
Not sure	< 5	(< 2)	< 5	(< 5)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic drug					<0.001
Pain specialist	163	(52)	16	(16)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physician	83	(26)	17	(17)	
Other type of specialist	65	(21)	61	(62)	
Nurse Practitioner or Physician Assistant	< 5	(< 2)	0	(0)	
Not sure	0	(0)	< 5	(< 5)	

ER, extended release; GED, General Education Degree; KAS, Knowledge Assessment Score; LA, long-acting; PCD, Patient Counseling Document; STD, standard deviation; US, United States

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database SM (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified.

2. The number of ER/LA opioid analgesic dispensings prior to the index date will be defined by claims data by dispensings on distinct dates.

3. Chi square test for categorical and t-test for continuous variables were used to compare respondents who had only one ER/LA opioid analgesic dispensing prior to index date with those who had more than one ER/LA opioid analgesic dispensing prior to index date.

4. US Census regions of residence based on claims data at the time of index date Northeast (ME, NH, VT, MA, RI, CT, NY, PA, NJ); South (DE, MD, DC, VA, WV, NC, SC, GA, FL, KY, TN, MS, AL, OK, TX, AR, LA); Midwest (WI, MI, IL, IN, OH, MO, ND, SD, NE, KS, MN, IA); West (ID, MT, WY, NV, UT, CO, AZ, NM, AK, WA, OR, CA, HI).

5. ER/LA opioid analgesics Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use).

TABLE 2F. DEMOGRAPHIC CHARACTERISTICS AMONG SURVEY RESPONDENTS, BY KNOWLEDGE ASSESSMENT SCORE (KAS) THRESHOLD [1]

	KAS < 70% [2] No		KAS < 70% [2] Yes		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**380**	**(92)**	**33**	**(8)**	
(95% confidence interval)	**(343 - 420)**		**(23 - 46)**		
Age in years, *mean (STD)*	*51.0 (10.98)*		*51.1 (13.47)*		0.177
18 to 34	41	(11)	6	(18)	
35 to 49	100	(26)	7	(21)	
50 to 64	224	(59)	17	(52)	
65+	15	(4)	< 5	(< 15)	
Gender					0.045
Female	240	(63)	15	(45)	
Male	140	(37)	18	(55)	
US Census region of residence					0.504
Northeast	66	(17)	6	(18)	
South	120	(32)	8	(24)	
Midwest	32	(8)	< 5	(< 15)	
West	158	(42)	17	(52)	
Unknown	< 5	(< 1)	< 5	(< 15)	
Hispanic or Latino ethnicity	9	(2)	< 5	(< 15)	0.812
Race					0.729
White or Caucasian	350	(92)	33	(100)	
Black or African American	11	(3)	0	(0)	
Mixed racial background	10	(3)	0	(0)	
Other	9	(2)	0	(0)	
Marital status					0.031
Single, never married	49	(13)	11	(33)	
Married/Living with partner	273	(72)	19	(58)	
Other marital status	58	(15)	< 5	(< 15)	
Income level, US dollars					0.794
Less than $25,000	45	(12)	< 5	(< 15)	
$25,000 to $49,999	90	(24)	9	(27)	
$50,000 to $74,999	77	(20)	5	(15)	
$75,000 to $99,999	43	(11)	6	(18)	
$100,000 or more	103	(27)	9	(27)	
Don't know	22	(6)	< 5	(< 15)	
Education level					0.448
Less than/Some high school, but no degree or GED	11	(3)	< 5	(< 15)	
High school or equivalent such as a GED	57	(15)	< 5	(< 15)	
Some college, but no degree	74	(19)	6	(18)	
Two-year degree (community or technical)	44	(12)	5	(15)	
College graduate	117	(31)	15	(45)	
Graduate school	71	(19)	< 5	(< 15)	
Other	6	(2)	< 5	(< 15)	
Specific ER/LA opioid analgesic(s) used [5]					0.954
Oral drugs that are not methadone only	245	(64)	21	(64)	
Patch and no methadone	94	(25)	8	(24)	
Patch only	32	(8)	< 5	(< 15)	
Patch and oral drug(s) that are not methadone	62	(16)	5	(15)	
Methadone	41	(11)	< 5	(< 15)	
Methadone only	19	(5)	< 5	(< 15)	
Methadone and oral drug(s) that are not methadone	17	(4)	< 5	(< 15)	
Methadone and patch	< 5	(< 1)	0	(0)	
Methadone oral drug(s) that are not methadone and patch	< 5	(< 1)	0	(0)	
New user					0.019
First use	60	(16)	9	(27)	
Used before	319	(84)	23	(70)	
Not sure	< 5	(< 1)	< 5	(< 15)	
Time since last prescription					0.001
Less than one month ago	210	(55)	11	(33)	
One month to less than two months ago	51	(13)	< 5	(< 15)	
Two months to less than three months ago	11	(3)	< 5	(< 15)	
Three months to less than six months ago	39	(10)	< 5	(< 15)	
Six months to less than nine months ago	34	(9)	< 5	(< 15)	
Nine months to less than 12 months ago	24	(6)	5	(15)	
12 months or more ago	7	(2)	< 5	(< 15)	
Not sure	< 5	(< 1)	0	(0)	
Time since most recent visit to the healthcare provider who prescribed ER/LA opioid analgesic					0.002
Less than one month ago	198	(52)	10	(30)	
One month to less than two months ago	73	(19)	< 5	(< 15)	
Two months to less than three months ago	30	(8)	6	(18)	
Three months to less than six months ago	38	(10)	6	(18)	
Six months to less than nine months ago	20	(5)	5	(15)	
Nine months to less than 12 months ago	11	(3)	0	(0)	
12 months or more ago	9	(2)	< 5	(< 15)	
Not sure	< 5	(< 1)	< 5	(< 15)	
Time since healthcare provider first prescribed ER/LA opioid analgesic					0.902
Less than one month ago	16	(4)	< 5	(< 15)	
One month to less than two months ago	9	(2)	< 5	(< 15)	
Two months to less than three months ago	6	(2)	0	(0)	
Three months to less than six months ago	39	(10)	< 5	(< 15)	
Six months to less than nine months ago	51	(13)	6	(18)	
Nine months to less than 12 months ago	49	(13)	5	(15)	
12 months or more ago	206	(54)	15	(45)	
Not sure	< 5	(< 1)	< 5	(< 15)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic drug					0.072
Pain specialist	172	(45)	7	(21)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physician	88	(23)	12	(36)	
Other type of specialist	112	(29)	14	(42)	
Nurse Practitioner or Physician Assistant	< 5	(< 1)	0	(0)	
Not sure	< 5	(< 1)	0	(0)	

ER, extended release; GED, General Education Degree; KAS, Knowledge Assessment Score; LA, long-acting; PCD, Patient Counseling Document; STD, standard deviation; US, United States.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database SM (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified.

2. The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug. A KAS less than 70% is defined as poor knowledge.

3. Chi square test for categorical and t-test for continuous variables were used to compare respondents with KAS <70% with those with KAS ≥70%.

4. US Census regions of residence based on claims data at the time of index date Northeast (ME, NH, VT, MA, RI, CT, NY, PA, NJ); South (DE, MD, DC, VA, WV, NC, SC, GA, FL, KY, TN, MS, AL, OK, TX, AR, LA); Midwest (WI, MI, IL, IN, OH, MO, ND, SD, NE, KS, MN, IA); West (ID, MT, WY, NV, UT, CO, AZ, NM, AK, WA, OR, CA, HI).

5. ER/LA opioid analgesics Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use).

TABLE 2G. DEMOGRAPHIC CHARACTERISTICS AMONG SURVEY RESPONDENTS, BY SATISFACTION WITH ACCESS TO ER/LA OPIOID ANALGESICS [1]

	Satisfied with access to ER/LA opioid analgesics [2]			
	Yes		No	
	N	*(%)*	*N*	*(%)*
Total number of respondents	**336**	**(90)**	**38**	**(10)**
Age in years, *mean (STD)*	*51.2 (11.03)*		*48.9 (12.01)*	
18 to 34	35	(10)	7	(18)
35 to 49	94	(28)	8	(21)
50 to 64	191	(57)	22	(58)
65+	16	(5)	< 5	(< 13)
Gender				
Female	204	(61)	22	(58)
Male	132	(39)	16	(42)
US Census region of residence				
Northeast	56	(17)	6	(16)
South	107	(32)	12	(32)
Midwest	26	(8)	< 5	(< 13)
West	143	(43)	18	(47)
Unknown	< 5	(< 1)	0	(0)
Hispanic or Latino ethnicity	8	(2)	< 5	(< 13)
Race				
White or Caucasian	313	(93)	33	(87)
Black or African American	8	(2)	< 5	(< 13)
Mixed racial background	8	(2)	< 5	(< 13)
Other	7	(2)	< 5	(< 13)
Marital status				
Single, never married	46	(14)	7	(18)
Married/Living with partner	246	(73)	27	(71)
Other marital status	44	(13)	< 5	(< 13)
Income level, US dollars				
Less than $25,000	43	(13)	< 5	(< 13)
$25,000 to $49,999	82	(24)	6	(16)
$50,000 to $74,999	65	(19)	8	(21)
$75,000 to $99,999	42	(13)	5	(13)
$100,000 or more	85	(25)	16	(42)
Don't know	19	(6)	< 5	(< 13)
Education level				
Less than/Some high school, but no degree or GED	10	(3)	< 5	(< 13)
High school or equivalent such as a GED	50	(15)	6	(16)
Some college, but no degree	66	(20)	6	(16)
Two-year degree (community or technical)	43	(13)	< 5	(< 13)
College graduate	103	(31)	16	(42)
Graduate school	60	(18)	< 5	(< 13)
Other	< 5	(< 1)	< 5	(< 13)
Specific ER/LA opioid analgesic(s) used [5]				
Oral drugs that are not methadone only	214	(64)	28	(74)
Patch and no methadone				
Patch only	31	(9)	< 5	(< 13)
Patch and oral drug(s) that are not methadone	55	(16)	6	(16)
Methadone				
Methadone only	16	(5)	< 5	(< 13)
Methadone and oral drug(s) that are not methadone	17	(5)	0	(0)
Methadone and patch	< 5	(< 1)	0	(0)
Methadone oral drug(s) that are not methadone and patch	0	(0)	< 5	(< 13)
New user				
First use	53	(16)	5	(13)
Used before	282	(84)	33	(87)
Not sure	< 5	(< 1)	0	(0)
Time since last prescription				
Less than one month ago	186	(55)	22	(58)
One month to less than two months ago	41	(12)	7	(18)
Two months to less than three months ago	12	(4)	0	(0)
Three months to less than six months ago	35	(10)	< 5	(< 13)
Six months to less than nine months ago	31	(9)	< 5	(< 13)
Nine months to less than 12 months ago	20	(6)	< 5	(< 13)
12 months or more ago	9	(3)	< 5	(< 13)
Not sure	< 5	(< 1)	< 5	(< 13)
Time since most recent visit to the healthcare provider who prescribed ER/LA opioid analgesi				
Less than one month ago	173	(51)	20	(53)
One month to less than two months ago	65	(19)	7	(18)
Two months to less than three months ago	32	(10)	< 5	(< 13)
Three months to less than six months ago	28	(8)	< 5	(< 13)
Six months to less than nine months ago	21	(6)	< 5	(< 13)
Nine months to less than 12 months ago	7	(2)	< 5	(< 13)
12 months or more ago	9	(3)	< 5	(< 13)
Not sure	< 5	(< 1)	0	(0)
Time since healthcare provider first prescribed ER/LA opioid analgesi				
Less than one month ago	15	(4)	< 5	(< 13)
One month to less than two months ago	8	(2)	< 5	(< 13)
Two months to less than three months ago	< 5	(< 1)	< 5	(< 13)
Three months to less than six months ago	34	(10)	< 5	(< 13)
Six months to less than nine months ago	44	(13)	6	(16)
Nine months to less than 12 months ago	45	(13)	< 5	(< 13)
12 months or more ago	183	(54)	20	(53)
Not sure	< 5	(< 1)	< 5	(< 13)
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic dru				
Pain specialist	138	(41)	27	(71)
Primary care physician, general practitioner, internal medicine specialist, or family practice physici	83	(25)	6	(16)
Other type of specialist	110	(33)	5	(13)
Nurse Practitioner or Physician Assistan	< 5	(< 1)	0	(0)
Not sure	< 5	(< 1)	0	(0)

ER, extended release; GED, General Education Degree; KAS, Knowledge Assessment Score; LA, long-acting; PCD, Patient Counseling Document; STD, standard deviation; US, United States.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified.

2. Respondents who "strongly agreed" or "agreed" with the statement "I am satisfied with my access to my current ER/LA opioid analgesic." Respondents who "neither agreed nor disagreed" were excluded.

3. Chi square test for categorical and t-test for continuous variables were used to compare respondents with KAS <70% with those with KA≥70%.

4. US Census regions of residence based on claims data at the time of index date Northeast (ME, NH, VT, MA, RI, CT, NY, PA, NJ); South (DE, MD, DC, VA, WV, NC, SC, GA, FL, KY, TN, MS, AL, OK, TX, AR, LA); Midwest (WI, MI, IL, IN, OH, MO, ND, SD, NE, KS, MN, IA); West (ID, MT, WY, NV, UT, CO, AZ, NM, AK, WA, OR, CA, HI).

5. ER/LA opioid analgesics Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use).

TABLE 3. SURVEY RESPONDENTS BY ER/LA OPIOID ANALGESIC TYPE [1]

	All survey respondents	
	N	*(%)*
Total number of respondents	**413**	
Specific ER/LA opioid analgesic(s) used [2]		
Oral drugs that are not methadone only		
Hydrocodone		
Zohydro® ER	< 5	(< 1)
Hydromorphone		
Exalgo®	< 5	(< 1)
Morphine		
Avinza®	< 5	(< 1)
Embeda®	0	(0)
Kadian®	< 5	(< 1)
MS Contin®	21	(5)
Morphine controlled or slow release, generic	32	(8)
Oxycodone		
OxyContin® slow or extended release	102	(25)
Oxycodone slow release, generic	68	(16)
Oxymorphone		
Opana® ER	10	(2)
Oxymorphone ER, generic	< 5	(< 1)
Tapentadol		
Nucynta® ER	10	(2)
ER opioids, multiple	9	(2)
Patch and no methadone		
Patch only		
Buprenorphine		
Butrans®	9	(2)
Fentanyl		
Duragesic®	< 5	(< 1)
Fentanyl, generic	24	(6)
Patch, multiple types	< 5	(< 1)
Patch and oral drug(s) that are not methadone		
Buprenorphine		
Butrans® and oral drug(s) that are not methadone	8	(2)
Fentanyl		
Duragesic® and oral drug(s) that are not methadone	5	(1)
Fentanyl, generic, and oral drug(s) that are not methadone	52	(13)
Patch, multiple types, and oral drug(s) that are not methadone	< 5	(< 1)
Methadone		
Methadone only		
Dolophine®	< 5	(< 1)
Methadose™	0	(0)
Methadone, generic	20	(5)
Methadone, multiple types	< 5	(< 1)
Methadone and oral drug(s) that are not methadone		
Dolophine® and oral drug(s) that are not methadone	0	(0)
Methadose™ and oral drug(s) that are not methadone	< 5	(< 1)
Methadone, generic, and oral drug(s) that are not methadone	14	(3)
Methadone, multiple types, and oral drug(s) that are not methadone	< 5	(< 1)
Methadone and patch		
Dolophine® and patch	0	(0)
Methadose™ and patch	0	(0)
Methadone, generic, and patch	< 5	(< 1)
Methadone, multiple types, and patch	< 5	(< 1)
Methadone, oral drug(s) that are not methadone, and patch		
Dolophine®, oral drug(s) that are not methadone, and patch	0	(0)
Methadose™, oral drug(s) that are not methadone, and patch	0	(0)
Methadone, generic, oral drug(s) that are not methadone, and patch	0	(0)
Methadone, multiple types, oral drug(s) that are not methadone, and patch	< 5	(< 1)

ER, extended release; MG, Medication Guide; LA, long-acting

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013 All results will be aggregated and de-identified

2 ER/LA opioid analgesics: Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use) Survey participants who responded "not sure" or "refused" were disqualified from completing the remainder of the survey Survey respondents may have concurrently filled more than one type of ER/LA opioid analgesic at their most recent pharmacy visit, but were asked to specify the specific ER/LA opioid analgesic according to the following hierarchy by type: methadone, patch, oral drug

TABLE 4A. RESPONDENTS WHO RECEIVED AND/OR READ THE MEDICATION GUIDE, BY ER/LA OPIOID ANALGESIC TYPE [1]

	All survey respondents		Survey respondents, by ER/LA opioid analgesic type [2]					
			Non-methadone oral drugs only		Patch		Methadone	
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*
Total number of respondents	**405**		**262**	**(65)**	**100**	**(25)**	**43**	**(11)**
Last filled ER/LA opioid analgesic prescription								
Less than one month ago	219	(54)	130	(50)	60	(60)	29	(67)
One month to less than two months ago	53	(13)	37	(14)	12	(12)	< 5	(< 12)
Two months to less than three months ago	15	(4)	7	(3)	< 5	(< 5)	6	(14)
Three months to less than six months ago	41	(10)	30	(11)	8	(8)	< 5	(< 12)
Six months to less than nine months ago	35	(9)	29	(11)	6	(6)	0	(0)
Nine months to less than 12 months ago	28	(7)	23	(9)	< 5	(< 5)	< 5	(< 12)
12 months or more ago	11	(3)	< 5	(< 2)	7	(7)	0	(0)
Not sure	< 5	(< 1)	< 5	(< 2)	< 5	(< 5)	0	(0)
New user								
First use	66	(16)	43	(16)	20	(20)	< 5	(< 12)
Used before	337	(83)	217	(83)	80	(80)	40	(93)
Not sure	< 5	(< 1)	< 5	(< 2)	0	(0)	0	(0)
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic drug								
Pain specialist	176	(43)	95	(36)	52	(52)	29	(67)
Primary care physician, general practitioner, internal medicine specialist, or family practice physician	99	(24)	65	(25)	25	(25)	9	(21)
Other type of specialist	124	(31)	98	(37)	22	(22)	< 5	(< 12)
Nurse Practitioner or Physician Assistant	< 5	(< 1)	< 5	(< 2)	< 5	(< 5)	< 5	(< 12)
Not sure	< 5	(< 1)	< 5	(< 2)	0	(0)	0	(0)
Received MG from pharmacist with last ER/LA opioid analgesic prescription fill								
Yes	373	(92)	243	(93)	91	(91)	39	(91)
No	18	(4)	10	(4)	6	(6)	< 5	(< 12)
Not sure	14	(3)	9	(3)	< 5	(< 5)	< 5	(< 12)
Received MG from pharmacist in the last 12 months								
Yes	374	(92)	244	(93)	90	(90)	40	(93)
No	18	(4)	10	(4)	6	(6)	< 5	(< 12)
Not sure	13	(3)	8	(3)	< 5	(< 5)	< 5	(< 12)
Received MG from non-pharmacist in the last 12 months								
Yes	53	(13)	35	(13)	11	(11)	7	(16)
No	330	(81)	215	(82)	81	(81)	34	(79)
Not sure	22	(5)	12	(5)	8	(8)	< 5	(< 12)
Non-pharmacist source of MG in the last 12 months[3]								
Healthcare provider's office or clinic	22	(42)	16	(46)	< 5	(< 5)	< 5	(< 12)
The Internet	20	(38)	13	(37)	< 5	(< 5)	< 5	(< 12)
Another healthcare professional	15	(28)	13	(37)	< 5	(< 5)	0	(0)
Family or friends	< 5	(< 1)	< 5	(< 2)	< 5	(< 5)	0	(0)
Somewhere else	11	(21)	7	(20)	< 5	(< 5)	< 5	(< 12)
Read MG								
Never read any	6	(1)	6	(2)	0	(0)	0	(0)
Read some, at least once	64	(16)	45	(17)	16	(16)	< 5	(< 12)
Read all, at least once	274	(68)	170	(65)	74	(74)	30	(70)
Read all, with each pharmacy fill	61	(15)	41	(16)	10	(10)	10	(23)
Offer to explain MG								
Yes	264	(65)	173	(66)	63	(63)	28	(65)
No	124	(31)	76	(29)	34	(34)	14	(33)
Not sure	17	(4)	13	(5)	< 5	(< 5)	< 5	(< 12)
Person offering to explain MG								
Pharmacist or someone at the pharmacy	249	(94)	163	(94)	60	(95)	26	(93)
Healthcare provider or someone in the healthcare provider's office/clinic	113	(43)	73	(42)	25	(40)	15	(54)
Member of patient's family or a friend	21	(8)	15	(9)	< 5	(< 5)	< 5	(< 12)
Caregiver other than patient's family member or friend	13	(5)	10	(6)	< 5	(< 5)	< 5	(< 12)
Other	< 5	(< 1)	< 5	(< 2)	< 5	(< 5)	< 5	(< 12)
Accepted offer to explain MG								
Yes	145	(55)	101	(58)	30	(48)	14	(50)
No	118	(45)	71	(41)	33	(52)	14	(50)
Not sure	< 5	(< 1)	< 5	(< 2)	0	(0)	0	(0)
Usefulness of the information in the MG								
Not useful at all	< 5	(< 1)	< 5	(< 2)	< 5	(< 5)	0	(0)
Not very useful	12	(3)	7	(3)	< 5	(< 5)	< 5	(< 12)
Somewhat useful	163	(40)	105	(40)	41	(41)	17	(41)
Very useful	224	(56)	146	(56)	55	(55)	23	(55)
Refused	< 5	(< 1)	< 5	(< 2)	0		< 5	(< 12)
Understanding of the information in the MG								
Did not understand it at all	< 5	(< 1)	< 5	(< 2)	< 5	(< 5)	0	(0)
Understood some of the informatior	5	(1)	< 5	(< 2)	< 5	(< 5)	0	(0)
Understood about half of the informatior	11	(3)	6	(2)	< 5	(< 5)	< 5	(< 12)
Understood most of the informatior	137	(34)	87	(33)	35	(35)	15	(35)
Understood all of the information	248	(61)	164	(63)	58	(58)	26	(60)
Refused	< 5		< 5		0		0	

ER, extended release; MG, Medication Guide; LA, long-acting.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received the Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months or read some or all of the Medication Guide at least once. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. ER/LA opioid analgesic: Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use).

3. Respondents may have received the MG from more than one non-pharmacist source. Percentage denominators comprise respondents who received a MG from a non-pharmacist in the last 12 months.

4. Respondents may have received offer to explain MG from more than one source.

TABLE 4B. RESPONDENTS WHO RECEIVED AND/OR READ THE MEDICATION GUIDE, BY MEDICATION GUIDE RECEIPT/READ/COMPREHENSION STATUS [1]

	Received Medication Guide [2]					Read Medication Guide [3]					Understood Medication Guide [4]				
	Yes		No		p-value [5]	Yes		No		p-value [5]	Yes		No		p-value [5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**389**	**(96)**	**16**	**(4)**		**399**	**(99)**	**6**	**(1)**		**396**	**(98)**	**8**	**(2)**	
95% confidence interval)	**(351 - 430)**		**(9 - 26)**			**(361 - 440)**		**(2 - 13)**			**(358 - 437)**		**(3 - 16)**		
Last filled ER/LA opioid analgesic prescription					<0.001					0.039					0.008
Less than one month ago	214	(55)	5	(31)		216	(54)	< 5	(< 83)		217	(55)	< 5	(< 63)	
One month to less than two months ago	52	(13)	< 5	(< 31)		53	(13)	0	(0)		52	(13)	< 5	(< 63)	
Two months to less than three months ago	14	(4)	< 5	(< 31)		15	(4)	0	(0)		15	(4)	0	(0)	
Three months to less than six months ago	38	(10)	< 5	(< 31)		41	(10)	0	(0)		39	(10)	< 5	(< 63)	
Six months to less than nine months ago	33	(8)	< 5	(< 31)		34	(9)	< 5	(< 83)		34	(9)	< 5	(< 63)	
Nine months to less than 12 months ago	27	(7)	< 5	(< 31)		26	(7)	< 5	(< 83)		27	(7)	< 5	(< 63)	
12 months or more ago	10	(3)	< 5	(< 31)		11	(3)	0	(0)		10	(3)	< 5	(< 63)	
Not sure	< 5	(< 1)	< 5	(< 31)		< 5	(< 1)	0	(0)		< 5	(< 1)	< 5	(< 63)	
New user					0.006					0.149					0.001
First use	62	(16)	< 5	(< 31)		64	(16)	< 5	(< 83)		60	(15)	5	(63)	
Used before	326	(84)	11	(69)		333	(83)	< 5	(< 83)		334	(84)	< 5	(< 63)	
Not sure	< 5	(< 1)	< 5	(< 31)		< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic dru					0.165					0.004					0.008
Pain specialist	167	(43)	9	(56)		176	(44)	0	(0)		174	(44)	< 5	(< 63)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physicia	96	(25)	< 5	(< 31)		98	(25)	< 5	(< 83)		98	(25)	< 5	(< 63)	
Other type of specialist	120	(31)	< 5	(< 31)		119	(30)	5	(83)		118	(30)	5	(63)	
Nurse Practitioner or Physician Assistan	< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)	
Not sure	< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)	
Received MG from pharmacist with last ER/LA opioid analgesic prescription fil					<0.001					<0.001					0.026
Yes	373	(96)	0	(0)		367	(92)	6	(100)		366	(92)	7	(88)	
No	11	(3)	7	(44)		18	(5)	0	(0)		17	(4)	< 5	(< 63)	
Not sure	5	(1)	9	(56)		14	(4)	0	(0)		13	(3)	0	(0)	
Received MG from pharmacist in the last 12 months					<0.001					<0.001					0.045
Yes	374	(96)	0	(0)		368	(92)	6	(100)		367	(93)	7	(88)	
No	10	(3)	8	(50)		18	(5)	0	(0)		17	(4)	< 5	(< 63)	
Not sure	5	(1)	8	(50)		13	(3)	0	(0)		12	(3)	0	(0)	
Received MG from non-pharmacist in the last 12 month					0.001					0.145					0.594
Yes	53	(14)	0	(0)		53	(13)	0	(0)		51	(13)	< 5	(< 63)	
No	318	(82)	12	(75)		325	(81)	5	(83)		325	(82)	5	(63)	
Not sure	18	(5)	< 5	(< 31)		21	(5)	< 5	(< 83)		20	(5)	< 5	(< 63)	
Non-pharmacist source of MG in the last 12 months [6]															
Healthcare provider's office or clinic	22	(42)	NA			22	(42)	NA			20	(39)	< 5	(< 63)	0.087
The Internet	20	(38)	NA			20	(38)	NA			19	(37)	< 5	(< 63)	0.715
Another healthcare professiona	15	(28)	NA			15	(28)	NA			15	(29)	0	(0)	0.365
Family or friends	< 5	(< 1)	NA			< 5	(< 1)	NA			< 5	(< 1)	0	(0)	0.724
Somewhere else	11	(21)	NA			11	(21)	NA			11	(22)	0	(0)	0.461
Read MG					<0.001					<0.001					<0.001
Never read any	6	(2)	0	(0)		0	(0)	6	(100)		6	(2)	0	(0)	
Read some, at least once	60	(15)	< 5	(< 31)		64	(16)	0	(0)		58	(15)	5	(63)	
Read all, at least once	263	(68)	11	(69)		274	(69)	0	(0)		271	(68)	< 5	(< 63)	
Read all, with each pharmacy fill	60	(15)	< 5	(< 31)		61	(15)	0	(0)		61	(15)	0	(0)	
Offer to explain MG					0.004					0.497					0.681
Yes	259	(67)	5	(31)		260	(65)	< 5	(< 83)		260	(66)	< 5	(< 63)	
No	114	(29)	10	(63)		122	(31)	< 5	(< 83)		119	(30)	< 5	(< 63)	
Not sure	16	(4)	< 5	(< 31)		17	(4)	0	(0)		17	(4)	0	(0)	
Person offering to explain MG [7]															
Pharmacist or someone at the pharmacy	244	(94)	5	(100)	0.028	246	(95)	< 5	(< 83)	<0.001	245	(94)	< 5	(< 63)	0.006
Healthcare provider or someone in the healthcare provider's office/clini	112	(43)	< 5	(< 31)	0.932	109	(42)	< 5	(< 83)	0.070	112	(43)	< 5	(< 63)	0.933
Member of patient's family or a friend	21	(8)	0	(0)	0.691	21	(8)	0	(0)	0.724	19	(7)	< 5	(< 63)	0.064
Caregiver other than patient's family member or frien	13	(5)	0	(0)	0.638	13	(5)	0	(0)	0.547	13	(5)	0	(0)	0.443
Other	< 5	(< 1)	0	(0)	0.924	< 5	(< 1)	0	(0)	0.934	< 5	(< 1)	0	(0)	0.943
Accepted offer to explain MG					0.902					0.674					0.370
Yes	142	(55)	< 5	(< 31)		142	(55)	< 5	(< 83)		142	(55)	< 5	(< 63)	
No	116	(45)	< 5	(< 31)		117	(45)	< 5	(< 83)		117	(45)	< 5	(< 63)	
Not sure	< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)	
Usefulness of the information in the MG					<0.001					<0.001					<0.001
Not useful at all	< 5	(< 1)	0	(0)		< 5	(< 1)	< 5	(< 83)		< 5	(< 1)	< 5	(< 63)	
Not very useful	10	(3)	< 5	(< 31)		11	(3)	< 5	(< 83)		11	(3)	< 5	(< 63)	
Somewhat useful	155	(40)	8	(57)		161	(41)	< 5	(< 83)		160	(41)	< 5	(< 63)	
Very useful	220	(57)	< 5	(< 31)		222	(56)	< 5	(< 83)		221	(56)	< 5	(< 63)	
Refused	0		< 5			< 5		0			< 5		0		
Understanding of the information in the MG					<0.001					<0.001					<0.001
Did not understand it at all	< 5	(< 1)	0	(0)		< 5	(< 1)	0	(0)		0	(0)	< 5	(< 63)	
Understood some of the information	5	(1)	0	(0)		5	(1)	0	(0)		0	(0)	5	(63)	
Understood about half of the information	11	(3)	0	(0)		11	(3)	0	(0)		11	(3)	0	(0)	
Understood most of the information	131	(34)	6	(40)		133	(33)	< 5	(< 83)		137	(35)	0	(0)	
Understood all of the information	239	(61)	9	(60)		246	(62)	< 5	(< 83)		248	(63)	0	(0)	
Refused	0		< 5	(< 31)		< 5		0			0		0		

ER, extended release; MG, Medication Guide; LA, long-acting

. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received the Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months or read some or all of the Medication Guide at least once. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months.

3. Read some or all of the Medication Guide at least once. Respondents who did not receive the Medication Guide from any of the specified sources were still asked whether they read the Medication Guide.

4. Understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide. Respondents who did not receive and did not read the Medication Guide were not asked their comprehension of the Medication Guide.

5. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood with those who did not receive/read/understood the MG, respectively.

6. Respondents may have received the MG from more than one non-pharmacist source. Percentage denominators comprise respondents who received a MG from a non-pharmacist in the last 12 months.

7. Respondents may have received offer to explain MG from more than one source.

TABLE 4C. RESPONDENTS WHO RECEIVED AND/OR READ THE MEDICATION GUIDE, BY PATIENT COUNSELING DOCUMENT RECEIPT/REFERENCED/COMPREHENSION STATUS [1]

	Received PCD [2]					Referenced PCD [3]					Understood PCD [4]				
	Yes		No		p-value [5]	Yes		No		p-value [5]	Yes		No		p-value [5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**175**	**(43)**	**230**	**(57)**		**109**	**(27)**	**296**	**(73)**		**244**	**(60)**	**26**	**(6)**	
(95% confidence interval)	**(150 - 203)**		**(201 - 262)**			**(90 - 131)**		**(263 - 332)**			**(214 - 277)**		**(17 - 38)**		
Last filled ER/LA opioid analgesic prescription					0.131					0.402					0.099
Less than one month ago	105	(60)	114	(50)		63	(58)	156	(53)		141	(58)	8	(31)	
One month to less than two months ago	25	(14)	28	(12)		17	(16)	36	(12)		34	(14)	5	(19)	
Two months to less than three months ago	8	(5)	7	(3)		< 5	(< 5)	11	(4)		9	(4)	< 5	(< 19)	
Three months to less than six months ago	13	(7)	28	(12)		10	(9)	31	(10)		18	(7)	5	(19)	
Six months to less than nine months ago	11	(6)	24	(10)		8	(7)	27	(9)		19	(8)	< 5	(< 19)	
Nine months to less than 12 months ago	9	(5)	19	(8)		7	(6)	21	(7)		16	(7)	< 5	(< 19)	
12 months or more ago	< 5	(< 3)	8	(3)		0	(0)	11	(4)		6	(2)	< 5	(< 19)	
Not sure	< 5	(< 3)	< 5	(< 2)		0	(0)	< 5	(< 2)		< 5	(< 2)	0	(0)	
New user					0.170					0.305					0.109
First use	24	(14)	42	(18)		14	(13)	52	(18)		36	(1)	5	(19)	
Used before	151	(86)	186	(81)		95	(87)	242	(82)		207	(8)	20	(77)	
Not sure	0	(0)	< 5	(< 2)		0	(0)	< 5	(< 2)		< 5	(< 2)	< 5	(< 19)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic drug					0.052					0.682					0.055
Pain specialist	82	(47)	94	(41)		51	(47)	125	(42)		109	(4)	15	(58)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physician	47	(27)	52	(23)		27	(25)	72	(24)		61	(2)	< 5	(< 19)	
Other type of specialist	46	(26)	78	(34)		30	(28)	94	(32)		73	(30)	9	(35)	
Nurse Practitioner or Physician Assistant	0	(0)	< 5	(< 2)		0	(0)	< 5	(< 2)		0	(0)	0	(0)	
Not sure	0	(0)	< 5	(< 2)		< 5	(< 5)	< 5	(< 2)		< 5	(< 2)	0	(0)	
Received MG from pharmacist with last ER/LA opioid analgesic prescription fill					0.035					0.038					0.037
Yes	165	(94)	208	(90)		105	(96)	268	(91)		230	(94)	23	(88)	
No	7	(4)	11	(5)		< 5	(< 5)	15	(5)		6	(2)	< 5	(< 19)	
Not sure	< 5	(< 3)	11	(5)		< 5	(< 5)	13	(4)		8	(3)	0	(0)	
Received MG from pharmacist in the last 12 months					0.010					0.102					0.003
Yes	167	(95)	207	(90)		104	(95)	270	(91)		229	(94)	22	(85)	
No	6	(3)	12	(5)		< 5	(< 5)	16	(5)		8	(3)	< 5	(< 19)	
Not sure	< 5	(< 3)	11	(5)		< 5	(< 5)	10	(3)		7	(3)	0	(0)	
Received MG from non-pharmacist in the last 12 months					0.025					0.011					0.288
Yes	29	(17)	24	(10)		23	(21)	30	(10)		35	(14)	7	(27)	
No	141	(81)	189	(82)		80	(73)	250	(84)		196	(80)	17	(65)	
Not sure	5	(3)	17	(7)		6	(6)	16	(5)		13	(5)	< 5	(< 19)	
Non-pharmacist source of MG in the last 12 months[6]															
Healthcare provider's office or clinic	13	(45)	9	(38)	0.590	8	(35)	14	(47)	0.384	13	(37)	6	(86)	0.018
The Internet	11	(38)	9	(38)	0.974	9	(39)	11	(37)	0.855	13	(37)	< 5	(< 19)	0.325
Another healthcare professional	8	(28)	7	(29)	0.899	6	(26)	9	(30)	0.754	10	(29)	< 5	(< 19)	0.433
Family or friends	< 5	(< 3)	< 5	(< 2)	0.669	< 5	(< 5)	< 5	(< 2)	0.717	< 5	(< 2)	0	(0)	0.517
Somewhere else	< 5	(< 3)	7	(29)	0.170	< 5	(< 5)	7	(23)	0.597	5	(14)	0	(0)	0.287
Read MG					<0.001					0.002					<0.001
Never read any	< 5	(< 3)	< 5	(< 2)		< 5	(< 5)	< 5	(< 2)		5	(2)	0	(0)	
Read some, at least once	14	(8)	50	(22)		7	(6)	57	(19)		24	(10)	10	(38)	
Read all, at least once	124	(71)	150	(65)		76	(70)	198	(67)		170	(70)	15	(58)	
Read all, with each pharmacy fill	35	(20)	26	(11)		24	(22)	37	(13)		45	(18)	< 5	(< 19)	
Offer to explain MG					<0.001					0.001					0.490
Yes	132	(75)	132	(57)		87	(80)	177	(60)		169	(69)	15	(58)	
No	35	(20)	89	(39)		19	(17)	105	(35)		62	(2)	10	(38)	
Not sure	8	(5)	9	(4)		< 5	(< 5)	14	(5)		13	(5)	< 5	(< 19)	
Person offering to explain MG[7]															
Pharmacist or someone at the pharmacy	125	(95)	124	(94)	0.481	81	(93)	168	(95)	0.805	160	(95)	14	(93)	0.049
Healthcare provider or someone in the healthcare provider's office/clinic	67	(51)	46	(35)	0.030	47	(54)	66	(37)	0.012	83	(49)	8	(53)	0.722
Member of patient's family or a friend	13	(10)	8	(6)	0.308	5	(6)	16	(9)	0.243	14	(8)	< 5	(< 19)	0.425
Caregiver other than patient's family member or friend	6	(5)	7	(5)	0.535	< 5	(< 5)	10	(6)	0.237	7	(4)	< 5	(< 19)	0.361
Other	< 5	(< 3)	< 5	(< 2)	0.612	< 5	(< 5)	< 5	(< 2)	0.337	< 5	(< 2)	0	(0)	0.858
Accepted offer to explain MG					0.085					0.026					0.793
Yes	81	(61)	64	(48)		58	(67)	87	(49)		96	(57)	9	(60)	
No	51	(39)	67	(51)		29	(33)	89	(50)		72	(43)	6	(40)	
Not sure	0	(0)	< 5	(< 2)		0	(0)	< 5	(< 2)		< 5	(< 2)	0	(0)	
Usefulness of the information in the MG					0.012					0.019					0.016
Not useful at all	< 5	(< 3)	< 5	(< 2)		0	(0)	< 5	(< 2)		< 5	(< 2)	< 5	(< 19)	
Not very useful	5	(3)	7	(3)		< 5	(< 5)	8	(3)		7	(3)	0	(0)	
Somewhat useful	57	(33)	106	(47)		31	(29)	132	(45)		90	(37)	10	(38)	
Very useful	112	(64)	112	(49)		73	(68)	151	(51)		145	(60)	14	(54)	
Refused	0		< 5			< 5		< 5			< 5		0		
Understanding of the information in the MG					0.092					0.096					<0.001
Did not understand it at all	< 5	(< 3)	< 5	(< 2)		0	(0)	< 5	(< 2)		< 5	(< 2)	< 5	(< 19)	
Understood some of the informatio	< 5	(< 3)	< 5	(< 2)		0	(0)	5	(2)		< 5	(< 2)	< 5	(< 19)	
Understood about half of the informatio	< 5	(< 3)	7	(3)		< 5	(< 5)	10	(3)		< 5	(< 2)	< 5	(< 19)	
Understood most of the informatio	47	(27)	90	(39)		31	(28)	106	(36)		74	(30)	10	(38)	
Understood all of the information	121	(69)	127	(56)		77	(71)	171	(58)		164	(67)	10	(38)	
Refused	0		< 5			0		< 5			0		0		

ER, extended release; MG, Medication Guide; LA, long-acting.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received the Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months or read some or all of the Medication Guide at least once. All results will be aggregated and de identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. Healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months.

3. Healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months.

4. Understood PCD, as self-reported by the respondent that they understood at least some, half, most, or all of the information discussed from the PCD. Respondents who did not receive and did not have a provider who referenced the PCD were not asked their comprehension of the PCD.

5. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/referenced/understood with those who did not receive/referenced/understood the PCD, respectively.

6. Respondents may have received the MG from more than one non-pharmacist source. Percentage denominators comprise respondents who received a MG from a non-pharmacist in the last 12 months.

7. Respondents may have received offer to explain MG from more than one source.

TABLE 4D. RESPONDENTS WHO RECEIVED AND/OR READ THE MEDICATION GUIDE, BY RECEIPT/READ/UNDERSTOOD STATUS OF BOTH OR NEITHER MEDICATION GUIDE AND PATIENT COUNSELING DOCUMENT [1]

	Received/Read/Understood Medication Guide and PCD [2]					Did Not Receive/Read/Understand Medication Guide or PCD [3]				
	Yes		No		p-value [4]	Yes		No		p-value [4]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**94**	**(23)**	**311**	**(77)**		**NA**	**(0)**	**405**	**(100)**	**NA**
(95% confidence interval)	**(76 - 115)**		**(277 - 348)**					**(367 - 446)**		
Last filled ER/LA opioid analgesic prescription					0.297					
Less than one month ago	55	(59)	164	(53)				219	(54)	
One month to less than two months ago	15	(16)	38	(12)				53	(13)	
Two months to less than three months ago	< 5	(< 5)	12	(4)				15	(4)	
Three months to less than six months ago	10	(11)	31	(10)				41	(10)	
Six months to less than nine months ago	8	(9)	27	(9)				35	(9)	
Nine months to less than 12 months ago	< 5	(< 5)	25	(8)				28	(7)	
12 months or more ago	0	(0)	11	(4)				11	(3)	
Not sure	0	(0)	< 5	(< 2)				< 5	(< 1)	
New user					0.507					
First use	13	(14)	53	(17)				66	(16)	
Used before	81	(86)	256	(82)				337	(83)	
Not sure	0	(0)	< 5	(< 2)				< 5	(< 1)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic dru					0.588					
Pain specialist	44	(47)	132	(42)				176	(43)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physici	23	(24)	76	(24)				99	(24)	
Other type of specialist	27	(29)	97	(31)				124	(31)	
Nurse Practitioner or Physician Assistan	0	(0)	< 5	(< 2)				< 5	(< 1)	
Not sure	0	(0)	< 5	(< 2)				< 5	(< 1)	
Received MG from pharmacist with last ER/LA opioid analgesic prescription fil					0.015					
Yes	92	(98)	281	(90)				373	(92)	
No	< 5	(< 5)	16	(5)				18	(4)	
Not sure	0	(0)	14	(5)				14	(3)	
Received MG from pharmacist in the last 12 month					0.052					
Yes	91	(97)	283	(91)				374	(92)	
No	< 5	(< 5)	17	(5)				18	(4)	
Not sure	< 5	(< 5)	11	(4)				13	(3)	
Received MG from non-pharmacist in the last 12 month					0.002					
Yes	22	(23)	31	(10)				53	(13)	
No	68	(72)	262	(84)				330	(81)	
Not sure	< 5	(< 5)	18	(6)				22	(5)	
Non-pharmacist source of MG in the last 12 months[5]										
Healthcare provider's office or clinic	8	(36)	14	(45)	0.522			22	(42)	
The Internet	8	(36)	12	(39)	0.862			20	(38)	
Another healthcare professiona	6	(27)	9	(29)	0.889			15	(28)	
Family or friends	< 5	(< 5)	< 5	(< 2)	0.767			< 5	(< 1)	
Somewhere else	< 5	(< 5)	7	(23)	0.697			11	(21)	
Read MG					0.001					
Never read any	0	(0)	6	(2)				6	(1)	
Read some, at least once	6	(6)	58	(19)				64	(16)	
Read all, at least once	67	(71)	207	(67)				274	(68)	
Read all, with each pharmacy fil	21	(22)	40	(13)				61	(15)	
Offer to explain MG					<0.001					
Yes	78	(83)	186	(60)				264	(65)	
No	13	(14)	111	(36)				124	(31)	
Not sure	< 5	(< 5)	14	(5)				17	(4)	
Person offering to explain MG[6]										
Pharmacist or someone at the pharmacy	73	(94)	176	(95)	0.985			249	(94)	
Healthcare provider or someone in the healthcare provider's office/clini	43	(55)	70	(38)	0.034			113	(43)	
Member of patient's family or a frien	5	(6)	16	(9)	0.688			21	(8)	
Caregiver other than patient's family member or frien	< 5	(< 5)	10	(5)	0.651			13	(5)	
Other	< 5	(< 5)	< 5	(< 2)	0.798			< 5	(< 1)	
Accepted offer to explain MG					0.044					
Yes	52	(67)	93	(50)				145	(55)	
No	26	(33)	92	(49)				118	(45)	
Not sure	0	(0)	< 5	(< 2)				< 5	(< 1)	
Usefulness of the information in the MG					0.034					
Not useful at all	0	(0)	< 5	(< 2)				< 5	(< 1)	
Not very useful	< 5	(< 5)	9	(3)				12	(3)	
Somewhat useful	27	(29)	136	(44)				163	(40)	
Very useful	64	(68)	160	(52)				224	(56)	
Refused	0		< 5					< 5	(< 1)	
Understanding of the information in the MG					0.075					
Did not understand it at all	0	(0)	< 5	(< 2)				< 5	(< 1)	
Understood some of the information	0	(0)	5	(2)				5	(1)	
Understood about half of the information	< 5	(< 5)	10	(3)				11	(3)	
Understood most of the information	24	(26)	113	(37)				137	(34)	
Understood all of the information	69	(73)	179	(58)				248	(61)	
Refused	0		< 5					< 5		

ER, extended release; MG, Medication Guide; LA, long-acting; PCD, Patient Counseling Document.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulation within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received the Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months or read some or all of the Medication Guide at least once. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; read some or all of the Medication Guide at least once; understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide; healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months; healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months; and understood PCD, as self-reported by the respondent that they understood about half, most, or all of the information discussed from the PCD.

3. Did not receive Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; never read any of the Medication Guide; did not understand the Medication Guide, as self-reported by the respondent that they did not understand at all or understood less than half of the information in the Medication Guide; healthcare provider did not give PCD when ER/LA opioid analgesic was prescribed the first time nor in the last 12 months; healthcare provider did not refer to or speak about PCD when current ER/LA opioid analgesic was prescribed; and did not understood the PCD, as self-reported by the respondent that they did not understand at all or understood less than half of the information discussed from the PCD.

4. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood both or neither MG and PCD with those who did not receive/read/understood both or neither MG and PCD, respectively.

5. Respondents may have received the MG from more than one non-pharmacist source. Percentage denominators comprise respondents who received a MG from a non-pharmacist in the last 12 months.

6. Respondents may have received offer to explain MG from more than one source.

TABLE 4E. RESPONDENTS WHO RECEIVED AND/OR READ THE MEDICATION GUIDE, BY RECEIPT OF MORE THAN ONE ER/LA OPIOID ANALGESIC PRIOR TO INDEX DATE [1]

	More than one ER/LA opioid analgesic dispensing [2]				
	Yes		No		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**310**	**(77)**	**95**	**(24)**	
(95% confidence interval)	**(276 - 347)**		**(77 - 116)**		
Last filled ER/LA opioid analgesic prescriptio					<0 001
Less than one month ago	205	(66)	14	(15)	
One month to less than two months ago	42	(14)	11	(12)	
Two months to less than three months ago	9	(3)	6	(6)	
Three months to less than six months ago	24	(8)	17	(18)	
Six months to less than nine months ago	8	(3)	27	(28)	
Nine months to less than 12 months ago	12	(4)	16	(17)	
12 months or more ago	9	(3)	< 5	(< 5)	
Not sure	< 5	(< 2)	< 5	(< 5)	
New user					<0 001
First use	29	(9)	37	(39)	
Used before	281	(91)	56	(59)	
Not sure	0	(0)	< 5	(< 5)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic dru					<0 001
Pain specialist	160	(52)	16	(17)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physici	82	(26)	17	(18)	
Other type of specialist	65	(21)	59	(62)	
Nurse Practitioner or Physician Assistant	< 5	(< 2)	0	(0)	
Not sure	0	(0)	< 5	(< 5)	
Received MG from pharmacist with last ER/LA opioid analgesic prescription fi					0 053
Yes	285	(92)	88	(93)	
No	16	(5)	< 5	(< 5)	
Not sure	9	(3)	5	(5)	
Received MG from pharmacist in the last 12 month					0 035
Yes	288	(93)	86	(91)	
No	15	(5)	< 5	(< 5)	
Not sure	7	(2)	6	(6)	
Received MG from non-pharmacist in the last 12 month					0 424
Yes	40	(13)	13	(14)	
No	255	(82)	75	(79)	
Not sure	15	(5)	7	(7)	
Non-pharmacist source of MG in the last 12 months [4]					
Healthcare provider's office or clinic	18	(45)	< 5	(< 5)	0 366
The Internet	14	(35)	6	(46)	0 471
Another healthcare professional	12	(30)	< 5	(< 5)	0 630
Family or friends	< 5	(< 2)	< 5	(< 5)	0 715
Somewhere else	9	(23)	< 5	(< 5)	0 583
Read MG					<0 001
Never read any	5	(2)	< 5	(< 5)	
Read some, at least once	35	(11)	29	(31)	
Read all, at least once	223	(72)	51	(54)	
Read all, with each pharmacy fil	47	(15)	14	(15)	
Offer to explain MG					0 592
Yes	205	(66)	59	(62)	
No	93	(30)	31	(33)	
Not sure	12	(4)	5	(5)	
Person offering to explain MG [5]					
Pharmacist or someone at the pharmacy	194	(95)	55	(93)	0 207
Healthcare provider or someone in the healthcare provider's office/clini	91	(44)	22	(37)	0 675
Member of patient's family or a frien	12	(6)	9	(15)	0 066
Caregiver other than patient's family member or frien	9	(4)	< 5	(< 5)	0 435
Other	< 5	(< 2)	0	(0)	0 470
Accepted offer to explain MG					0 760
Yes	115	(56)	30	(51)	
No	89	(43)	29	(49)	
Not sure	< 5	(< 2)	0	(0)	
Usefulness of the information in the MG					0 395
Not useful at all	< 5	(< 2)	< 5	(< 5)	
Not very useful	9	(3)	< 5	(< 5)	
Somewhat useful	121	(39)	42	(45)	
Very useful	176	(57)	48	(51)	
Refused	< 5		< 5		
Understanding of the information in the MG					<0 001
Did not understand it at all	< 5	(< 2)	< 5	(< 5)	
Understood some of the information	< 5	(< 2)	< 5	(< 5)	
Understood about half of the information	10	(3)	< 5	(< 5)	
Understood most of the information	99	(32)	38	(40)	
Understood all of the information	199	(64)	49	(52)	
Refused	0		< 5		

ER, extended release; MG, Medication Guide; LA, long-acting

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received the Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months or read some or all of the Medication Guide at least once All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 The number of ER/LA opioid analgesic dispensings prior to the index date will be defined by claims data by dispensings on distinct dates

3 Chi square test for categorical and t-test for continuous variables were used to compare respondents who had only one ER/LA opioid analgesic dispensing prior to index date with those who had more than one ER/LA opioid analgesic dispensing prior to index date

4 Respondents may have received the MG from more than one non-pharmacist source Percentage denominators comprise respondents who received a MG from a non-pharmacist in the last 12 months

5 Respondents may have received offer to explain MG from more than one source

TABLE 4F. RESPONDENTS WHO RECEIVED AND/OR READ THE MEDICATION GUIDE, BY KNOWLEDGE ASSESSMENT SCORE (KAS) THRESHOLD [1]

	KAS < 70% [2]				
	No		Yes		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**373**	**(92)**	**32**	**(8)**	
(95% confidence interval)	**(336 - 413)**		**(22 - 45)**		
Last filled ER/LA opioid analgesic prescriptio					0 001
Less than one month ago	208	(56)	11	(34)	
One month to less than two months ago	50	(13)	< 5	(< 16)	
Two months to less than three months ago	11	(3)	< 5	(< 16)	
Three months to less than six months ago	38	(10)	< 5	(< 16)	
Six months to less than nine months ago	32	(9)	< 5	(< 16)	
Nine months to less than 12 months ago	24	(6)	< 5	(< 16)	
12 months or more ago	7	(2)	< 5	(< 16)	
Not sure	< 5	(< 1)	0	(0)	
New user					0 019
First use	58	(16)	8	(25)	
Used before	314	(84)	23	(72)	
Not sure	< 5	(< 1)	< 5	(< 16)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic dru					0 072
Pain specialist	169	(45)	7	(22)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physici	87	(23)	12	(38)	
Other type of specialist	111	(30)	13	(41)	
Nurse Practitioner or Physician Assistant	< 5	(< 1)	0	(0)	
Not sure	< 5	(< 1)	0	(0)	
Received MG from pharmacist with last ER/LA opioid analgesic prescription fi					0 388
Yes	344	(92)	29	(91)	
No	17	(5)	< 5	(< 16)	
Not sure	12	(3)	< 5	(< 16)	
Received MG from pharmacist in the last 12 month					0 054
Yes	348	(93)	26	(81)	
No	14	(4)	< 5	(< 16)	
Not sure	11	(3)	< 5	(< 16)	
Received MG from non-pharmacist in the last 12 month					0 035
Yes	48	(13)	5	(16)	
No	307	(82)	23	(72)	
Not sure	18	(5)	< 5	(< 16)	
Non-pharmacist source of MG in the last 12 months [4]					
Healthcare provider's office or clinic	20	(42)	< 5	(< 16)	0 943
The Internet	19	(40)	< 5	(< 16)	0 390
Another healthcare professional	13	(27)	< 5	(< 16)	0 542
Family or friends	< 5	(< 1)	< 5	(< 16)	0 145
Somewhere else	9	(19)	< 5	(< 16)	0 265
Read MG					0 160
Never read any	5	(1)	< 5	(< 16)	
Read some, at least once	55	(15)	9	(28)	
Read all, at least once	255	(68)	19	(59)	
Read all, with each pharmacy fil	58	(16)	< 5	(< 16)	
Offer to explain MG					0 014
Yes	249	(67)	15	(47)	
No	110	(29)	14	(44)	
Not sure	14	(4)	< 5	(< 16)	
Person offering to explain MG [5]					
Pharmacist or someone at the pharmacy	240	(96)	9	(60)	<0 001
Healthcare provider or someone in the healthcare provider's office/clini	104	(42)	9	(60)	0 389
Member of patient's family or a friend	19	(8)	< 5	(< 16)	0 702
Caregiver other than patient's family member or friend	12	(5)	< 5	(< 16)	0 941
Other	< 5	(< 1)	0	(0)	0 859
Accepted offer to explain MG					0 959
Yes	137	(55)	8	(53)	
No	111	(45)	7	(47)	
Not sure	< 5	(< 1)	0	(0)	
Usefulness of the information in the MG					0 013
Not useful at all	< 5	(< 1)	< 5	(< 16)	
Not very useful	11	(3)	< 5	(< 16)	
Somewhat useful	144	(39)	19	(61)	
Very useful	214	(58)	10	(32)	
Refused	< 5		< 5		
Understanding of the information in the MG					0 212
Did not understand it at all	< 5	(< 1)	< 5	(< 16)	
Understood some of the information	< 5	(< 1)	< 5	(< 16)	
Understood about half of the information	10	(3)	< 5	(< 16)	
Understood most of the information	127	(34)	10	(31)	
Understood all of the information	229	(62)	19	(59)	
Refused	< 5		0		

ER, extended release; MG, Medication Guide; LA, long-acting

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received the Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months or read some or all of the Medication Guid at least once All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug A KAS less than 70% is defined as poor knowledge

3 Chi square test for categorical and t-test for continuous variables were used to compare respondents with KAS <70% with those with KAS≥70%

4 Respondents may have received the MG from more than one non-pharmacist source Percentage denominators comprise respondents who received a MG from a non-pharmacist in the last 12 months

5 Respondents may have received offer to explain MG from more than one source

TABLE 5A. RESPONDENTS WHO RECEIVED AND/OR REFERENCED THE PATIENT COUNSELING DOCUMENT, BY ER/LA OPIOID ANALGESIC TYPE [1]

	All survey respondents		Survey respondents, by ER/LA opioid analgesic type [2]					
			Non-methadone oral drugs only		Patch		Methadone	
	N	*(%)*		*(%)*	*N*	*(%)*	*N*	*(%)*
Total number of respondents	**187**		**120**	**(64)**	**43**	**(23)**	**24**	**(13)**
Most recent visit to the healthcare provider who prescribed the most recent ER/LA opioid analges								
Less than one month ago	110	(59)	72	(60)	21	(49)	17	(71)
One month to less than two months ago	30	(16)	19	(16)	8	(19)	< 5	(< 21)
Two months to less than three months ago	12	(6)	5	(4)	5	(12)	< 5	(< 21)
Three months to less than six months ago	13	(7)	9	(8)	< 5	(< 12)	< 5	(< 21)
Six months to less than nine months ago	8	(4)	5	(4)	< 5	(< 12)	0	(0)
Nine months to less than 12 months ago	6	(3)	6	(5)	0	(0)	0	(0)
12 months or more ago	6	(3)	< 5	(< 4)	< 5	(< 12)	< 5	(< 21)
Not sure	< 5	(< 3)	< 5	(< 4)	0	(0)	0	(0)
Time since healthcare provider first prescribed the most recent ER/LA opioid analges								
Less than one month ago	9	(5)	8	(7)	< 5	(< 12)	0	(0)
One month to less than two months ago	7	(4)	5	(4)	< 5	(< 12)	< 5	(< 21)
Two months to less than three months ago	< 5	(< 3)	< 5	(< 4)	0	(0)	< 5	(< 21)
Three months to less than six months ago	19	(10)	12	(10)	< 5	(< 12)	< 5	(< 21)
Six months to less than nine months ago	15	(8)	10	(8)	5	(12)	0	(0)
Nine months to less than 12 months ago	19	(10)	15	(13)	< 5	(< 12)	< 5	(< 21)
12 months or more ago	113	(60)	68	(57)	29	(67)	16	(67)
Not sure	< 5	(< 3)	< 5	(< 4)	< 5	(< 12)	< 5	(< 21)
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic drug								
Pain specialist	87	(47)	47	(39)	23	(53)	17	(71)
Primary care physician, general practitioner, internal medicine specialist, or family practice physician	51	(27)	35	(29)	11	(26)	5	(21)
Other type of specialist	48	(26)	37	(31)	9	(21)	< 5	(< 21)
Nurse Practitioner or Physician Assistant	0	(0)	0	(0)	0	(0)	0	(0)
Not sure	< 5	(< 3)	< 5	(< 4)	0	(0)	0	(0)
Received PCD from healthcare provider when first prescribed the current ER/LA opioid analges								
Yes	155	(83)	99	(83)	35	(81)	21	(88)
No	11	(6)	7	(6)	< 5	(< 12)	< 5	(< 21)
Not sure	21	(11)	14	(12)	6	(14)	< 5	(< 21)
Received PCD from healthcare provider when prescribed the current ER/LA opioid analgesic in the last 12 months								
Yes	111	(59)	72	(60)	25	(58)	14	(58)
No	53	(28)	32	(27)	15	(35)	6	(25)
Not sure	23	(12)	16	(13)	< 5	(< 12)	< 5	(< 21)
Healthcare provider referred to or discussed PCD when prescribing the current ER/LA opioid analgesic in the last 12 months								
Yes	109	(58)	69	(58)	27	(63)	13	(54)
No	50	(27)	33	(28)	12	(28)	5	(21)
Not sure	28	(15)	18	(15)	< 5	(< 12)	6	(25)
Healthcare provider discussed opioid choice, including the benefits and risks associated with opioid therapy, and important safety information when prescribing the current ER/LA opioid analgesic in the last 12 months								
Yes	169	(90)	106	(88)	41	(95)	22	(92)
No	14	(7)	11	(9)	< 5	(< 12)	< 5	(< 21)
Not sure	< 5	(< 3)	< 5	(< 4)	0	(0)	< 5	(< 21)
Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic when it was prescribed in the last 12 months								
Yes	118	(63)	76	(63)	30	(70)	12	(50)
No	62	(33)	40	(33)	12	(28)	10	(42)
Not sure	7	(4)	< 5	(< 4)	< 5	(< 12)	< 5	(< 21)
Healthcare provider discussed what to do if a dose was missed of the current ER/LA opioid analgesic when it was prescribed in the last 12 months								
Yes	138	(74)	91	(76)	31	(72)	16	(67)
No	41	(22)	23	(19)	11	(26)	7	(29)
Not sure	8	(4)	6	(5)	< 5	(< 12)	< 5	(< 21)
Healthcare provider completed a Patient Prescriber Agreement (PPA) or patient contract when the current ER/LA opioid analgesic was prescribed in the last 12 months								
Yes	105	(56)	64	(53)	24	(56)	17	(71)
No	45	(24)	31	(26)	12	(28)	< 5	(< 21)
Not sure	37	(20)	25	(21)	7	(16)	5	(21)
Understanding of the information discussed from the PCD								
Did not understand it at all	< 5	(< 3)	0	(0)	0	(0)	< 5	(< 21)
Understood some of the informatio	< 5	(< 3)	< 5	(< 4)	< 5	(< 12)	0	(0)
Understood about half of the informatio	5	(3)	< 5	(< 4)	< 5	(< 12)	< 5	(< 21)
Understood most of the informatio	48	(26)	29	(24)	9	(21)	10	(44)
Understood all of the information	129	(70)	86	(72)	32	(74)	11	(48)
Refused	< 5		< 5		0		< 5	

ER, extended release; LA, long-acting; PCD, Patient Counseling Document; PPA, Patient Prescriber Agreement.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received a PCD from their healthcare provider when the current ER/LA opioid analgesic was first prescribed or prescribed in the last 12 months or had a healthcare provider who referred to or discussed the PCD when the current ER/LA opioid analgesic was prescribed in the last 12 months. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. ER/LA opioid analgesic: Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use).

TABLE 5B. RESPONDENTS WHO RECEIVED AND/OR REFERENCED THE PATIENT COUNSELING DOCUMENT, BY MEDICATION GUIDE RECEIPT/READ/COMPREHENSION STATUS [1]

	Received Medication Guide [2]					Read Medication Guide [3]					Understood Medication Guide [4]				
	Yes		No		p-value [5]	Yes		No		p-value [5]	Yes		No		p-value [5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**184**	**(98)**	**< 5**	**(< 3)**		**184**	**(98)**	**< 5**	**(< 3)**		**184**	**(98)**	**< 5**	**(< 3)**	
95% confidence interval)	**(158 - 213)**					**(158 - 213)**					**(158 - 213)**				
Most recent visit to the healthcare provider who prescribed the most recent ER/LA opioid analgesi					0.015					0.008					0.026
Less than one month ago	110	(60)	0	(0)		109	(59)	< 5	(< 100)		109	(59)	< 5	(< 100)	
One month to less than two months ago	30	(16)	0	(0)		30	(16)	0	(0)		30	(16)	0	(0)	
Two months to less than three months ago	11	(6)	< 5	(< 100)		12	(7)	0	(0)		10	(5)	< 5	(< 100)	
Three months to less than six months ago	13	(7)	0	(0)		13	(7)	0	(0)		13	(7)	0	(0)	
Six months to less than nine months ago	8	(4)	0	(0)		7	(4)	< 5	(< 100)		8	(4)	0	(0)	
Nine months to less than 12 months ago	6	(3)	0	(0)		5	(3)	< 5	(< 100)		6	(3)	0	(0)	
12 months or more ago	< 5	(< 3)	< 5	(< 100)		6	(3)	0	(0)		6	(3)	0	(0)	
Not sure	< 5	(< 3)	0	(0)		< 5	(< 3)	0	(0)		< 5	(< 3)	0	(0)	
Time since healthcare provider first prescribed the most recent ER/LA opioid analgesi					0.165					0.004					0.008
Less than one month ago	9	(5)	0	(0)		9	(5)	0	(0)		9	(5)	0	(0)	
One month to less than two months ago	7	(4)	0	(0)		7	(4)	0	(0)		7	(4)	0	(0)	
Two months to less than three months ago	< 5	(< 3)	0	(0)		< 5	(< 3)	0	(0)		< 5	(< 3)	0	(0)	
Three months to less than six months ago	19	(10)	0	(0)		19	(10)	0	(0)		19	(10)	0	(0)	
Six months to less than nine months ago	15	(8)	0	(0)		15	(8)	0	(0)		15	(8)	0	(0)	
Nine months to less than 12 months ago	19	(10)	0	(0)		18	(10)	< 5	(< 100)		18	(10)	< 5	(< 100)	
12 months or more ago	110	(60)	< 5	(< 100)		111	(60)	< 5	(< 100)		112	(61)	< 5	(< 100)	
Not sure	< 5	(< 3)	0	(0)		< 5	(< 3)	0	(0)		< 5	(< 3)	< 5	(< 100)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic dru					0.165					0.004					0.008
Pain specialist	85	(46)	< 5	(< 100)		87	(47)	0	(0)		86	(47)	< 5	(< 100)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physicia	51	(28)	0	(0)		51	(28)	0	(0)		51	(28)	0	(0)	
Other type of specialist	47	(26)	< 5	(< 100)		45	(24)	< 5	(< 100)		46	(25)	< 5	(< 100)	
Nurse Practitioner or Physician Assistan	0	(0)	0	(0)		0	(0)	0	(0)		0	(0)	0	(0)	
Not sure	< 5	(< 3)	0	(0)		< 5	(< 3)	0	(0)		< 5	(< 3)	0	(0)	
Received PCD from healthcare provider when first prescribed the current ER/LA opioid analgesi					0.007					0.093					0.492
Yes	153	(83)	< 5	(< 100)		153	(83)	< 5	(< 100)		153	(83)	< 5	(< 100)	
No	11	(6)	0	(0)		10	(5)	< 5	(< 100)		10	(5)	< 5	(< 100)	
Not sure	20	(11)	< 5	(< 100)		21	(11)	0	(0)		21	(11)	0	(0)	
Received PCD from healthcare provider when prescribed the current ER/LA opioid analgesic in the last 12 months					0.009					0.392					0.112
Yes	111	(60)	0	(0)		109	(59)	< 5	(< 100)		109	(59)	< 5	(< 100)	
No	50	(27)	< 5	(< 100)		53	(29)	0	(0)		52	(28)	< 5	(< 100)	
Not sure	23	(13)	0	(0)		22	(12)	< 5	(< 100)		23	(13)	0	(0)	
Healthcare provider referred to or discussed PCD when prescribing the current ER/LA opioid analgesic in the last 12 months					0.100					0.577					0.002
Yes	107	(58)	< 5	(< 100)		107	(58)	< 5	(< 100)		109	(59)	0	(0)	
No	49	(27)	< 5	(< 100)		49	(27)	< 5	(< 100)		48	(26)	< 5	(< 100)	
Not sure	28	(15)	0	(0)		28	(15)	0	(0)		27	(15)	< 5	(< 100)	
Healthcare provider discussed opioid choice, including the benefits and risks associated with opioid therapy, and important afety information when prescribing the current ER/LA opioid analgesic in the last 12 months					0.134					0.763					<0.001
Yes	167	(91)	< 5	(< 100)		166	(90)	< 5	(< 100)		166	(90)	< 5	(< 100)	
No	14	(8)	0	(0)		14	(8)	0	(0)		14	(8)	0	(0)	
Not sure	< 5	(< 3)	< 5	(< 100)		< 5	(< 3)	0	(0)		< 5	(< 3)	0	(0)	
Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic when it was prescribed in the ast 12 months					0.939					0.452					0.008
Yes	116	(63)	< 5	(< 100)		116	(63)	< 5	(< 100)		117	(64)	< 5	(< 100)	
No	61	(33)	< 5	(< 100)		61	(33)	< 5	(< 100)		60	(33)	< 5	(< 100)	
Not sure	7	(4)	0	(0)		7	(4)	0	(0)		7	(4)	0	(0)	
Healthcare provider discussed what to do if a dose was missed of the current ER/LA opioid analgesic when it was prescribed n the last 12 months					0.207					0.541					0.011
Yes	135	(73)	< 5	(< 100)		136	(74)	< 5	(< 100)		137	(74)	< 5	(< 100)	
No	41	(22)	0	(0)		40	(22)	< 5	(< 100)		39	(21)	< 5	(< 100)	
Not sure	8	(4)	0	(0)		8	(4)	0	(0)		8	(4)	0	(0)	
Healthcare provider completed a Patient Prescriber Agreement (PPA) or patient contract when the current ER/LA opioid nalgesic was prescribed in the last 12 months					0.420					0.240					0.228
Yes	105	(57)	0	(0)		103	(56)	< 5	(< 100)		105	(57)	0	(0)	
No	43	(23)	< 5	(< 100)		45	(24)	0	(0)		42	(23)	< 5	(< 100)	
Not sure	36	(20)	< 5	(< 100)		36	(20)	< 5	(< 100)		37	(20)	0	(0)	
Understanding of the information discussed from the PCI					0.095					0.536					<0.001
Did not understand it at all	< 5	(< 3)	0	(0)		< 5	(< 3)	0	(0)		< 5	(< 3)	0	(0)	
Understood some of the information	< 5	(< 3)	0	(0)		< 5	(< 3)	0	(0)		< 5	(< 3)	< 5	(< 100)	
Understood about half of the informatior	5	(3)	0	(0)		5	(3)	0	(0)		< 5	(< 3)	< 5	(< 100)	
Understood most of the information	48	(26)	0	(0)		48	(26)	0	(0)		48	(26)	0	(0)	
Understood all of the informatior	126	(69)	< 5	(< 100)		126	(69)	< 5	(< 100)		128	(70)	< 5	(< 100)	
Refused	< 5		0			< 5		0			< 5		0		

ER, extended release; LA, long-acting; PCD, Patient Counseling Document; PPA, Patient Prescriber Agreemen

. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in he HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received a PCD from their healthcare provider when the current ER/LA opioid analgesic was first prescribed or prescribed in the last 12 months or had a healthcare provider who referred to or discussed the PCD when the current ER/LA opioid analgesic was prescribed in the last 12 months. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months

3. Read some or all of the Medication Guide at least once. Respondents who did not receive the Medication Guide from any of the specified sources were still asked whether they read the Medication Guid

4. Understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide. Respondents who did not receive and did not read the Medication Guide were not asked their comprehension of the Medication Guide.

5. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood with those who did not receive/read/understood the MG respectively.

TABLE 5C. RESPONDENTS WHO RECEIVED AND/OR REFERENCED THE PATIENT COUNSELING DOCUMENT, BY PATIENT COUNSELING DOCUMENT RECEIPT/REFERENCED/COMPREHENSION STATUS [1]

	Received PCD [2]					Referenced PCD [3]					Understood PCD [4]				
	Yes		No		p-value [5]	Yes		No		p-value [5]	Yes		No		p-value [5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**175**	**(94)**	**12**	**(6)**		**109**	**(58)**	**78**	**(42)**		**182**	**(98)**	**< 5**	**(< 3)**	
95% confidence interval)	**(150 - 203)**		**(6 - 21)**			**(90 - 131)**		**(62 - 97)**			**(157 - 210)**				
Most recent visit to the healthcare provider who prescribed the most recent ER/LA opioid analgesi					0.068					0.201					0.137
Less than one month ago	101	(58)	9	(75)		68	(62)	42	(54)		107	(59)	< 5	(< 100)	
One month to less than two months ago	30	(17)	0	(0)		17	(16)	13	(17)		29	(16)	0	(0)	
Two months to less than three months ago	11	(6)	< 5	(< 42)		6	(6)	6	(8)		11	(6)	< 5	(< 100)	
Three months to less than six months ago	13	(7)	0	(0)		8	(7)	5	(6)		13	(7)	0	(0)	
Six months to less than nine months ago	8	(5)	0	(0)		5	(5)	< 5	(< 6)		8	(4)	0	(0)	
Nine months to less than 12 months ago	< 5	(< 3)	< 5	(< 42)		< 5	(< 5)	< 5	(< 6)		6	(3)	0	(0)	
12 months or more ago	6	(3)	0	(0)		< 5	(< 5)	< 5	(< 6)		6	(3)	0	(0)	
Not sure	< 5	(< 3)	0	(0)		0	(0)	< 5	(< 6)		< 5	(< 3)	0	(0)	
Time since healthcare provider first prescribed the most recent ER/LA opioid analgesi					0.052					0.682					0.055
Less than one month ago	9	(5)	0	(0)		7	(6)	< 5	(< 6)		9	(5)	0	(0)	
One month to less than two months ago	7	(4)	0	(0)		6	(6)	< 5	(< 6)		7	(4)	0	(0)	
Two months to less than three months ago	< 5	(< 3)	0	(0)		0	(0)	< 5	(< 6)		< 5	(< 3)	0	(0)	
Three months to less than six months ago	18	(10)	< 5	(< 42)		14	(13)	5	(6)		18	(10)	< 5	(< 100)	
Six months to less than nine months ago	15	(9)	0	(0)		10	(9)	5	(6)		15	(8)	0	(0)	
Nine months to less than 12 months ago	17	(10)	< 5	(< 42)		15	(14)	< 5	(< 6)		18	(10)	< 5	(< 100)	
12 months or more ago	104	(59)	9	(75)		56	(51)	57	(73)		110	(60)	< 5	(< 100)	
Not sure	< 5	(< 3)	0	(0)		< 5	(< 5)	< 5	(< 6)		< 5	(< 3)	0	(0)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic dru					0.052					0.682					0.055
Pain specialist	82	(47)	5	(42)		51	(47)	36	(46)		84	(46)	< 5	(< 100)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physicia	47	(27)	< 5	(< 42)		27	(25)	24	(31)		50	(27)	0	(0)	
Other type of specialist	46	(26)	< 5	(< 42)		30	(28)	18	(23)		47	(26)	< 5	(< 100)	
Nurse Practitioner or Physician Assistan	0	(0)	0	(0)		0	(0)	0	(0)		0	(0)	0	(0)	
Not sure	0	(0)	< 5	(< 42)		< 5	(< 5)	0	(0)		< 5	(< 3)	0	(0)	
Received PCD from healthcare provider when first prescribed the current ER/LA opioid analgesi					<0.001					<0.001					<0.001
Yes	155	(89)	0	(0)		88	(81)	67	(86)		151	(83)	< 5	(< 100)	
No	8	(5)	< 5	(< 42)		5	(5)	6	(8)		10	(5)	< 5	(< 100)	
Not sure	12	(7)	9	(75)		16	(15)	5	(6)		21	(12)	0	(0)	
Received PCD from healthcare provider when prescribed the current ER/LA opioid analgesic in the last 12 months					<0.001					<0.001					<0.001
Yes	111	(63)	0	(0)		81	(74)	30	(38)		109	(60)	< 5	(< 100)	
No	46	(26)	7	(58)		16	(15)	37	(47)		53	(29)	0	(0)	
Not sure	18	(10)	5	(42)		12	(11)	11	(14)		20	(11)	< 5	(< 100)	
Healthcare provider referred to or discussed PCD when prescribing the current ER/LA opioid analgesic in the last 12 months					<0.001					<0.001					<0.001
Yes	97	(55)	12	(100)		109	(100)	0	(0)		108	(59)	< 5	(< 100)	
No	50	(29)	0	(0)		0	(0)	50	(64)		48	(26)	< 5	(< 100)	
Not sure	28	(16)	0	(0)		0	(0)	28	(36)		26	(14)	< 5	(< 100)	
Healthcare provider discussed opioid choice, including the benefits and risks associated with opioid therapy, and important afety information when prescribing the current ER/LA opioid analgesic in the last 12 months					<0.001					<0.001					0.373
Yes	158	(90)	11	(92)		101	(93)	68	(87)		164	(90)	< 5	(< 100)	
No	14	(8)	0	(0)		6	(6)	8	(10)		14	(8)	0	(0)	
Not sure	< 5	(< 3)	< 5	(< 42)		< 5	(< 5)	< 5	(< 6)		< 5	(< 3)	0	(0)	
Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic when it was prescribed in the ast 12 months					0.001					<0.001					0.012
Yes	112	(64)	6	(50)		76	(70)	42	(54)		118	(65)	0	(0)	
No	56	(32)	6	(50)		28	(26)	34	(44)		57	(31)	< 5	(< 100)	
Not sure	7	(4)	0	(0)		5	(5)	< 5	(< 6)		7	(4)	0	(0)	
Healthcare provider discussed what to do if a dose was missed of the current ER/LA opioid analgesic when it was prescribed n the last 12 months					<0.001					<0.001					<0.001
Yes	130	(74)	8	(67)		87	(80)	51	(65)		136	(75)	0	(0)	
No	37	(21)	< 5	(< 42)		17	(16)	24	(31)		38	(21)	< 5	(< 100)	
Not sure	8	(5)	0	(0)		5	(5)	< 5	(< 6)		8	(4)	0	(0)	
Healthcare provider completed a Patient Prescriber Agreement (PPA) or patient contract when the current ER/LA opioid nalgesic was prescribed in the last 12 months					<0.001					<0.001					0.654
Yes	97	(55)	8	(67)		66	(61)	39	(50)		102	(56)	< 5	(< 100)	
No	44	(25)	< 5	(< 42)		22	(20)	23	(29)		43	(24)	< 5	(< 100)	
Not sure	34	(19)	< 5	(< 42)		21	(19)	16	(21)		37	(20)	0	(0)	
Understanding of the information discussed from the PCI					<0.001					<0.001					<0.001
Did not understand it at all	< 5	(< 3)	0	(0)		< 5	(< 5)	0	(0)		0	(0)	< 5	(< 100)	
Understood some of the information	< 5	(< 3)	0	(0)		0	(0)	< 5	(< 6)		0	(0)	< 5	(< 100)	
Understood about half of the informatior	5	(3)	0	(0)		0	(0)	5	(7)		5	(3)	0	(0)	
Understood most of the information	46	(27)	< 5	(< 42)		28	(26)	20	(26)		48	(26)	0	(0)	
Understood all of the informatior	119	(69)	10	(83)		80	(73)	49	(65)		129	(71)	0	(0)	
Refused	< 5		0			0		< 5			0		0		

ER, extended release; LA, long-acting; PCD, Patient Counseling Document; PPA, Patient Prescriber Agreemen

. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received a PCD from their healthcare provider when the current ER/LA opioid analgesic was first prescribed or prescribed in the last 12 months or had a healthcare provider who referred to or discussed the PCD when the current ER/LA opioid analgesic was prescribed in the last 12 months. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. Healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months
3. Healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months

4. Understood PCD, as self-reported by the respondent that they understood at least some, half, most, or all of the information discussed from the PCD. Respondents who did not receive and did not have a provider who referenced the PCD were not asked their comprehension of the PCD.

5. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/referenced/understood with those who did not receive/referenced/understood the PCD, respectively.

TABLE 5D. RESPONDENTS WHO RECEIVED AND/OR REFERENCED THE PATIENT COUNSELING DOCUMENT, BY RECEIPT/READ/UNDERSTOOD STATUS OF BOTH OR NEITHER MEDICATION GUIDE AND PATIENT COUNSELING DOCUMENT [1]

	Received/Read/Understood Medication Guide and PCD [2]					Did Not Receive/Read/Understand Medication Guide or PCD [3]				
	Yes		No		p-value [4]	Yes		No		p-value [4]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**94**	**(50)**	**93**	**(50)**		**NA**	**(0)**	**187**	**(100)**	**NA**
(95% confidence interval)	**(76 - 115)**		**(75 - 114)**					**(161 - 216)**		
Most recent visit to the healthcare provider who prescribed the most recent ER/LA opioid analgesi					0.265					
Less than one month ago	58	(62)	52	(56)				110	(59)	
One month to less than two months ago	17	(18)	13	(14)				30	(16)	
Two months to less than three months ago	5	(5)	7	(8)				12	(6)	
Three months to less than six months ago	8	(9)	5	(5)				13	(7)	
Six months to less than nine months ago	< 5	(< 5)	< 5	(< 5)				8	(4)	
Nine months to less than 12 months ago	< 5	(< 5)	5	(5)				6	(3)	
12 months or more ago	< 5	(< 5)	5	(5)				6	(3)	
Not sure	0	(0)	< 5	(< 5)				< 5	(< 3)	
Time since healthcare provider first prescribed the most recent ER/LA opioid analgesi					0.588					
Less than one month ago	7	(7)	< 5	(< 5)				9	(5)	
One month to less than two months ago	6	(6)	< 5	(< 5)				7	(4)	
Two months to less than three months ago	0	(0)	< 5	(< 5)				< 5	(< 3)	
Three months to less than six months ago	13	(14)	6	(6)				19	(10)	
Six months to less than nine months ago	10	(11)	5	(5)				15	(8)	
Nine months to less than 12 months ago	13	(14)	6	(6)				19	(10)	
12 months or more ago	44	(47)	69	(74)				113	(60)	
Not sure	< 5	(< 5)	< 5	(< 5)				< 5	(< 3)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic dru					0.588					
Pain specialist	44	(47)	43	(46)				87	(47)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physici	23	(24)	28	(30)				51	(27)	
Other type of specialist	27	(29)	21	(23)				48	(26)	
Nurse Practitioner or Physician Assistan	0	(0)	0	(0)				0	(0)	
Not sure	0	(0)	< 5	(< 5)				< 5	(< 3)	
Received PCD from healthcare provider when first prescribed the current ER/LA opioid analges					<0.001					
Yes	85	(90)	70	(75)				155	(83)	
No	< 5	(< 5)	9	(10)				11	(6)	
Not sure	7	(7)	14	(15)				21	(11)	
Received PCD from healthcare provider when prescribed the current ER/LA opioid analgesic in the last 12 months					<0.001					
Yes	80	(85)	31	(33)				111	(59)	
No	8	(9)	45	(48)				53	(28)	
Not sure	6	(6)	17	(18)				23	(12)	
Healthcare provider referred to or discussed PCD when prescribing the current ER/LA opioid analgesic in the last 12 months					<0.001					
Yes	94	(100)	15	(16)				109	(58)	
No	0	(0)	50	(54)				50	(27)	
Not sure	0	(0)	28	(30)				28	(15)	
Healthcare provider discussed opioid choice, including the benefits and risks associated with opioid therapy, and important safety information when prescribing the current ER/LA opioid analgesic in the last 12 months					0.000					
Yes	87	(93)	82	(88)				169	(90)	
No	6	(6)	8	(9)				14	(7)	
Not sure	< 5	(< 5)	< 5	(< 5)				< 5	(< 3)	
Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic when it was prescribed in the la 12 months					<0.001					
Yes	68	(72)	50	(54)				118	(63)	
No	21	(22)	41	(44)				62	(33)	
Not sure	5	(5)	< 5	(< 5)				7	(4)	
Healthcare provider discussed what to do if a dose was missed of the current ER/LA opioid analgesic when it was prescribed in the last 12 months					<0.001					
Yes	78	(83)	60	(65)				138	(74)	
No	11	(12)	30	(32)				41	(22)	
Not sure	5	(5)	< 5	(< 5)				8	(4)	
Healthcare provider completed a Patient Prescriber Agreement (PPA) or patient contract when the current ER/LA opioid analgesic was prescribed in the last 12 months					0.002					
Yes	57	(61)	48	(52)				105	(56)	
No	20	(21)	25	(27)				45	(24)	
Not sure	17	(18)	20	(22)				37	(20)	
Understanding of the information discussed from the PCI					<0.001					
Did not understand it at all	0	(0)	< 5	(< 5)				< 5	(< 3)	
Understood some of the informatio	0	(0)	< 5	(< 5)				< 5	(< 3)	
Understood about half of the informatio	0	(0)	5	(6)				5	(3)	
Understood most of the informatio	26	(28)	22	(24)				48	(26)	
Understood all of the informatio	68	(72)	61	(67)				129	(70)	
Refused	0		< 5					< 5		

ER, extended release; LA, long-acting; PCD, Patient Counseling Document; PPA, Patient Prescriber Agreement.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received a PCD from their healthcare provider when the current ER/LA opioid analgesic was first prescribed or prescribed in the last 12 months or had a healthcare provider who referred to or discussed the PCD when the current ER/LA opioid analgesic was prescribed in the last 12 months. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; read some or all of the Medication Guide at least once; understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide; healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months; healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months; and understood PCD, as self-reported by the respondent that they understood about half, most, or all of the information discussed from the PCD.

3. Did not receive Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; never read any of the Medication Guide; did not understand the Medication Guide, as self-reported by the respondent that they did not understand at all or understood less than half of the information in the Medication Guide; healthcare provider did not give PCD when ER/LA opioid analgesic was prescribed the first time nor in the last 12 months; healthcare provider did not refer or speak about PCD when current ER/LA opioid analgesic was prescribed; and did not understood the PCD, as self-reported by the respondent that they did not understand at all or understood less than half of the information discussed from the PCD.

4. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood both or neither MG and PCD with those who did not receive/read/understood both or neither MG and PCD, respectively.

TABLE 5E. RESPONDENTS WHO RECEIVED AND/OR REFERENCED THE PATIENT COUNSELING DOCUMENT, BY RECEIPT OF MORE THAN ONE ER/LA OPIOID ANALGESIC PRIOR TO INDEX DATE [1]

	More than one ER/LA opioid analgesic dispensing [2]				
	Yes		No		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**154**	**(82)**	**33**	**(18)**	
(95% confidence interval)	**(131 - 180)**		**(23 - 46)**		
Most recent visit to the healthcare provider who prescribed the most recent ER/LA opioid analgesic					<0 001
Less than one month ago	93	(60)	17	(52)	
One month to less than two months ago	27	(18)	< 5	(< 15)	
Two months to less than three months ago	9	(6)	< 5	(< 15)	
Three months to less than six months ago	10	(6)	< 5	(< 15)	
Six months to less than nine months ago	< 5	(< 3)	< 5	(< 15)	
Nine months to less than 12 months ago	< 5	(< 3)	< 5	(< 15)	
12 months or more ago	5	(3)	< 5	(< 15)	
Not sure	< 5	(< 3)	0	(0)	
Time since healthcare provider first prescribed the most recent ER/LA opioid analgesic					<0 001
Less than one month ago	6	(4)	< 5	(< 15)	
One month to less than two months ago	6	(4)	< 5	(< 15)	
Two months to less than three months ago	< 5	(< 3)	0	(0)	
Three months to less than six months ago	14	(9)	5	(15)	
Six months to less than nine months ago	5	(3)	10	(30)	
Nine months to less than 12 months ago	14	(9)	5	(15)	
12 months or more ago	105	(68)	8	(24)	
Not sure	< 5	(< 3)	< 5	(< 15)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic dru					<0 001
Pain specialist	81	(53)	6	(18)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physicia	42	(27)	9	(27)	
Other type of specialist	31	(20)	17	(52)	
Nurse Practitioner or Physician Assistan	0	(0)	0	(0)	
Not sure	0	(0)	< 5	(< 15)	
Received PCD from healthcare provider when first prescribed the current ER/LA opioid analgesic					0 004
Yes	132	(86)	23	(70)	
No	8	(5)	< 5	(< 15)	
Not sure	14	(9)	7	(21)	
Received PCD from healthcare provider when prescribed the current ER/LA opioid analgesic in the last 12 months					0 029
Yes	86	(56)	25	(76)	
No	48	(31)	5	(15)	
Not sure	20	(13)	< 5	(< 15)	
Healthcare provider referred to or discussed PCD when prescribing the current ER/LA opioid analgesic in the last 12 months					0 030
Yes	87	(56)	22	(67)	
No	45	(29)	5	(15)	
Not sure	22	(14)	6	(18)	
Healthcare provider discussed opioid choice, including the benefits and risks associated with opioid therapy, and important safety information when prescribing the current ER/LA opioid analgesic in the last 12 months					0 006
Yes	142	(92)	27	(82)	
No	10	(6)	< 5	(< 15)	
Not sure	< 5	(< 3)	< 5	(< 15)	
Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic when it was prescribed in the last 12 months					0 418
Yes	98	(64)	20	(61)	
No	51	(33)	11	(33)	
Not sure	5	(3)	< 5	(< 15)	
Healthcare provider discussed what to do if a dose was missed of the current ER/LA opioid analgesic when it was prescribed in the last 12 months					0 258
Yes	115	(75)	23	(70)	
No	33	(21)	8	(24)	
Not sure	6	(4)	< 5	(< 15)	
Healthcare provider completed a Patient Prescriber Agreement (PPA) or patient contract when the current ER/LA opioid analgesic was prescribed in the last 12 months					0 002
Yes	90	(58)	15	(45)	
No	30	(19)	15	(45)	
Not sure	34	(22)	< 5	(< 15)	
Understanding of the information discussed from the PCD					0 066
Did not understand it at all	< 5	(< 3)	0	(0)	
Understood some of the information	< 5	(< 3)	< 5	(< 15)	
Understood about half of the information	< 5	(< 3)	< 5	(< 15)	
Understood most of the information	39	(26)	9	(27)	
Understood all of the information	108	(71)	21	(64)	
Refused	< 5		0		

ER, extended release; LA, long-acting; PCD, Patient Counseling Document; PPA, Patient Prescriber Agreement

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received a PCD from their healthcare provider when the current ER/LA opioid analgesic was first prescribed or prescribed in the last 12 months or had a healthcare provider who referred to or discussed the PCD when the current ER/LA opioid analgesic was prescribed in the last 12 months All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 The number of ER/LA opioid analgesic dispensings prior to the index date will be defined by claims data by dispensings on distinct dates

3 Chi square test for categorical and t-test for continuous variables were used to compare respondents who had only one ER/LA opioid analgesic dispensing prior to index date with thos who had more than one ER/LA opioid analgesic dispensing prior to index date

TABLE 5F. RESPONDENTS WHO RECEIVED AND/OR REFERENCED THE PATIENT COUNSELING DOCUMENT, BY KNOWLEDGE ASSESSMENT SCORE (KAS) THRESHOLD [1]

	KAS < 70% [2]				
	No		Yes		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**174**	**(93)**	**13**	**(7)**	
(95% confidence interval)	**(149 - 202)**		**(7 - 22)**		
Most recent visit to the healthcare provider who prescribed the most recent ER/LA opioid analgesic					0 002
Less than one month ago	104	(60)	6	(46)	
One month to less than two months ago	30	(17)	0	(0)	
Two months to less than three months ago	10	(6)	< 5	(< 39)	
Three months to less than six months ago	10	(6)	< 5	(< 39)	
Six months to less than nine months ago	7	(4)	< 5	(< 39)	
Nine months to less than 12 months ago	6	(3)	0	(0)	
12 months or more ago	6	(3)	0	(0)	
Not sure	< 5	(< 3)	< 5	(< 39)	
Time since healthcare provider first prescribed the most recent ER/LA opioid analgesic					0 072
Less than one month ago	9	(5)	0	(0)	
One month to less than two months ago	6	(3)	< 5	(< 39)	
Two months to less than three months ago	< 5	(< 3)	0	(0)	
Three months to less than six months ago	17	(10)	< 5	(< 39)	
Six months to less than nine months ago	14	(8)	< 5	(< 39)	
Nine months to less than 12 months ago	19	(11)	0	(0)	
12 months or more ago	105	(60)	8	(62)	
Not sure	< 5	(< 3)	< 5	(< 39)	
Type of healthcare provider that first prescribed the survey index ER/LA opioid analgesic dru					0 072
Pain specialist	83	(48)	< 5	(< 39)	
Primary care physician, general practitioner, internal medicine specialist, or family practice physicia	45	(26)	6	(46)	
Other type of specialist	45	(26)	< 5	(< 39)	
Nurse Practitioner or Physician Assistan	0	(0)	0	(0)	
Not sure	< 5	(< 3)	0	(0)	
Received PCD from healthcare provider when first prescribed the current ER/LA opioid analgesic					0 852
Yes	144	(83)	11	(85)	
No	11	(6)	0	(0)	
Not sure	19	(11)	< 5	(< 39)	
Received PCD from healthcare provider when prescribed the current ER/LA opioid analgesic in the last 12 months					0 246
Yes	106	(61)	5	(38)	
No	49	(28)	< 5	(< 39)	
Not sure	19	(11)	< 5	(< 39)	
Healthcare provider referred to or discussed PCD when prescribing the current ER/LA opioid analgesic in the last 12 months					0 751
Yes	102	(59)	7	(54)	
No	48	(28)	< 5	(< 39)	
Not sure	24	(14)	< 5	(< 39)	
Healthcare provider discussed opioid choice, including the benefits and risks associated with opioid therapy, and important safety information when prescribing the current ER/LA opioid analgesic in the last 12 months					0 168
Yes	157	(90)	12	(92)	
No	14	(8)	0	(0)	
Not sure	< 5	(< 3)	< 5	(< 39)	
Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic when it was prescribed in the last 12 months					0 923
Yes	110	(63)	8	(62)	
No	58	(33)	< 5	(< 39)	
Not sure	6	(3)	< 5	(< 39)	
Healthcare provider discussed what to do if a dose was missed of the current ER/LA opioid analgesic when it was prescribed in the last 12 months					0 492
Yes	128	(74)	10	(77)	
No	39	(22)	< 5	(< 39)	
Not sure	7	(4)	< 5	(< 39)	
Healthcare provider completed a Patient Prescriber Agreement (PPA) or patient contract when the current ER/LA opioid analgesic was prescribed in the last 12 months					0 074
Yes	99	(57)	6	(46)	
No	43	(25)	< 5	(< 39)	
Not sure	32	(18)	5	(38)	
Understanding of the information discussed from the PCD					0 988
Did not understand it at all	< 5	(< 3)	0	(0)	
Understood some of the information	< 5	(< 3)	0	(0)	
Understood about half of the information	5	(3)	0	(0)	
Understood most of the information	43	(25)	5	(38)	
Understood all of the information	121	(70)	8	(62)	
Refused	< 5		0		

ER, extended release; LA, long-acting; PCD, Patient Counseling Document; PPA, Patient Prescriber Agreement

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013, and received a PCD from their healthcare provider when the current ER/LA opioid analgesic was first prescribed or prescribed in the last 12 months or had a healthcare provider who referred to or discussed the PCD when the current ER/LA opioid analgesic was prescribed in the last 12 months All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug A KAS less than 70% is defined as poor knowledge

3 Chi square test for categorical and t-test for continuous variables were used to compare respondents with KAS <70% with those with KAS≥70%

TABLE 6A. RESPONDENT KNOWLEDGE ASSESSMENT, BY ER/LA OPIOID ANALGESIC TYPE [1]

	All survey respondents		Survey respondents, by ER/LA opioid analgesic type [2]					
			Non-methadone oral drugs only		Patch		Methadone	
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*
Total number of respondents	**413**		**266**	**(64)**	**102**	**(25)**	**45**	**(11)**
The patient understands the serious risks associated with the use of their ER/LA opioid analges								
Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death.	386	(94)	246	(93)	97	(95)	43	(96)
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.	345	(84)	229	(86)	82	(80)	34	(76)
The patient knows what to do if they take too much drug								
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fin	363	(88)	228	(86)	92	(91)	43	(96)
Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics.	400	(97)	258	(97)	100	(98)	42	(93)
The patient understands the need to store the drug in a safe plac								
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household	271	(66)	170	(64)	64	(63)	37	(82)
Do not throw any unused ER/LA opioid analgesic in the trash	375	(91)	242	(91)	91	(89)	42	(93)
A child could die if they take or use the respondent's ER/LA opioid analgesic	384	(93)	243	(91)	99	(97)	42	(93)
The patient knows they should not share the drug with anyon								
Do not give ER/LA opioid analgesics to other people who have the same condition as you	406	(98)	262	(99)	101	(99)	43	(96)
Selling or giving away ER/LA opioid analgesics is against the law	402	(97)	259	(97)	100	(98)	43	(96)
The patient understands how to use the drug safely								
Talk to a healthcare provider prior to stopping ER/LA opioid analgesic	346	(84)	208	(78)	95	(93)	43	(96)
Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control pain.	389	(94)	249	(94)	99	(97)	41	(91)
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics.	385	(93)	250	(94)	92	(90)	43	(96)
Read the attached MG every time an ER/LA opioid prescription is filled	231	(56)	152	(57)	56	(55)	23	(51)
Inform healthcare provider about all the other medications being used.	398	(96)	256	(96)	100	(98)	42	(93)
Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental hea problems.	375	(91)	240	(90)	95	(93)	40	(89)
Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplement	368	(89)	240	(90)	89	(87)	39	(87)
It is okay to drink caffeine while using ER/LA opioid analgesic	202	(49)	129	(49)	49	(49)	24	(55)
ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication. [3]	206	(77)	206	(77)		NA		NA
Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was misse [3]	244	(92)	244	(92)		NA		NA
Inform healthcare provider of any fever.	74	(73)		NA	74	(73)		NA
Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists	84	(82)		NA	84	(82)		NA
Do not cut ER/LA opioid analgesic patches in half to use less medicine.	84	(82)		NA	84	(82)		NA

ER, extended release; LA, long-acting.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. ER/LA opioid analgesic: Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use).

3. Survey question only asked of non-methadone oral drugs only respondents.

4. Survey question only asked of patch and no methadone respondents.

TABLE 6B. RESPONDENT KNOWLEDGE ASSESSMENT, BY MEDICATION GUIDE RECEIPT/READ/COMPREHENSION STATUS [1]

	Received Medication Guide [2]					Read Medication Guide [3]					Understood Medication Guide				
	Yes		No		p-value [5]	Yes		No		p-value [5]	Yes		No		p-value [5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**389**	**(94)**	**24**	**(6)**		**399**	**(97)**	**14**	**(3)**		**399**	**(98)**	**10**	**(2)**	
The patient understands the serious risks associated with the use of their ER/LA opioid analges															
Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death.	365	(94)	21	(88)	0.129	374	(94)	12	(86)	0.602	374	(94)	9	(90)	0.422
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.	323	(83)	22	(92)	0.628	331	(83)	14	(100)	0.414	334	(84)	7	(70)	0.702
The patient knows what to do if they take too much drug															
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fin	344	(89)	19	(79)	0.396	354	(89)	9	(64)	0.023	351	(88)	9	(90)	0.851
Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics.	376	(97)	24	(100)	0.661	387	(97)	13	(93)	0.014	386	(97)	10	(100)	0.845
The patient understands the need to store the drug in a safe plac															
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household	256	(66)	15	(63)	0.670	262	(66)	9	(64)	0.824	264	(66)	5	(50)	0.511
Do not throw any unused ER/LA opioid analgesic in the trash	354	(91)	21	(88)	0.791	363	(91)	12	(86)	0.088	363	(91)	8	(80)	0.471
A child could die if they take or use the respondent's ER/LA opioid analgesic	362	(93)	22	(92)	0.966	370	(93)	14	(100)	0.579	370	(93)	10	(100)	0.676
The patient knows they should not share the drug with anyon															
Do not give ER/LA opioid analgesics to other people who have the same condition as you	383	(98)	23	(96)	0.504	392	(98)	14	(100)	0.883	393	(99)	9	(90)	0.075
Selling or giving away ER/LA opioid analgesics is against the law	378	(97)	24	(100)	0.404	388	(97)	14	(100)	0.529	388	(97)	10	(100)	0.595
The patient understands how to use the drug safely															
Talk to a healthcare provider prior to stopping ER/LA opioid analgesic	328	(84)	18	(75)	0.128	335	(84)	11	(79)	0.407	338	(85)	6	(60)	0.030
Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control pain.	367	(94)	22	(92)	0.519	377	(94)	12	(86)	<0.001	376	(94)	10	(100)	0.737
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics.	363	(93)	22	(92)	0.167	371	(93)	14	(100)	0.590	372	(93)	9	(90)	0.527
Read the attached MG every time an ER/LA opioid prescription is filled	218	(56)	13	(54)	0.821	225	(56)	6	(43)	0.563	224	(56)	5	(50)	0.437
Inform healthcare provider about all the other medications being used.	374	(96)	24	(100)	0.619	384	(96)	14	(100)	0.761	384	(96)	10	(100)	0.823
Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental hea problems.	354	(91)	21	(88)	0.391	362	(91)	13	(93)	0.835	364	(91)	7	(70)	0.001
Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplement	348	(89)	20	(83)	0.518	356	(89)	12	(86)	0.269	355	(89)	9	(90)	0.913
It is okay to drink caffeine while using ER/LA opioid analgesic	192	(50)	10	(43)	0.210	195	(49)	7	(50)	0.388	198	(50)	< 5	(< 100)	0.302
ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication. [3]	195	(78)	11	(73)	0.359	199	(78)	7	(70)	0.318	203	(79)	< 5	(< 100)	0.001
Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was misse[3]	230	(92)	14	(93)	0.572	235	(93)	9	(90)	0.280	236	(92)	5	(100)	0.865
Inform healthcare provider of any fever.	71	(73)	< 5	(< 21)	0.906	72	(72)	< 5	(< 36)	0.730	72	(74)	< 5	(< 100)	0.015
Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists	80	(82)	< 5	(< 21)	0.793	83	(83)	< 5	(<36)	0.382	81	(84)	< 5	(< 100)	0.002
Do not cut ER/LA opioid analgesic patches in half to use less medicine.	82	(85)	< 5	(< 21)	0.034	84	(84)	0	(0)	0.079	81	(84)	< 5	(< 100)	0.059

ER, extended release; LA, long-acting; MG, Medication Guide.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months.

3. Read some or all of the Medication Guide at least once. Respondents who did not receive the Medication Guide from any of the specified sources were still asked whether they read the Medication Guide.

4. Understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide. Respondents who did not receive and did not read the Medication Guide were not asked their comprehension of the Medication Guide.

5. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood with those who did not receive/read/understood the MG, respecti

6. Survey question only asked of non-methadone oral drugs only respondents.

7. Survey question only asked of patch and no methadone respondents.

TABLE 6C. RESPONDENT KNOWLEDGE ASSESSMENT, BY PATIENT COUNSELING DOCUMENT RECEIPT/REFERENCED/COMPREHENSION STATUS [1]

	Received PCD [2]					Referenced PCD [3]					Understood PCD [4]				
	Yes		No		p-value [5]	Yes		No		p-value [5]	Yes		No		p-value [5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**175**	**(42)**	**238**	**(58)**		**109**	**(26)**	**304**	**(74)**		**244**	**(90)**	**28**	**(10)**	
The patient understands the serious risks associated with the use of their ER/LA opioid analges															
Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death.	165	(94)	221	(93)	0.261	102	(94)	284	(94)	0.617	231	(95)	23	(85)	0.003
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.	140	(80)	205	(87)	0.277	93	(85)	252	(83)	0.889	201	(82)	27	(100)	0.003
The patient knows what to do if they take too much dru															
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fin	164	(94)	199	(84)	0.016	105	(96)	258	(85)	0.019	222	(91)	24	(89)	0.027
Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics.	169	(97)	231	(97)	0.843	104	(95)	296	(97)	0.137	234	(96)	27	(96)	0.267
The patient understands the need to store the drug in a safe plac															
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household	125	(71)	146	(61)	0.094	84	(77)	187	(62)	0.009	172	(70)	16	(57)	0.095
Do not throw any unused ER/LA opioid analgesic in the trash	161	(92)	214	(90)	0.645	102	(94)	273	(90)	0.393	221	(91)	23	(82)	0.351
A child could die if they take or use the respondent's ER/LA opioid analgesic	158	(90)	226	(95)	0.020	98	(90)	286	(94)	0.125	222	(91)	26	(93)	0.326
The patient knows they should not share the drug with anyon															
Do not give ER/LA opioid analgesics to other people who have the same condition as you	170	(97)	236	(99)	0.240	105	(96)	301	(99)	0.102	238	(98)	28	(100)	0.703
Selling or giving away ER/LA opioid analgesics is against the law	168	(96)	234	(98)	0.148	104	(95)	298	(98)	0.146	235	(96)	28	(100)	0.301
The patient understands how to use the drug safely															
Talk to a healthcare provider prior to stopping ER/LA opioid analgesic	153	(87)	193	(81)	0.017	95	(87)	251	(83)	0.531	207	(85)	22	(79)	0.519
Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control pain.	163	(93)	226	(95)	0.120	104	(95)	285	(94)	0.334	225	(92)	28	(100)	0.310
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics.	165	(94)	220	(92)	0.317	105	(96)	280	(92)	0.045	227	(93)	24	(86)	0.288
Read the attached MG every time an ER/LA opioid prescription is filled	110	(63)	121	(51)	0.047	64	(59)	167	(55)	0.744	145	(59)	18	(64)	0.476
Inform healthcare provider about all the other medications being used.	168	(96)	230	(97)	0.938	104	(95)	294	(97)	0.699	236	(97)	27	(96)	0.839
Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental hea problems.	155	(89)	220	(92)	0.349	95	(87)	280	(92)	0.025	219	(90)	26	(93)	0.790
Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplement	152	(87)	216	(91)	0.192	99	(91)	269	(88)	0.732	217	(89)	26	(93)	0.724
It is okay to drink caffeine while using ER/LA opioid analgesic	82	(47)	120	(51)	0.026	54	(50)	148	(49)	0.166	118	(49)	11	(41)	0.238
ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication. [3]	89	(79)	117	(76)	0.923	51	(74)	155	(79)	0.794	124	(79)	9	(53)	0.028
Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was misse [3]	104	(93)	140	(92)	0.820	64	(93)	180	(92)	0.928	146	(94)	16	(100)	0.041
Inform healthcare provider of any fever.	32	(80)	42	(68)	0.403	24	(89)	50	(67)	0.164	45	(76)	6	(75)	0.958
Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists	34	(85)	50	(81)	0.475	22	(81)	62	(83)	0.298	50	(85)	6	(75)	0.251
Do not cut ER/LA opioid analgesic patches in half to use less medicine.	38	(95)	46	(74)	0.053	24	(89)	60	(80)	0.590	52	(88)	7	(88)	0.655

ER, extended release; LA, long-acting; PCD, Patient Counseling Document.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 mo ths of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. Healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months.

3. Healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months.

4. Understood PCD, as self-reported by the respondent that they understood at least some, half, most, or all of the information discussed from the PCD. Respondents who did not receive and did not have a provider who referenced the PCD were not asked their comprehension o the PCD.

5. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/referenced/understood with those who did not receive/referenced/understood the PCD, respecti

6. Survey question only asked of non-methadone oral drugs only respondents.

7. Survey question only asked of patch and no methadone respondents.

TABLE 6D. RESPONDENT KNOWLEDGE ASSESSMENT, BY RECEIPT/READ/UNDERSTOOD STATUS OF BOTH OR NEITHER MEDICATION GUIDE AND PATIENT COUNSELING DOCUMENT[1]

	Received/Read/Understood Medication Guide and PCD[2]					Did Not Receive/Read/Understand Medication Guide or PCD[3]				
	Yes		No		p-value[4]	Yes		No		p-value[4]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**94**	**(23)**	**319**	**(77)**		**5**	**(1)**	**408**	**(99)**	
The patient understands the serious risks associated with the use of their ER/LA opioid analgesi										
Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death.	88	(94)	298	(94)	0.400	< 5	(< 100)	382	(94)	0.304
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy.	80	(85)	265	(83)	0.894	5	(100)	340	(84)	0.802
The patient knows what to do if they take too much dru										
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fin	91	(97)	272	(86)	0.025	< 5	(< 100)	359	(88)	0.489
Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics.	90	(96)	310	(97)	0.274	5	(100)	395	(97)	0.921
The patient understands the need to store the drug in a safe plac										
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the househol	72	(77)	199	(62)	0.035	< 5	(< 100)	269	(66)	0.479
Do not throw any unused ER/LA opioid analgesic in the trash	87	(93)	288	(90)	0.607	5	(100)	370	(91)	0.774
A child could die if they take or use the respondent's ER/LA opioid analgesic	84	(89)	300	(94)	0.046	5	(100)	379	(93)	0.826
The patient knows they should not share the drug with anyon										
Do not give ER/LA opioid analgesics to other people who have the same condition as you	91	(97)	315	(99)	0.149	5	(100)	401	(98)	0.957
Selling or giving away ER/LA opioid analgesics is against the law	89	(95)	313	(98)	0.069	5	(100)	397	(97)	0.710
The patient understands how to use the drug safely										
Talk to a healthcare provider prior to stopping ER/LA opioid analgesics.	84	(89)	262	(82)	0.171	< 5	(< 100)	342	(84)	0.774
Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control the pain.	89	(95)	300	(94)	0.363	< 5	(< 100)	385	(94)	0.002
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics.	90	(96)	295	(92)	0.062	5	(100)	380	(93)	0.832
Read the attached MG every time an ER/LA opioid prescription is filled	60	(64)	171	(54)	0.191	< 5	(< 100)	227	(56)	0.520
Inform healthcare provider about all the other medications being used.	89	(95)	309	(97)	0.508	5	(100)	393	(96)	0.909
Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems.	82	(87)	293	(92)	0.066	5	(100)	370	(91)	0.774
Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplement	85	(90)	283	(89)	0.754	5	(100)	363	(89)	0.734
It is okay to drink caffeine while using ER/LA opioid analgesics	44	(47)	158	(50)	0.084	< 5	(< 100)	200	(49)	0.642
ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication.[3]	45	(75)	161	(78)	0.918	< 5	(< 100)	205	(78)	0.084
Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed.[3]	56	(93)	188	(92)	0.952	< 5	(< 100)	241	(92)	0.990
Inform healthcare provider of any fever.[4]	21	(88)	53	(68)	0.278	< 5	(< 100)	73	(72)	0.946
Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists.[4]	19	(79)	65	(83)	0.229	0	(0)	84	(83)	0.055
Do not cut ER/LA opioid analgesic patches in half to use less medicine.[4]	22	(92)	62	(79)	0.567	0	(0)	84	(83)	0.011

ER, extended release; LA, long-acting; MG, Medication Guide; PCD, Patient Counseling Document.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral ormulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; read some or all of the Medication Guide at least once; understood Medication Guide, as self-reported by the respondent that hey understood about half, most, or all of the information in the Medication Guide; healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months; healthcare provider referred to discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months; and understood PCD, as self-reported by the respondent that they understood about half, most, or all of the information discussed from the PCD.

3. Did not receive Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; never read any of the Medication Guide; did not understand the Medication Guide, as self-reported by the respondent that hey did not understand at all or understood less than half of the information in the Medication Guide; healthcare provider did not give PCD when ER/LA opioid analgesic was prescribed the first time nor in the last 12 months; healthcare provider did not refer to or speak about PCD when current ER/LA opioid analgesic was prescribed; and did not understood the PCD, as self-reported by the respondent that they did not understand at all or understood less han half of the information discussed from the PCD.

4. Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood both or neither MG and PCD with those who did not receive/read/understood both or neither MG and PCD, respectively.

5. Survey question only asked of non-methadone oral drugs only respondents.

6. Survey question only asked of patch and no methadone respondents.

TABLE 6E. RESPONDENT KNOWLEDGE ASSESSMENT, BY RECEIPT OF MORE THAN ONE ER/LA OPIOID ANALGESIC PRIOR TO INDEX DATE [1]

	More than one ER/LA opioid analgesic dispensing [2]				
	Yes		No		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**315**	**(76)**	**98**	**(24)**	
The patient understands the serious risks associated with the use of their ER/LA opioid analgesic					
Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death	298	(95)	88	(90)	0 083
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy	255	(81)	90	(92)	0 085
The patient knows what to do if they take too much drug					
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine	278	(89)	85	(87)	0 816
Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics	304	(97)	96	(98)	0 546
The patient understands the need to store the drug in a safe place					
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household	221	(70)	50	(51)	0 002
Do not throw any unused ER/LA opioid analgesic in the trash	289	(92)	86	(88)	0 030
A child could die if they take or use the respondent's ER/LA opioid analgesics	295	(94)	89	(91)	0 317
The patient knows they should not share the drug with anyone					
Do not give ER/LA opioid analgesics to other people who have the same condition as you	312	(99)	94	(96)	0 062
Selling or giving away ER/LA opioid analgesics is against the law	306	(97)	96	(98)	0 661
The patient understands how to use the drug safely					
Talk to a healthcare provider prior to stopping ER/LA opioid analgesics	290	(92)	56	(57)	<0 001
Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control the pain	294	(93)	95	(97)	0 396
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics	292	(93)	93	(95)	0 559
Read the attached MG every time an ER/LA opioid prescription is filled	170	(54)	61	(62)	0 199
Inform healthcare provider about all the other medications being used	303	(96)	95	(97)	0 531
Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems	290	(92)	85	(87)	0 248
Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplements	279	(89)	89	(91)	0 764
It is okay to drink caffeine while using ER/LA opioid analgesics	164	(52)	38	(39)	0 142
ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication [3]	156	(83)	50	(63)	<0 001
Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed [3]	175	(94)	69	(88)	<0 001
Inform healthcare provider of any fever [4]	64	(75)	10	(59)	0 144
Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists [4]	68	(80)	16	(94)	0 141
Do not cut ER/LA opioid analgesic patches in half to use less medicine [4]	74	(87)	10	(59)	0 016

ER, extended release; LA, long-acting; MG, Medication Guide

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013 All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 The number of ER/LA opioid analgesic dispensings prior to the index date will be defined by claims data by dispensings on distinct dates

3 Chi square test for categorical and t-test for continuous variables were used to compare respondents who had only one ER/LA opioid analgesic dispensing prior to index date with those who had more than one ER/LA opioid analgesic dispensing prior to index date

4 Survey question only asked of non-methadone oral drugs only respondents

5 Survey question only asked of patch and no methadone respondents

TABLE 6F. RESPONDENT KNOWLEDGE ASSESSMENT, BY KNOWLEDGE ASSESSMENT SCORE (KAS) THRESHOLD [1]

	KAS < 70% [2]				
	No		Yes		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**380**	**(92)**	**33**	**(8)**	
The patient understands the serious risks associated with the use of their ER/LA opioid analgesic					
Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death	361	(95)	25	(76)	<0 001
ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy	328	(87)	17	(52)	<0 001
The patient knows what to do if they take too much drug					
Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine	345	(91)	18	(55)	<0 001
Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics	374	(98)	26	(79)	<0 001
The patient understands the need to store the drug in a safe place					
Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household	261	(69)	10	(30)	<0 001
Do not throw any unused ER/LA opioid analgesic in the trash	355	(93)	20	(61)	<0 001
A child could die if they take or use the respondent's ER/LA opioid analgesics	361	(95)	23	(70)	<0 001
The patient knows they should not share the drug with anyone					
Do not give ER/LA opioid analgesics to other people who have the same condition as you	375	(99)	31	(94)	0 002
Selling or giving away ER/LA opioid analgesics is against the law	374	(98)	28	(85)	<0 001
The patient understands how to use the drug safely					
Talk to a healthcare provider prior to stopping ER/LA opioid analgesics	328	(86)	18	(55)	<0 001
Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control the pain	366	(96)	23	(70)	<0 001
It is not okay to drink alcohol while taking or using ER/LA opioid analgesics	360	(95)	25	(76)	<0 001
Read the attached MG every time an ER/LA opioid prescription is filled	225	(59)	6	(18)	<0 001
Inform healthcare provider about all the other medications being used	370	(97)	28	(85)	<0 001
Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems	353	(93)	22	(67)	<0 001
Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplements	352	(93)	16	(48)	<0 001
It is okay to drink caffeine while using ER/LA opioid analgesics	192	(51)	10	(30)	0 097
ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication [3]	197	(80)	9	(43)	0 001
Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed [3]	229	(94)	15	(71)	<0 001
Inform healthcare provider of any fever [4]	71	(76)	< 5	(< 15)	0 124
Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists [4]	82	(87)	< 5	(< 15)	<0 001
Do not cut ER/LA opioid analgesic patches in half to use less medicine [4]	79	(84)	5	(63)	0 492

ER, extended release; LA, long-acting; MG, Medication Guide

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013 All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug A KAS less than 70% is defined as poor knowledge

3 Chi square test for categorical and t-test for continuous variables were used to compare respondents with KAS <70% with those with KAS≥70%

4 Survey question only asked of non-methadone oral drugs only respondents

5 Survey question only asked of patch and no methadone respondents

TABLE 7A. RESPONDENT SATISFACTION WITH ACCESS TO ER/LA OPIOID ANALGESIC TREATMENT, BY ER/LA OPIOID ANALGESIC TYPE [1]

	All survey respondents		Survey respondents, by ER/LA opioid analgesic type [2]					
			Non-methadone oral drugs only		Patch		Methadone	
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*
Total number of respondents	**413**		**266**	**(64)**	**102**	**(25)**	**45**	**(11)**
Can get a prescription for ER/LA opioid analgesics from my healthcare provider when needed for pair	302	(73)	191	(72)	78	(76)	33	(73)
Satisfied with ability to get a prescription for ER/LA opioid analgesics	329	(80)	210	(79)	81	(79)	38	(86)
Healthcare provider asked about medical history when prescribing ER/LA opioid analgesics	385	(93)	247	(93)	98	(96)	40	(89)
Healthcare provider talked about how much medication to take or use when ER/LA opioid analgesics were prescribed	393	(95)	257	(97)	94	(92)	42	(93)
Healthcare provider talked about what to do with extra medication when ER/LA opioid analgesics were prescribed	218	(53)	145	(55)	49	(49)	24	(53)
Satisfied with access to ER/LA opioid analgesics	336	(82)	214	(80)	86	(84)	36	(82)
Does not have to go to healthcare provider too often when more ER/LA opioid analgesics are needed	223	(54)	144	(54)	50	(49)	29	(64)
Satisfied with ability to get ER/LA opioid analgesics from a pharmacy	326	(79)	209	(79)	80	(78)	37	(82)

ER, extended release; LA, long-acting

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database^{SM} (HIRD), 01 December 2012 through 30 November 2013 All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 ER/LA opioid analgesic: Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use)

TABLE 7B. RESPONDENT SATISFACTION WITH ACCESS TO ER/LA OPIOID ANALGESIC TREATMENT, BY MEDICATION GUIDE RECEIPT/READ/COMPREHENSION STATUS[1]

	Received Medication Guide [2]					Read Medication Guide [3]					Understood Medication Guide [4]				
	Yes		No		p-value [5]	Yes		No		p-value [5]	Yes		No		p-value [5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**389**	**(94)**	**24**	**(6)**		**399**	**(97)**	**14**	**(3)**		**399**	**(98)**	**10**	**(2)**	
Can get a prescription for ER/LA opioid analgesics from my healthcare provider when needed for pain	290	(75)	12	(50)	0 027	293	(73)	9	(64)	0 528	296	(74)	< 5	(< 50)	<0 001
Satisfied with ability to get a prescription for ER/LA opioid analgesics	315	(81)	14	(61)	<0 001	319	(80)	10	(71)	0 410	319	(80)	7	(70)	0 655
Healthcare provider asked about medical history when prescribing ER/LA opioid analgesics	364	(94)	21	(88)	0 373	371	(93)	14	(100)	0 590	371	(93)	10	(100)	0 686
Healthcare provider talked about how much medication to take or use when ER/LA opioid analgesics were prescribed	370	(95)	23	(96)	0 772	380	(95)	13	(93)	0 610	379	(95)	10	(100)	0 768
Healthcare provider talked about what to do with extra medication when ER/LA opioid analgesics were prescribed	209	(54)	9	(39)	0 105	213	(54)	5	(36)	0 579	214	(54)	< 5	(< 50)	0 206
Satisfied with access to ER/LA opioid analgesics	319	(82)	17	(71)	0 522	323	(81)	13	(93)	0 644	324	(81)	8	(80)	0 998
Does not have to go to healthcare provider too often when more ER/LA opioid analgesics are needed	208	(53)	15	(63)	0 137	214	(54)	9	(64)	0 440	214	(54)	7	(70)	0 343
Satisfied with ability to get ER/LA opioid analgesics from a pharmacy	308	(79)	18	(75)	0 824	316	(79)	10	(71)	0 597	315	(79)	7	(70)	0 422

ER, extended release; LA, long-acting

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013 All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months

3 Read some or all of the Medication Guide at least once Respondents who did not receive the Medication Guide from any of the specified sources were still asked whether they read the Medication Guide

4 Understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide Respondents who did not receive and did not read the Medication Guide were not asked their comprehension of the Medication Guide

5 Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood with those who did not receive/read/understood the MG, respectively

TABLE 7C. RESPONDENT SATISFACTION WITH ACCESS TO ER/LA OPIOID ANALGESIC TREATMENT, BY PATIENT COUNSELING DOCUMENT RECEIPT/REFERENCED/COMPREHENSION STATUS[1]

	Received PCD[2]					Referenced PCD[3]					Understood PCD[4]				
	Yes		No		p-value[5]	Yes		No		p-value[5]	Yes		No		p-value[5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**175**	**(42)**	**238**	**(58)**		**109**	**(26)**	**304**	**(74)**		**244**	**(90)**	**28**	**(10)**	
Can get a prescription for ER/LA opioid analgesics from my healthcare provider when needed for pain	134	(77)	168	(71)	0 009	82	(75)	220	(72)	0 031	178	(73)	15	(54)	0 029
Satisfied with ability to get a prescription for ER/LA opioid analgesics	148	(85)	181	(76)	0 176	94	(87)	235	(77)	0 058	197	(81)	24	(86)	0 923
Healthcare provider asked about medical history when prescribing ER/LA opioid analgesics	163	(93)	222	(93)	0 745	102	(94)	283	(93)	0 899	226	(93)	25	(89)	0 037
Healthcare provider talked about how much medication to take or use when ER/LA opioid analgesics were prescribed	172	(98)	221	(93)	0 040	108	(99)	285	(94)	0 079	235	(96)	27	(96)	0 444
Healthcare provider talked about what to do with extra medication when ER/LA opioid analgesics were prescribed	119	(68)	99	(42)	<0 001	75	(69)	143	(47)	0 001	151	(62)	14	(50)	0 637
Satisfied with access to ER/LA opioid analgesics	152	(87)	184	(78)	0 075	95	(87)	241	(80)	0 326	199	(82)	22	(79)	0 515
Does not have to go to healthcare provider too often when more ER/LA opioid analgesics are needed	102	(58)	121	(51)	0 205	63	(58)	160	(53)	0 573	128	(52)	15	(54)	0 955
Satisfied with ability to get ER/LA opioid analgesics from a pharmacy	143	(82)	183	(77)	0 350	91	(83)	235	(77)	0 109	196	(80)	19	(68)	0 275

ER, extended release; LA, long-acting

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013 All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 Healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months

3 Healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months

4 Understood PCD, as self-reported by the respondent that they understood at least some, half, most, or all of the information discussed from the PCD Respondents who did not receive and did not have a provider who referenced the PCD were not asked their comprehension of the PCD

5 Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/referenced/understood with those who did not receive/referenced/understood the PCD, respectively

TABLE 7D. RESPONDENT SATISFACTION WITH ACCESS TO ER/LA OPIOID ANALGESIC TREATMENT, BY RECEIPT/READ/UNDERSTOOD STATUS OF BOTH OR NEITHER MEDICATION GUIDE AND PATIENT COUNSELING DOCUMENT [1]

	Received/Read/Understood Medication Guide and PCD [2]					Did Not Receive/Read/Understand Medication Guide or PCD [3]				
	Yes		No		p-value [4]	Yes		No		p-value [4]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**94**	**(23)**	**319**	**(77)**		**5**	**(1)**	**408**	**(99)**	
Can get a prescription for ER/LA opioid analgesics from my healthcare provider when needed for pain	70	(74)	232	(73)	0 037	< 5	(< 100)	299	(73)	0 785
Satisfied with ability to get a prescription for ER/LA opioid analgesics	82	(87)	247	(78)	0 209	< 5	(< 100)	325	(80)	0 738
Healthcare provider asked about medical history when prescribing ER/LA opioid analgesics	87	(93)	298	(93)	0 866	5	(100)	380	(93)	0 832
Healthcare provider talked about how much medication to take or use when ER/LA opioid analgesics were prescribed	93	(99)	300	(94)	0 141	5	(100)	388	(95)	0 879
Healthcare provider talked about what to do with extra medication when ER/LA opioid analgesics were prescribed	67	(72)	151	(48)	<0 001	< 5	(< 100)	216	(53)	0 629
Satisfied with access to ER/LA opioid analgesics	82	(87)	254	(80)	0 360	5	(100)	331	(81)	0 763
Does not have to go to healthcare provider too often when more ER/LA opioid analgesics are needed	55	(59)	168	(53)	0 572	< 5	(< 100)	220	(54)	0 199
Satisfied with ability to get ER/LA opioid analgesics from a pharmacy	80	(85)	246	(77)	0 097	5	(100)	321	(79)	0 509

ER, extended release; LA, long-acting; MG, Medication Guide; PCD, Patient Counseling Document

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013 All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; read some or all of the Medication Guide at least once; understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide; healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months; healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months; and understood PCD, as self-reported by the respondent that they understood about half, most, or all of the information discussed from the PCD

3 Did not receive Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; never read any of the Medication Guide; did not understand the Medication Guide, as self-reported by the respondent that they did not understand at all or understood less than half of the information in the Medication Guide; healthcare provider did not give PCD when ER/LA opioid analgesic was prescribed the first time nor in the last 12 months; healthcare provider did not refer to or speak about PCD when current ER/LA opioid analgesic was prescribed; and did not understood the PCD, as self-reported by the respondent that they did not understand at all or understood less than half of the information discussed from the PCD

4 Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood both or neither MG and PCD with those who did not receive/read/understood both or neither MG and PCD, respectively

TABLE 7E. RESPONDENT SATISFACTION WITH ACCESS TO ER/LA OPIOID ANALGESIC TREATMENT, BY RECEIPT OF MORE THAN ONE ER/LA OPIOID ANALGESIC PRIOR TO INDEX DATE [1]

	More than one ER/LA opioid analgesic dispensing [2]				
	Yes		No		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**315**	**(76)**	**98**	**(24)**	
Can get a prescription for ER/LA opioid analgesics from my healthcare provider when needed for pain.	243	(77)	59	(60)	0.003
Satisfied with ability to get a prescription for ER/LA opioid analgesics.	256	(82)	73	(74)	0.008
Healthcare provider asked about medical history when prescribing ER/LA opioid analgesics.	294	(93)	91	(93)	0.894
Healthcare provider talked about how much medication to take or use when ER/LA opioid analgesics were prescribed.	301	(96)	92	(94)	0.382
Healthcare provider talked about what to do with extra medication when ER/LA opioid analgesics were prescribed.	173	(55)	45	(47)	0.058
Satisfied with access to ER/LA opioid analgesics.	254	(81)	82	(85)	0.057
Does not have to go to healthcare provider too often when more ER/LA opioid analgesics are needed.	165	(52)	58	(59)	0.004
Satisfied with ability to get ER/LA opioid analgesics from a pharmacy.	245	(78)	81	(83)	0.060

ER, extended release; LA, long-acting.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database SM (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2.The number of ER/LA opioid analgesic dispensings prior to the index date will be defined by claims data by dispensings on distinct dates.

3. Chi square test for categorical and t-test for continuous variables were used to compare respondents who had only one ER/LA opioid analgesic dispensing prior to index date with those who had more than one ER/LA opioid analgesic dispensing prior to index date.

TABLE 7F. RESPONDENT SATISFACTION WITH ACCESS TO ER/LA OPIOID ANALGESIC TREATMENT, BY KNOWLEDGE ASSESSMENT SCORE (KAS) THRESHOLD [1]

	KAS < 70% [2]				
	No		Yes		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**380**	**(92)**	**33**	**(8)**	
Can get a prescription for ER/LA opioid analgesics from my healthcare provider when needed for pain.	285	(75)	17	(52)	0.006
Satisfied with ability to get a prescription for ER/LA opioid analgesics.	310	(82)	19	(59)	<0.001
Healthcare provider asked about medical history when prescribing ER/LA opioid analgesics.	359	(94)	26	(79)	<0.001
Healthcare provider talked about how much medication to take or use when ER/LA opioid analgesics were prescribed.	363	(96)	30	(91)	0.002
Healthcare provider talked about what to do with extra medication when ER/LA opioid analgesics were prescribed.	207	(55)	11	(34)	0.043
Satisfied with access to ER/LA opioid analgesics.	309	(81)	27	(84)	0.008
Does not have to go to healthcare provider too often when more ER/LA opioid analgesics are needed.	209	(55)	14	(42)	0.304
Satisfied with ability to get ER/LA opioid analgesics from a pharmacy.	301	(79)	25	(76)	0.735

ER, extended release; LA, long-acting.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug. A KAS less than 70% is defined as poor knowledge.

3. Chi square test for categorical and t-test for continuous variables were used to compare respondents with KAS <70% with those with KAS ≥70%.

TABLE 8A. RESPONDENT-REPORTED HEALTHCARE PROVIDER ACTIVITIES IN THE PAST 2 MONTHS, BY ER/LA OPIOID ANALGESIC TYPE [1]

	All survey respondents		Survey respondents, by ER/LA opioid analgesic type [2]					
			Non-methadone oral drugs only		Patch		Methadone	
	N	*(%)*	*N*	*(%)*	*N*	*(%)*	*N*	*(%)*
Total number of respondents	**413**	**(100)**	**266**	**(64)**	**102**	**(25)**	**45**	**(11)**
Used the PCD on ER/LA Opioids for discussions (Always, Regularly, or Sometimes)	165	(40)	106	(40)	38	(37)	21	(47)
Cautioned about important risks associated with ER/LA opioid analgesics, including overdose or taking or using too much (Always, Regularly, or Sometimes)	286	(69)	188	(71)	63	(62)	35	(78)
Discussed how to safely discontinue ER/LA opioid analgesics if they are no longer needed (Always, Regularly, or Sometimes)	229	(56)	152	(57)	49	(48)	28	(64)
Counseled on the most common side effects from using ER/LA opioid analgesics (Always, Regularly, or Sometimes)	303	(73)	194	(73)	75	(74)	34	(76)
Instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics (Always, Regularly, or Sometimes)	199	(48)	130	(49)	46	(45)	23	(51)
Instructed about keeping ER/LA opioid analgesics safe and away from children (Always, Regularly, or Sometimes)	253	(61)	164	(62)	65	(64)	24	(53)
Instructed not to share ER/LA opioid analgesics with anyone else (Always, Regularly, or Sometimes)	264	(64)	165	(62)	65	(64)	34	(76)

ER, extended release; LA, long-acting; PCD, Patient Counseling Document

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013 All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 ER/LA opioid analgesic: Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use)

TABLE 8B. RESPONDENT-REPORTED HEALTHCARE PROVIDER ACTIVITIES IN THE PAST 2 MONTHS, BY MEDICATION GUIDE RECEIPT/READ/COMPREHENSION STATUS [1]

	Received Medication Guide [2]					Read Medication Guide [3]					Understood Medication Guide [4]				
	Yes		No		p-value [5]	Yes		No		p-value [5]	Yes		No		p-value [5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**389**	**(94)**	**24**	**(6)**		**399**	**(97)**	**14**	**(3)**		**399**	**(98)**	**10**	**(2)**	
Used the PCD on ER/LA Opioids for discussions (Always, Regularly, or Sometimes)	161	(41)	< 5	(< 21)	<0 001	162	(41)	< 5	(< 36)	0 475	163	(41)	< 5	(< 50)	0 627
Cautioned about important risks associated with ER/LA opioid analgesics, including overdose or taking or using too much (Always, Regularly, or Sometimes)	271	(70)	15	(63)	0 220	275	(69)	11	(79)	0 718	277	(70)	5	(50)	0 014
Discussed how to safely discontinue ER/LA opioid analgesics if they are no longer needed (Always, Regularly, or Sometimes)	215	(55)	14	(61)	0 001	219	(55)	10	(71)	0 822	224	(56)	< 5	(20)	0 085
Counseled on the most common side effects from using ER/LA opioid analgesics (Always, Regularly, or Sometimes)	290	(75)	13	(54)	0 101	295	(74)	8	(57)	0 749	294	(74)	7	(70)	0 824
Instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics (Always, Regularly, or Sometimes)	192	(49)	7	(29)	0 482	195	(49)	< 5	(< 36)	0 186	195	(49)	< 5	(< 50)	0 072
Instructed about keeping ER/LA opioid analgesics safe and away from children (Always, Regularly, or Sometimes)	240	(62)	13	(54)	0 664	246	(62)	7	(50)	0 789	247	(62)	< 5	(< 50)	0 009
Instructed not to share ER/LA opioid analgesics with anyone else (Always, Regularly, or Sometimes)	253	(65)	11	(46)	0 423	257	(64)	7	(50)	0 405	259	(65)	< 5	(< 50)	0 001

ER, extended release; LA, long-acting; PCD, Patient Counseling Document

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013 All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months

3 Read some or all of the Medication Guide at least once Respondents who did not receive the Medication Guide from any of the specified sources were still asked whether they read the Medication Guide

4 Understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide Respondents who did not receive and did not read the Medication Guide were not asked their comprehension of the Medication Guide

5 Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood with those who did not receive/read/understood the MG, respectively

TABLE 8C. RESPONDENT-REPORTED HEALTHCARE PROVIDER ACTIVITIES IN THE PAST 2 MONTHS, BY PATIENT COUNSELING DOCUMENT RECEIPT/REFERENCED/COMPREHENSION STATUS[1]

	Received PCD[2]					Referenced PCD[3]					Understood PCD[4]				
	Yes		No		p-value[5]	Yes		No		p-value[5]	Yes		No		p-value[5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**175**	**(42)**	**238**	**(58)**		**109**	**(26)**	**304**	**(74)**		**244**	**(90)**	**28**	**(10)**	
Used the PCD on ER/LA Opioids for discussions (Always, Regularly, or Sometimes)	113	(65)	52	(22)	<0 001	83	(76)	82	(27)	<0 001	134	(55)	6	(21)	0 006
Cautioned about important risks associated with ER/LA opioid analgesics, including overdose or taking or using too much (Always, Regularly, or Sometimes)	146	(83)	140	(59)	<0 001	94	(86)	192	(63)	<0 001	188	(77)	19	(68)	0 657
Discussed how to safely discontinue ER/LA opioid analgesics if they are no longer needed (Always, Regularly, or Sometimes)	114	(65)	115	(49)	0 001	78	(72)	151	(50)	<0 001	151	(62)	11	(39)	0 030
Counseled on the most common side effects from using ER/LA opioid analgesics (Always, Regularly, or Sometimes)	151	(86)	152	(64)	<0 001	101	(93)	202	(66)	<0 001	195	(80)	20	(71)	0 243
Instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics (Always, Regularly, or Sometimes)	119	(68)	80	(34)	<0 001	79	(72)	120	(39)	<0 001	144	(59)	11	(39)	0 049
Instructed about keeping ER/LA opioid analgesics safe and away from children (Always, Regularly, or Sometimes)	133	(76)	120	(51)	<0 001	88	(81)	165	(55)	<0 001	178	(73)	15	(54)	0 235
Instructed not to share ER/LA opioid analgesics with anyone else (Always, Regularly, or Sometimes)	138	(79)	126	(53)	<0 001	95	(87)	169	(56)	<0 001	180	(74)	17	(61)	0 542

ER, extended release; LA, long-acting; PCD, Patient Counseling Document

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013 All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 Healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months

3 Healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months

4 Understood PCD, as self-reported by the respondent that they understood at least some, half, most, or all of the information discussed from the PCD Respondents who did not receive and did not have a provider who referenced the PCD were not asked their comprehension of the PCD

5 Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/referenced/understood with those who did not receive/referenced/understood the PCD, respectively

TABLE 8D. RESPONDENT-REPORTED HEALTHCARE PROVIDER ACTIVITIES IN THE PAST 2 MONTHS, BY RECEIPT/READ/UNDERSTOOD STATUS OF BOTH OR NEITHER MEDICATION GUIDE AND PATIENT COUNSELING DOCUMENT [1]

	Received/Read/Understood Medication Guide and PCD [2]					Did Not Receive/Read/Understand Medication Guide or PCD [3]				
	Yes		No		p-value [4]	Yes		No		p-value [4]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**94**	**(23)**	**319**	**(77)**		**5**	**(1)**	**408**	**(99)**	
Used the PCD on ER/LA Opioids for discussions (Always, Regularly, or Sometimes)	74	(79)	91	(29)	<0 001	0	(0)	165	(41)	0 507
Cautioned about important risks associated with ER/LA opioid analgesics, including overdose or taking or using too much (Always, Regularly, or Sometimes)	83	(88)	203	(64)	<0 001	5	(100)	281	(69)	0 643
Discussed how to safely discontinue ER/LA opioid analgesics if they are no longer needed (Always, Regularly, or Sometimes)	69	(73)	160	(50)	<0 001	< 5	(< 100)	226	(56)	0 585
Counseled on the most common side effects from using ER/LA opioid analgesics (Always, Regularly, or Sometimes)	87	(93)	216	(68)	<0 001	< 5	(< 100)	299	(73)	0 836
Instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics (Always, Regularly, or Sometimes)	71	(76)	128	(40)	<0 001	< 5	(< 100)	197	(48)	0 252
Instructed about keeping ER/LA opioid analgesics safe and away from children (Always, Regularly, or Sometimes)	78	(83)	175	(55)	<0 001	< 5	(< 100)	251	(62)	0 438
Instructed not to share ER/LA opioid analgesics with anyone else (Always, Regularly, or Sometimes)	82	(87)	182	(57)	<0 001	< 5	(< 100)	262	(64)	0 485

ER, extended release; LA, long-acting; MG, Medication Guide; PCD, Patient Counseling Document

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database^{SM} (HIRD), 01 December 2012 through 30 November 2013 All results will be aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; read some or all of the Medication Guide at least once; understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide; healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months; healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months; and understood PCD, as self-reported by the respondent that they understood about half, most, or all of the information discussed from the PCD

3 Did not receive Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; never read any of the Medication Guide; did not understand the Medication Guide, as self-reported by the respondent that they did not understand at all or understood less than half of the information in the Medication Guide; healthcare provider did not give PCD when ER/LA opioid analgesic was prescribed the first time nor in the last 12 months; healthcare provider did not refer to or speak about PCD when current ER/LA opioid analgesic was prescribed; and did not understood the PCD, as self-reported by the respondent that they did not understand at all or understood less than half of the information discussed from the PCD

4 Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood both or neither MG and PCD with those who did not receive/read/understood both or neither MG and PCD, respectively

TABLE 8E. RESPONDENT-REPORTED HEALTHCARE PROVIDER ACTIVITIES IN THE PAST 2 MONTHS, BY RECEIPT OF MORE THAN ONE ER/LA OPIOID ANALGESIC PRIOR TO INDEX DATE [1]

	More than one ER/LA opioid analgesic dispensing [2]				
	Yes		No		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**315**	**(76)**	**98**	**(24)**	
Used the PCD on ER/LA Opioids for discussions. (Always, Regularly, or Sometimes)	135	(43)	30	(31)	0.368
Cautioned about important risks associated with ER/LA opioid analgesics, including overdose or taking or using too much. (Always, Regularly, or Sometimes)	225	(72)	61	(62)	0.036
Discussed how to safely discontinue ER/LA opioid analgesics if they are no longer needed. (Always, Regularly, or Sometimes)	174	(55)	55	(56)	0.276
Counseled on the most common side effects from using ER/LA opioid analgesics. (Always, Regularly, or Sometimes)	234	(74)	69	(70)	0.008
Instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics. (Always, Regularly, or Sometimes)	160	(51)	39	(40)	0.031
Instructed about keeping ER/LA opioid analgesics safe and away from children. (Always, Regularly, or Sometimes)	201	(64)	52	(53)	0.214
Instructed not to share ER/LA opioid analgesics with anyone else. (Always, Regularly, or Sometimes)	212	(67)	52	(53)	0.018

ER, extended release; LA, long-acting; PCD, Patient Counseling Document.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database [SM] (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. The number of ER/LA opioid analgesic dispensings prior to the index date will be defined by claims data by dispensings on distinct dates.

3. Did not receive Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; never read any of the Medication Guide; did not understand the Medication Guide, as self-reported by the respondent that they did not understand at all or understood less than half of the information in the Medication Guide; healthcare provider did not give PCD when ER/LA opioid analgesic was prescribed the first time nor in the last 12 months; healthcare provider did not refer to or speak about PCD when current ER/LA opioid analgesic was prescribed; and did not understood the PCD, as self-reported by the respondent that they did not understand at all or understood less than half of the information discussed from the PCD.

TABLE 8F. RESPONDENT-REPORTED HEALTHCARE PROVIDER ACTIVITIES IN THE PAST 2 MONTHS, BY KNOWLEDGE ASSESSMENT SCORE (KAS) THRESHOLD [1]

	KAS < 70% [2]				
	No		Yes		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**380**	**(92)**	**33**	**(8)**	
Used the PCD on ER/LA Opioids for discussions. (Always, Regularly, or Sometimes)	156	(41)	9	(27)	0.764
Cautioned about important risks associated with ER/LA opioid analgesics, including overdose or taking or using too much. (Always, Regularly, or Sometimes)	268	(71)	18	(55)	0.008
Discussed how to safely discontinue ER/LA opioid analgesics if they are no longer needed. (Always, Regularly, or Sometimes)	214	(56)	15	(47)	0.017
Counseled on the most common side effects from using ER/LA opioid analgesics. (Always, Regularly, or Sometimes)	281	(74)	22	(67)	0.640
Instructed about the importance and how to safely dispose of any unused ER/LA opioid analgesics. (Always, Regularly, or Sometimes)	188	(49)	11	(33)	0.206
Instructed about keeping ER/LA opioid analgesics safe and away from children. (Always, Regularly, or Sometimes)	240	(63)	13	(39)	0.004
Instructed not to share ER/LA opioid analgesics with anyone else. (Always, Regularly, or Sometimes)	247	(65)	17	(52)	0.411

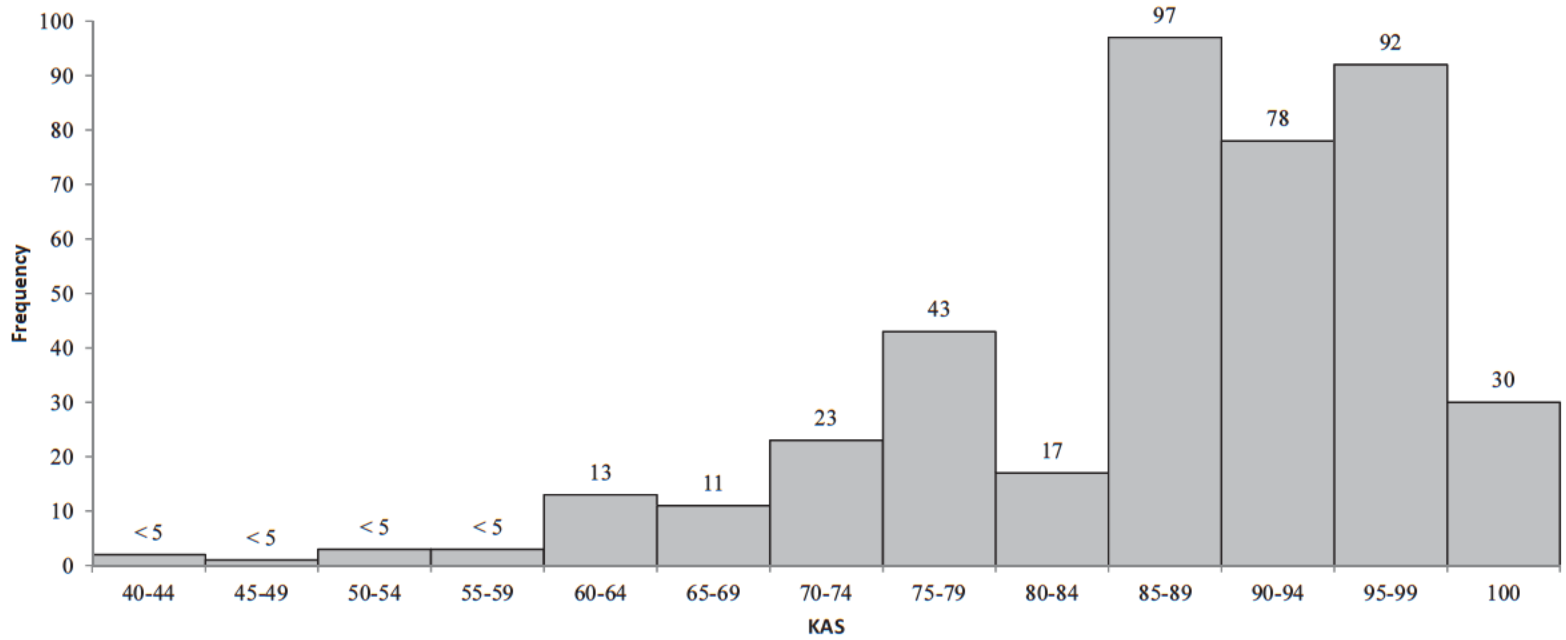
ER, extended release; LA, long-acting; PCD, Patient Counseling Document.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database SM (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

2. The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug. A KAS less than 70% is defined as poor knowledge.

3. Did not receive Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; never read any of the Medication Guide; did not understand the Medication Guide, as self-reported by the respondent that they did not understand at all or understood less than half of the information in the Medication Guide; healthcare provider did not give PCD when ER/LA opioid analgesic was prescribed the first time nor in the last 12 months; healthcare provider did not refer to or speak about PCD when current ER/LA opioid analgesic was prescribed; and did not understood the PCD, as self-reported by the respondent that they did not understand at all or understood less than half of the information discussed from the PCD.

FIGURE 2. DISTRIBUTION OF KNOWLEDGE ASSESSMENT SCORE (KAS)



ER, extended release; KAS, Knowledge Assessment Score; LA, long-acting.

1. Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database[SM] (HIRD), 01 December 2012 through 30 November 2013. All results will be aggregated and de-identified. Percentage denominators comprise respondents who did not refuse to answer the survey question.

The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug. A KAS less than 70% is defined as poor knowledge.

TABLE 9A. RESPONDENT KNOWLEDGE ASSESSMENT SCORE (KAS), BY ER/LA OPIOID ANALGESIC TYPE [1]

	All survey respondents		Survey respondents, by ER/LA opioid analgesic type [2]					
			Non-methadone oral drugs only		Patch		Methadone	
	N	*(%)*	*N*	*(%)*		*(%)*	*N*	*(%)*
Total number of respondents	**413**		**266**	**(64)**	**102**	**(25)**	**45**	**(11)**
Knowledge Assessment Score (KAS)[3], *mean (STD)*	85 6 (10 38)		85 4 (10 38)		85 5 (10 16)		86 9 (10 99)	
KAS[3], *median*	88 2		84 2		89 7		88 2	
KAS[3], *minimum*	42 1		42 1		60 0		52 9	
KAS[3], interquartile range (IQR)	80 0 - 94 7		78 9 - 94 7		80 0 - 95 0		82 4 - 94 1	
KAS[3], *maximum*	100 0		100 0		100 0		100 0	
KAS[3] threshold								
>= 70%	380	(92)	245	(92)	94	(92)	41	(91)
< 70%	33	(8)	21	(8)	8	(8)	< 5	(< 11)
KAS[3], by key risk message, *mean (STD)*								
The patient understands the serious risks associated with the use of their ER/LA opioid analgesic[4]	88 7 (22 87)		89 6 (21 23)		87 7 (24 81)		85 6 (27 43)	
The patient knows what to do if they take too much drug [5]	92 6 (19 08)		91 5 (20 23)		94 6 (17 10)		94 4 (15 89)	
The patient understands the need to store the drug in a safe place [6]	83 1 (21 74)		82 1 (21 87)		83 0 (22 86)		89 6 (17 15)	
The patient knows they should not share the drug with anyone[7]	97 8 (10 22)		97 9 (9 97)		98 5 (8 49)		95 6 (14 39)	
The patient understands how to use the drug safely [8]	81 9 (13 59)		81 8 (13 82)		81 8 (11 93)		82 2 (15 86)	

ER, extended release; IQR, interquartile range; KAS, Knowledge Assessment Score; LA, long-acting; STD, standard deviation

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research DatabaseSM (HIRD), 01 December 2012 through 30 November 2013 All results are aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 ER/LA opioid analgesic: Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use)

3 The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug A KAS less than 70% is defined as poor knowledge

4 As defined by the following survey questions: Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death; ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy

5 As defined by the following survey questions: Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine; Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics

6 As defined by the following survey questions: Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household; Do not throw any unused ER/LA opioid analgesic in the trash; A child could die if they take or use the respondent's ER/LA opioid analgesics

7 As defined by the following survey questions: Do not give ER/LA opioid analgesics to other people who have the same condition as you; Selling or giving away ER/LA opioid analgesics is against the la

8 As defined by the following survey questions: Talk to a healthcare provider prior to stopping ER/LA opioid analgesics; Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control the pain; It is not okay to drink alcohol while taking or using ER/LA opioid analgesics; Read the attached MG every time an ER/LA opioid prescription is filled; Inform healthcare provider about all the other medications being used; Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems; Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplements; It is okay to drink caffeine while using ER/LA opioid analgesics; ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication (survey question only asked of non-methadone oral drugs only respondents); Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed 3 (survey question only asked of non-methadone oral drugs only respondents); Inform healthcare provider of any fever (survey question only asked of patch and no methadone respondents); Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists (survey question only asked of patch and no methadone respondents); Do not cut ER/LA opioid analgesic patches in half to use less medicine (survey question only asked of patch and no methadone respondents)

TABLE 9B. RESPONDENT KNOWLEDGE ASSESSMENT SCORE (KAS), BY MEDICATION GUIDE RECEIPT/READ/COMPREHENSION STATUS [1]

	Received Medication Guide [2]			Read Medication Guide [3]			Understood Medication Guide [4]		
	Yes	No	p-value [5]	Yes	No	p-value [5]	Yes	No	p-value [5]
	N (%)	*N* (%)		*N* (%)	*N* (%)		*N* (%)	*N* (%)	
Total number of respondents	**389 (94)**	**24 (6)**		**399 (97)**	**14 (3)**		**399 (98)**	**10 (2)**	
Knowledge Assessment Score (KAS) [6], *mean (STD)*	85 8 (10 41)	83 0 (9 61)	0 202	85 7 (10 38)	83 1 (10 25)	0 368	85 8 (10 30)	76 6 (9 26)	0 005
KAS [6], *median*	88 2	84 2		88 2	84 2		88 2	79 5	
KAS [6], *minimum*	42 1	63 2		42 1	63 2		42 1	60 0	
KAS [6], interquartile range (IQR)	80 0 - 94 7	78 9 - 89 2		80 0 - 94 7	80 0 - 88 2		80 0 - 94 7	70 0 - 84 2	
KAS [6], *maximum*	100 0	100 0		100 0	100 0		100 0	89 5	
KAS [6] threshold			0 401			0 377			0 147
>= 70%	359 (92)	21 (88)		368 (92)	12 (86)		369 (92)	8 (80)	
< 70%	30 (8)	< 5 (< 21)		31 (8)	< 5 (< 36)		30 (8)	< 5 (< 50)	
KAS [6], by key risk message, *mean (STD)*									
The patient understands the serious risks associated with the use of their ER/LA opioid analgesic [7]	88 7 (22 74)	89 6 (25 45)	0 848	88 6 (23 03)	92 9 (18 16)	0 491	88 9 (22 80)	80 0 (25 82)	0 223
The patient knows what to do if they take too much drug [5]	92 8 (18 98)	89 6 (20 74)	0 423	93 1 (18 32)	78 6 (32 31)	0 005	92 6 (19 13)	95 0 (15 81)	0 695
The patient understands the need to store the drug in a safe place [9]	83 3 (21 75)	80 6 (21 80)	0 550	83 1 (21 90)	83 3 (17 30)	0 972	83 3 (21 64)	76 7 (27 44)	0 343
The patient knows they should not share the drug with anyone [10]	97 8 (10 23)	97 9 (10 21)	0 962	97 7 (10 39)	100 0 (0 00)	0 418	97 9 (10 11)	95 0 (15 81)	0 383
The patient understands how to use the drug safely [11]	82 1 (13 66)	77 9 (11 95)	0 145	82 0 (13 60)	78 6 (13 31)	0 362	82 2 (13 49)	68 7 (10 64)	0 002

ER, extended release; IQR, interquartile range; KAS, Knowledge Assessment Score; LA, long-acting; MG, Medication Guide; STD, standard deviation

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013 All results are aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months

3 Read some or all of the Medication Guide at least once Respondents who did not receive the Medication Guide from any of the specified sources were still asked whether they read the Medication Guide

4 Understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide Respondents who did not receive and did not read the Medication Guide were not asked their comprehension of the Medication Guide

5 Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood with those who did not receive/read/understood the MG, respectively

6 The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug A KAS less than 70% is defined as poor knowledge

7 As defined by the following survey questions: Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death; ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy

8 As defined by the following survey questions: Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine; Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics

9 As defined by the following survey questions: Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household; Do not throw any unused ER/LA opioid analgesic in the trash; A child could die if they take or use the respondent's ER/LA opioid analgesics

10 As defined by the following survey questions: Do not give ER/LA opioid analgesics to other people who have the same condition as you; Selling or giving away ER/LA opioid analgesics is against the law

11 As defined by the following survey questions: Talk to a healthcare provider prior to stopping ER/LA opioid analgesics; Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control the pain; It is not okay to drink alcohol while taking or using ER/LA opioid analgesics; Read the attached MG every time an ER/LA opioid prescription is filled; Inform healthcare provider about all the other medications being used; Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems; Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplements; It is okay to drink caffeine while using ER/LA opioid analgesics; ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication (survey question only asked of non-methadone oral drugs only respondents); Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed 3 (survey question only asked of non-methadone oral drugs only respondents); Inform healthcare provider of any fever (survey question only asked of patch and no methadone respondents); Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists (survey question only asked of patch and no methadone respondents); Do not cut ER/LA opioid analgesic patches in half to use less medicine (survey question only asked of patch and no methadone respondents)

TABLE 9C. RESPONDENT KNOWLEDGE ASSESSMENT SCORE (KAS), BY PATIENT COUNSELING DOCUMENT RECEIPT/REFERENCED/COMPREHENSION STATUS [1]

	Received PCD [2]				Referenced/Reviewed PCD [3]				Understood PCD [4]			
	Yes		No		p-value [5]	Yes		No		p-value [5]	Yes		No		p-value [5]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**175**	**(42)**	**238**	**(58)**		**109**	**(26)**	**304**	**(74)**		**244**	**(90)**	**28**	**(10)**	
Knowledge Assessment Score (KAS) [6], *mean (STD)*	86 3 (10 15)		85 0 (10 53)		0 209	87 0 (10 26)		85 1 (10 39)		0 108	86 0 (10 24)		84 8 (12 03)		0 552
KAS [6], *median*	89 5		85 0			89 5		85 0			89 5		87 5		
KAS [6], *minimum*	42 1		42 1			42 1		42 1			42 1		47 4		
KAS [6], interquartile range (IQR)	80 0 - 94 7		80 0 - 94 1			84 2 - 94 7		79 5 - 94 1			80 0 - 94 7		80 0 - 92 4		
KAS [6], *maximum*	100 0		100 0			100 0		100 0			100 0		100 0		
KAS [6] threshold					0 466					0 482					0 964
>= 70%	163	(93)	217	(91)		102	(94)	278	(91)		226	(93)	26	(93)	
< 70%	12	(7)	21	(9)		7	(6)	26	(9)		18	(7)	< 5	(< 18)	
KAS [6], by key risk message, *mean (STD)*															
The patient understands the serious risks associated with the use of their ER/LA opioid analgesic [7]	87 1 (24 4)		89 9 (21 66)		0 231	89 4 (23 64)		88 4 (22 62)		0 696	88 5 (23 38)		92 6 (18 1)		0 382
The patient knows what to do if they take too much drug [5]	95 1 (15 79)		90 8 (21 01)		0 021	95 9 (15 41)		91 4 (20 13)		0 038	93 4 (18 09)		92 9 (22 42)		0 875
The patient understands the need to store the drug in a safe place [9]	84 6 (20 45)		82 1 (22 62)		0 249	86 9 (17 58)		81 8 (22 93)		0 037	84 0 (21 27)		77 4 (28 77)		0 134
The patient knows they should not share the drug with anyone [10]	96 6 (12 67)		98 7 (7 85)		0 033	95 9 (13 83)		98 5 (8 49)		0 020	96 9 (12 03)		100 0 (0 00)		0 178
The patient understands how to use the drug safely [11]	82 9 (13 18)		81 1 (13 86)		0 205	82 8 (13 90)		81 5 (13 48)		0 378	82 4 (13 22)		80 8 (12 94)		0 556
Survey self-reported comprehension of specific core concepts discussed per the PCD															
Benefits and risks [12]	158	(90)	163	(68)	<0 001	101	(93)	220	(72)	<0 001	212	(87)	22	(79)	0 373
Safe discontinuation [13]	112	(64)	109	(46)	<0 001	76	(70)	145	(48)	<0 001	150	(61)	9	(32)	0 012
Missed dose [14]	130	(74)	122	(51)	<0 001	87	(80)	165	(54)	<0 001	175	(72)	9	(32)	<0 001
Patient Prescriber Agreement [15]	97	(55)	94	(40)	<0 001	66	(61)	125	(41)	<0 001	126	(52)	12	(43)	0 654

ER, extended release; IQR, interquartile range; KAS, Knowledge Assessment Score; LA, long-acting; PCD, Patient Counseling Document; STD, standard deviation

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research DatabaseSM (HIRD), 01 December 2012 through 30 November 2013 All results are aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 Healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first timeor in the last 12 months

3 Healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months

4 Understood PCD, as self-reported by the respondent that they understood at least some, half, most, or all of the information discussed from the PCD Respondents who did not receive and did not have a provider who referenced the PCD were not asked their comprehension of the PCD

5 Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/referenced/understood with those who did not receive/referenced/understood the PCD, respectively

6 The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug A KAS less than 70% is defined as poor knowledge

7 As defined by the following survey questions: Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death; ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy

8 As defined by the following survey questions: Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine; Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics

9 As defined by the following survey questions: Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household; Do not throw any unused ER/LA opioid analgesic in the trash; A child could die if they take or use the respondent's ER/LA opioid analgesics

10 As defined by the following survey questions: Do not give ER/LA opioid analgesics to other people who have the same condition as you; Selling or giving away ER/LA opioid analgesics is against the law

11 As defined by the following survey questions: Talk to a healthcare provider prior to stopping ER/LA opioid analgesics; Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control the pain; It is not okay to drink alcohol while taking or using ER/LA opioid analgesics; Read the attached MG every time an ER/LA opioid prescription is filled; Inform healthcare provider about all the other medications being used; Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems; Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplements; It is okay to drink caffeine while using ER/LA opioid analgesics; ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication (survey question only asked of non-methadone oral drugs only respondents); Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed 3 (survey question only asked of non-methadone oral drugs only respondents); Inform healthcare provider of any fever (survey question only asked of patch and no methadone respondents); Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists (survey question only asked of patch and no methadone respondents); Do not cut ER/LA opioid analgesic patches in half to use less medicine (survey question only asked of patch and no methadone respondents)

12 Healthcare provider discussed why he/she chose the current ER/LA opioid analgesic, when it was prescribed in the last 12 months, including the benefits and risks associated with opioid therapy, and important safety information related to this type of medication

13 Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic, when it was prescribed in the last 12 months

14 Healthcare provider discussed what to do if the patient missed a dose, when the current ER/LA opioid analgesic was prescribed in the last 12 months

15 Healthcare provider completed a Patient Prescriber Agreement (PPA), when the current ER/LA opioid analgesic was prescribed in the last 12 months

TABLE 9D. RESPONDENT KNOWLEDGE ASSESSMENT SCORE (KAS), BY RECEIPT/READ/UNDERSTOOD STATUS OF BOTH OR NEITHER MEDICATION GUIDE AND PATIENT COUNSELING DOCUMENT [1]

	Received/Read/Understood Medication Guide and PCD[2]					Did Not Receive/Read/Understand Medication Guide or PCD[3]				
	Yes		No		p-value[4]	Yes		No		p-value[4]
	N	*(%)*	*N*	*(%)*		*N*	*(%)*	*N*	*(%)*	
Total number of respondents	**94**	**(23)**	**319**	**(77)**		**5**	**(1)**	**408**	**(99)**	
Knowledge Assessment Score (KAS)[5], *mean (STD)*	87 1 (10 46)		85 2 (10 33)		0 114	84 4 (11 66)		85 6 (10 38)		0 799
KAS [5], *median*	89 5		85 0			84 2		88 2		
KAS [5], *minimum*	42 1		42 1			68 4		42 1		
KAS [5], interquartile range (IQR)	82 4 - 94 7		80 0 - 94 1			80 0 - 89 5		80 0 - 94 7		
KAS [5], *maximum*	100 0		100 0			100 0		100 0		
KAS [5] threshold					0 513					0 319
>= 70%	88	(94)	292	(92)		< 5	(< 100)	376	(92)	
< 70%	6	(6)	27	(8)		< 5	(< 100)	32	(8)	
KAS [5], by key risk message, *mean (STD)*										
The patient understands the serious risks associated with the use of their ER/LA opioid analgesic[6]	89 4 (23 04)		88 5 (22 86)		0 755	90 0 (22 36)		88 7 (22 91)		0 900
The patient knows what to do if they take too much drug[7]	96 3 (15 10)		91 5 (20 00)		0 034	90 0 (22 36)		92 6 (19 07)		0 758
The patient understands the need to store the drug in a safe place[8]	86 2 (17 90)		82 2 (22 69)		0 123	80 0 (18 26)		83 2 (21 79)		0 746
The patient knows they should not share the drug with anyone[9]	95 7 (14 03)		98 4 (8 73)		0 025	100 0 (0 00)		97 8 (10 28)		0 632
The patient understands how to use the drug safely[10]	83 3 (14 16)		81 4 (13 41)		0 252	80 5 (15 42)		81 9 (13 59)		0 828
Survey self-reported comprehension of specific core concepts discussed per the PC										
Benefits and risks[11]	87	(93)	234	(73)	<0 001	< 5	(< 100)	317	(78)	0 915
Safe discontinuation[12]	68	(72)	153	(48)	<0 001	< 5	(< 100)	219	(54)	0 695
Missed dose[13]	78	(83)	174	(55)	<0 001	< 5	(< 100)	249	(61)	0 840
Patient Prescriber Agreement[14]	57	(61)	134	(42)	0 002	< 5	(< 100)	189	(46)	0 961

ER, extended release; IQR, interquartile range; KAS, Knowledge Assessment Score; LA, long-acting; MG, Medication Guide; PCD, Patient Counseling Document; STD, standard deviation

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research Database℠ (HIRD), 01 December 2012 through 30 November 2013 All results are aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; read some or all of the Medication Guide at least once; understood Medication Guide, as self-reported by the respondent they understood about half, most, or all of the information in the Medication Guide; healthcare provider gave PCD when ER/LA opioid analgesic was prescribed the first time or in the last 12 months; healthcare provider referre or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months; and understood PCD, as self-reported by the respondent that they understood about half, most, or all of the information discussed from the PCD

3 Did not receive Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months; never read any of the Medication Guide; did not understand the Medication Guide, as self-reported by the respond nt that they did not understand at all or understood less than half of the information in the Medication Guide; healthcare provider did not give PCD when ER/LA opioid analgesic was prescribed the first time nor in the last 12 mon hs; healthcare provider did not refer to or speak about PCD when current ER/LA opioid analgesic was prescribed; and did not understood the PCD, as self-reported by the respondent that they did not understand at all or understood less than half of the information discussed from the PCD

4 Chi square test for categorical and t-test for continuous variables were used to compare respondents who received/read/understood both or neither MG and PCD with those who did not receive/read/understood both or neither MG and PCD, respectively

5 The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable o the respondent's survey index drug A KAS less than 70% is defined as poor knowledge

6 As defined by the following survey questions: Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death; ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy

7 As defined by the following survey questions: Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine; Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics

8 As defined by the following survey questions: Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household; Do not throw any unused ER/LA opioid analgesic in the trash; A child cou d die if they take or use the respondent's ER/LA opioid analgesics

9 As defined by the following survey questions: Do not give ER/LA opioid analgesics to other people who have the same condition as you; Selling or giving away ER/LA opioid analgesics is against the law

10 As defined by the following survey questions: Talk to a healthcare provider prior to stopping ER/LA opioid analgesics; Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control the pain; It is not okay to drink alcohol while taking or using ER/LA opioid analgesics; Read the attached MG every time an ER/LA opioid prescription is filled; Inform healthcare provider about all the other medications being used; Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems; Inform healthcare provider about over-the-counter medicines, vitamin , and dietary supplements; It is okay to drink caffeine while using ER/LA opioid analgesics; ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication (survey question only asked of non-methadone oral drugs only respondents); Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed 3 (survey question only asked of non-methadone oral drugs only respondents); Inform healthcare provider of any fever (survey question only asked of patch and no methadone respondents); Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists (survey quest on only asked of patch and no methadone respondents); Do not cut ER/LA opioid analgesic patches in half to use less medicine (survey question only asked of patch and no methadone respondents)

11 Healthcare provider discussed why he/she chose the current ER/LA opioid analgesic, when it was prescribed in the last 12 months, including the benefits and risks associated with opioid therapy, and important safety information related to this type of medication

12 Healthcare provider discussed how to safely discontinue the current ER/LA opioid analgesic, when it was prescribed in the last 12 months

13 Healthcare provider discussed what to do if the patient missed a dose, when the current ER/LA opioid analgesic was prescribed in the last 12 months

14 Healthcare provider completed a Patient Prescriber Agreement (PPA), when the current ER/LA opioid analgesic was prescribed in the last 12 months

TABLE 9E. RESPONDENT KNOWLEDGE ASSESSMENT SCORE (KAS), BY RECEIPT OF MORE THAN ONE ER/LA OPIOID ANALGESIC PRIOR TO INDEX DATE [1]

	More than one ER/LA opioid analgesic dispensing [2]				
	Yes		No		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**315**	**(76)**	**98**	**(24)**	
Knowledge Assessment Score (KAS)[4], *mean (STD)*	86 6 (9 59)		82 3 (12 03)		<0 001
KAS[4], *median*	89 5		84 2		
KAS[4], *minimum*	42 1		42 1		
KAS[4], interquartile range (IQR)	84 2 - 94 7		78 9 - 89 5		
KAS[4], *maximum*	100 0		100 0		
KAS[4] threshold					0 027
>= 70%	295	(94)	85	(87)	
< 70%	20	(6)	13	(13)	
KAS[4], by key risk message, *mean (STD)*					
The patient understands the serious risks associated with the use of their ER/LA opioid analgesic [5]	88 1 (23 49)		90 8 (20 74)		0 298
The patient knows what to do if they take too much drug [5]	92 7 (18 99)		92 3 (19 47)		0 874
The patient understands the need to store the drug in a safe place [7]	85 2 (20 24)		76 5 (24 97)		0 001
The patient knows they should not share the drug with anyone [8]	98 1 (9 59)		96 9 (12 05)		0 329
The patient understands how to use the drug safely [9]	83 3 (12 43)		77 3 (16 04)		<0 001

ER, extended release; IQR, interquartile range; KAS, Knowledge Assessment Score; LA, long-acting; PCD, Patient Counseling Document; STD, standard deviation

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research DatabaseSM (HIRD), 01 December 2012 through 30 November 2013 All results are aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 The number of ER/LA opioid analgesic dispensings prior to the index date will be defined by claims data by dispensings on distinct dates

3 Chi square test for categorical and t-test for continuous variables were used to compare respondents who had only one ER/LA opioid analgesic dispensing prior to index date with those who had more than one ER/LA opioid analgesic dispensing prior to index date

4 The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug A KAS less than 70% is defined as poor knowledge

5 As defined by the following survey questions: Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death; ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy

6 As defined by the following survey questions: Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine; Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics

7 As defined by the following survey questions: Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household; Do not throw any unused ER/LA opioid analgesic in the trash; A child could die if they take or use the respondent's ER/LA opioid analgesics

8 As defined by the following survey questions: Do not give ER/LA opioid analgesics to other people who have the same condition as you; Selling or giving away ER/LA opioid analgesics is against the law

9 As defined by the following survey questions: Talk to a healthcare provider prior to stopping ER/LA opioid analgesics; Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control the pain; It is not okay to drink alcohol while taking or using ER/LA opioid analgesics; Read the attached MG every time an ER/LA opioid prescription is filled; Inform healthcare provider about all the other medications being used; Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems; Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplements; It is okay to drink caffeine while using ER/LA opioid analgesics; ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication (survey question only asked of non-methadone oral drugs only respondents); Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed 3 (survey question only asked of non-methadone oral drugs only respondents); Inform healthcare provider of any fever (survey question only asked of patch and no methadone respondents); Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists (survey question only asked of patch and no methadone respondents); Do not cut ER/LA opioid analgesic patches in half to use less medicine (survey question only asked of patch and no methadone respondents)

TABLE 9F. RESPONDENT KNOWLEDGE ASSESSMENT SCORE (KAS), BY KNOWLEDGE ASSESSMENT SCORE (KAS) THRESHOLD [1]

	KAS < 70% [2]				
	No		Yes		p-value [3]
	N	*(%)*	*N*	*(%)*	
Total number of respondents	**380**	**(92)**	**33**	**(8)**	
Knowledge Assessment Score (KAS) [4], *mean (STD)*	87 8 (7 34)		60 6 (6 93)		<0 001
KAS [4], *median*	89 5		63 2		
KAS [4], *minimum*	70 0		42 1		
KAS [4], interquartile range (IQR)	84 2 - 94 7		57 9 - 64 7		
KAS [4], *maximum*	100 0		68 4		
KAS [4], by key risk message, *mean (STD)*					
The patient understands the serious risks associated with the use of their ER/LA opioid analgesic [5]	90 9 (20 32)		63 6 (33 71)		<0 001
The patient knows what to do if they take too much drug [6]	94 9 (15 19)		66 7 (34 61)		<0 001
The patient understands the need to store the drug in a safe place [7]	85 7 (18 84)		53 5 (29 98)		<0 001
The patient knows they should not share the drug with anyone [8]	98 6 (8 39)		89 4 (20 76)		<0 001
The patient understands how to use the drug safely [9]	84 2 (10 62)		54 9 (15 07)		<0 001

ER, extended release; IQR, interquartile range; KAS, Knowledge Assessment Score; LA, long-acting; PCD, Patient Counseling Document; STD, standard deviation

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research DatabaseSM (HIRD), 01 December 2012 through 30 November 2013 All results are aggregated and de-identified Percentage denominators comprise respondents who did not refuse to answer the survey question

2 The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug A KAS less than 70% is defined as poor knowledge

3 Chi square test for categorical and t-test for continuous variables were used to compare respondents with KAS <70% with those with KAS ≥70%

4 The KAS is calculated as the proportion of knowledge questions that the respondent answered correctly, defined as the number of correctly answered questions divided by the total number of knowledge questions applicable to the respondent's survey index drug A KAS less than 70% is defined as poor knowledge

5 As defined by the following survey questions: Overdoses may cause life-threatening breathing problems, respiratory depression, or abnormally slow breathing that can lead to death; ER/LA opioid analgesics can make you dizzy, lightheaded, or sleepy

6 As defined by the following survey questions: Seek emergency medical help for ER/LA opioid analgesic overdose, even if the respondent feels fine; Seek emergency medical help for side effects such as trouble breathing, shortness of breath, fast heartbeat, chest pain, or swelling of their face, tongue, or throat after taking or using ER/LA opioid analgesics

7 As defined by the following survey questions: Do not store ER/LA opioid analgesics in a medicine cabinet with other medications in the household; Do not throw any unused ER/LA opioid analgesic in the trash; A child could die if they take or use the respondent's ER/LA opioid analgesics

8 As defined by the following survey questions: Do not give ER/LA opioid analgesics to other people who have the same condition as you; Selling or giving away ER/LA opioid analgesics is against the law

9 As defined by the following survey questions: Talk to a healthcare provider prior to stopping ER/LA opioid analgesics; Talk to a healthcare provider about taking or using more ER/LA opioid analgesics if the current dose doesn't control the pain; It is not okay to drink alcohol while taking or using ER/LA opioid analgesics; Read the attached MG every time an ER/LA opioid prescription is filled; Inform healthcare provider about all the other medications being used; Inform healthcare provider about any history of abuse of street or prescription drugs, alcohol addiction, or mental health problems; Inform healthcare provider about over-the-counter medicines, vitamins, and dietary supplements; It is okay to drink caffeine while using ER/LA opioid analgesics; ER/LA opioid analgesic pills should not be split or crushed if the respondent is having trouble swallowing their medication (survey question only asked of non-methadone oral drugs only respondents); Do not take more when it is time for the next dose if a dose of ER/LA opioid analgesics was missed (survey question only asked of non-methadone oral drugs only respondents); Inform healthcare provider of any fever (survey question only asked of patch and no methadone respondents); Do not use a hot tub or sauna while using ER/LA opioid analgesics if pain persists (survey question only asked of patch and no methadone respondents); Do not cut ER/LA opioid analgesic patches in half to use less medicine (survey question only asked of patch and no methadone respondents)

TABLE 10. RISK FACTORS FOR KNOWLEDGE ASSESSMENT SCORE (KAS) < 70% [1]

	OR	95% CI
Univariate analysis [2]		
Age		
18 to 34	REF	
35 to 49	0 48	0 15 - 1 51
50 to 64	0 52	0 19 - 1 39
65+	1 37	0 30 - 6 17
Gender		
Female	0 49	0 24 - 1 00
Male	REF	
US Census region of residence [3]		
Northeast	REF	
South	0 89	0 30 - 2 62
Midwest	NE	NE
West	1 01	0 38 - 2 66
Unknown	NE	NE
Hispanic or Latino ethnicity	1 29	0 16 - 10 49
Race		
White or Caucasian	NE	NE
Not White or Caucasian	REF	
Marital status		
Single, never married	REF	
Married/Living with partner	0 31	0 14 - 0 69
Other marital status	0 23	0 06 - 0 87
Income level, US dollars		
Less than $50,000	0 95	0 39 - 2 30
$50,000 to $99,999	1 05	0 42 - 2 63
$100,000 or more	REF	
Education level		
College graduate	1 39	0 68 - 2 85
Not a college graduate	REF	
Specific ER/LA opioid analgesic(s) used [4]		
Oral drugs that are not methadone only	REF	
Patch	0 99	0 43 - 2 32
Methadone	1 14	0 37 - 3 49
Continuous health plan eligibility for at least one year prior to the most recent dispensing of an ER/LA opioid analgesic	0 45	0 22 - 0 94
Duration of ER/LA opioid analgesic(s) used most recently before the survey, months		
Less than six months	REF	
Six to less than 12 months	0 37	0 08 - 1 63
At least 12 months	0 64	0 29 - 1 41
Number of previous dispensings of ER/LA opioid analgesics prior to the index date		
Zero	REF	
One to five	0 56	0 22 - 1 42
Six to 10	0 28	0 06 - 1 32
At least 11	0 42	0 18 - 1 00
Number of distinct drugs dispensed during the past six months prior to the index date		
Zero	REF	
One to five	1 27	0 15 - 10 88
Six to 10	0 79	0 09 - 6 79
At least 11	0 47	0 05 - 4 18
Medical condition(s) for which ER/LA opioid analgesics are indicated [5]		
Amputation in the lower limbs or extremities	NE	NE
Arthritis, arthropathies, osteoarthritis, and musculoskeletal pain	0 88	0 29 - 2 62
Chronic pain	0 79	0 38 - 1 66
Fibromyalgia	0 88	0 39 - 1 94
Malignancy	1 21	0 48 - 3 06
Multiple sclerosis	NE	NE
Neuropathic pain	0 25	0 07 - 0 82
Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers	NE	NE
Stroke	NE	NE
Other	0 37	0 05 - 2 76
Unspecified abdominal pain	0 58	0 25 - 1 38
None of the above	0 88	0 11 - 6 96
Medication Guide		
Received the Medication Guide [6]	0 59	0 17 - 2 07
Read the Medication Guide [7]	0 51	0 11 - 2 36
Understood the Medication Guide [8]	0 33	0 07 - 1 60
Patient Counseling Document (PCD)		
Received the PCD [9]	0 76	0 36 - 1 59
Provider referenced the PCD [10]	0 73	0 31 - 1 74
Understood the PCD [11]	1 04	0 23 - 4 71
New user		
First use	2 00	0 89 - 4 52
Used before	REF	

Time since last prescription		
Less than one month ago	REF	
One month to less than six months ago	1 89	0 78 - 4 6
Six months or more ago	3 32	1 40 - 7 86
Time since most recent visit to the healthcare provider who prescribed ER/LA opioid analgesic		
Less than one month ago	REF	
One month to less than six months ago	2 11	0 92 - 4 83
Six months or more ago	3 87	1 44 - 10 39
Time since healthcare provider first prescribed ER/LA opioid analgesic		
Less than one month ago	REF	
One month to less than six months ago	1 48	0 16 - 13 6
Six months or more ago	1 39	0 18 - 10 9
Type of healthcare provider prescribing opioid		
Pain specialist	REF	
Primary care physician	3 35	1 27 - 8 81
Other specialist	3 07	1 20 - 7 85
Nurse practitioner or physician assistant	NE	NE
Other/Not sure	NE	NE
Multivariate analysis		
Marital status		
Married/Living with partner	REF	
Other marital status	1 90	0 90 - 3 99
Medical condition for which ER/LA opioid analgesics are indicated[5]		
Neuropathic pain	REF	
Other medical condition/None	3 40	1 00 - 11 52
Type of healthcare provider prescribing opioid		
Pain specialist	REF	
Primary care physician, other specialist, nurse practitioner, physician assistant, other/Refused	2 70	1 13 - 6 44
Gender		
Female	REF	
Male	1 99	0 96 - 4 14

CI, confidence interval; ER, extended release; GED, General Education Degree; LA, long-acting; NE, not estimable; OR, odds ratio; PCD, Patient Counseling Document; REF, referent; STD, standard deviation; US, United States

1 Currently active at the time of index date, commercially-insured, survey-eligible adults, age 18 years and older, who have filled at least one prescription for ER/LA opioid analgesics including transdermal patch, methadone, and oral formulations within the most recent 12 months of claims data in the HealthCore Integrated Research DatabaseSM (HIRD), 01 December 2012 through 30 November 2013 All results are aggregated and de-identified

2 Categories will be collapsed as needed based on observed data distributions

3 US Census regions of residence based on claims data at the time of index date: Northeast (ME, NH, VT, MA, RI, CT, NY, PA, NJ); South (DE, MD, DC, VA, WV, NC, SC, GA, FL, KY, TN, MS, AL, OK, TX, AR, LA); Midwest (WI, MI, IL, IN, OH, MO, ND, SD, NE, KS, MN, IA); West (ID, MT, WY, NV, UT, CO, AZ, NM, AK, WA, OR, CA, HI)

4 ER/LA opioid analgesic: Oral drugs (ER oral-dosage form containing hydromorphone, hydrocodone, morphine, oxycodone, oxymorphone, or tapentadol); patch (any fentanyl and buprenorphine-containing transdermal delivery system); methadone (any methadone tablet or solution indicated for analgesic use)

5 Medical condition(s) for which ER/LA opioid analgesics are indicated, as defined by International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis, ICD-9-CM procedure, and Current Procedural Terminology (CPT) codes: Amputation in the lower limbs or extremities (ICD-9-CM procedure 84 1x; CPT codes 27880 through 27889, 28800 through 28825); Arthritis, arthropathies, osteoarthritis, and musculoskeletal pain (ICD-9-CM diagnosis 710 x through 729 x [excluding 729 1x, fibromyalgia]); Chronic pain, including central pain syndrome and generalized pain (ICD-9-CM diagnosis 338 0x, 338 2x, 338 4x, 780 96); Fibromyalgia, including myalgia and myositis, unspecified (ICD-9-CM diagnosis 729 1x); Malignancy (ICD-9-CM diagnosis 140 x through 209 x); Multiple sclerosis (ICD-9-CM diagnosis 340 x; Neuropathic pain, including herpes zoster with other nervous system complication, diabetes with neurological manifestations or polyneuropathy in diabetes, spinal cord disease not otherwise specified, peripheral autonomic neuropathy in disorders classified elsewhere, reflex sympathetic dystrophy, multiple sclerosis, unspecified demyelinating disease of central nervous system, trigeminal nerve disorders, facial nerve disorders, nerve root and plexus disorders, mononeuritis (of lower limb, multiplex, lower limb, and unspecified site), hereditary and idiopathic peripheral neuropathy, chronic inflammatory demyelinating polyneuritis, neuralgia, neuritis, and radiculitis, injury to facial nerve, spinal cord injury without evidence of spinal bone injury, injury to brachial plexus, injury to cutaneous sensory or digital nerve of upper limb or other specified nerve(s) of shoulder girdle and upper limb (ICD-9-CM diagnosis 053 1x, 250 6x, 336 9x, 337 1x, 337 2x, 340 x, 341 9x, 350 x, 351 x, 353 x, 354 x, 355 x, 356 x, 357 2x, 357 81, 729 2x, 951 4x, 952 x, 953 4x, 955 5x through 955 7x); Peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers, including atherosclerosis of native arteries or bypass graft of the extremities and peripheral angiopathy in diseases classified elsewhere (ICD-9-CM diagnosis 440 2x, 440 3x, 443 81, 443 9x); Stroke, including occlusion and stenosis of precerebral and cerebral arteries and cerebrovascular disease (acute but ill-defined, other and ill-defined, or late effects of) (ICD-9-CM diagnosis 433 x through 434 x, 436 x through 438 x); Other, including pain disorders related to psychological factors (ICD-9-CM diagnosis 307 8x), temporomandibular joint-pain-dysfunction syndrome (ICD-9-CM diagnosis 524 60), chronic pancreatitis (ICD-9-CM diagnosis 577 1x), pathologic hip fracture (ICD-9-CM diagnosis 733 14), chronic fatigue syndrome (ICD-9-CM diagnosis 780 71), and open or closed hip fracture (ICD-9-CM diagnosis 820 8x, 820 9x); and Unspecified abdominal pain (ICD-9-CM diagnosis 789 0x)

6 Received Medication Guide with any prescription of an ER/LA opioid analgesic in the last 12 months

7 Read some or all of the Medication Guide at least once

8 Understood Medication Guide, as self-reported by the respondent that they understood about half, most, or all of the information in the Medication Guide

9 Healthcare provider gave PCD when ER/LA opioid analgesic was first prescribed the first time or in the last 12 months

10 Healthcare provider referred to or discussed PCD when current ER/LA opioid analgesic was prescribed in the last 12 months

11 Understood PCD, as self-reported by the respondent that they understood at least some, half, most, or all of the information discussed per the PCD

Appendix D - RADARS Protocol

Title: Extended-Release (ER) and Long-Acting (LA) Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS): RADARS® System Surveillance Protocol

Date: 20 May 2014

TABLE OF CONTENTS

1. PROTOCOL SYNOPSIS

Rationale	To provide surveillance monitoring for rates of abuse, misuse, overdose, addiction, and death associated with the use of extended release (ER) or long-acting (LA) opioids.
Objectives	To conduct surveillance for abuse, misuse, overdose, addiction, and death and to evaluate if the REMS meets its surveillance goals, and if it does not, to modify it appropriately based on the metrics. Briefly, therefore, the overall surveillance objective is to evaluate for trends before and after the shared REMS is implemented to collectively assess for changes in abuse, misuse, overdose, addiction, and death for different risk groups and settings.
Data sources	RADARS® System Poison Center Program, Treatment Center Program, and College Survey Program; IMS Health and United States (US) Census data.
Design	This is an observational ecological study utilizing quarterly data from January 2010 through December 2016. The study design is unique to each metric and data source.
Population	The Poison Center Program obtains data from the general population of the US, Treatment Center Programs obtain data from those entering treatment for opioid addiction, and the College Survey Program surveys self-identified students attending a 2- or 4- year college, university, or technical school.
Primary outcomes	Abuse, misuse, and death
Report Frequency	Annually

2. RATIONALE

In response to a growing number of reports of abuse, misuse, overdose, addiction, and death associated with ER/LA opioids, on February 6, 2009, the FDA sent letters to manufactures of certain opioid drug products indicating that these drugs would be required to have a Risk Evaluation and Mitigation Strategy (REMS) to ensure the benefits of the drugs continue to outweigh the risks. The specific goal of the REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. The affected drugs include branded and generic drug products, including:

- Extended release, oral dosage forms containing hydromorphone, morphine, oxycodone, oxymorphone, or tapentadol;
- Fentanyl and buprenorphine-containing transdermal delivery systems; *and*
- Methadone tablets and solutions that are indicated for use as analgesics.

When used properly, such drugs can play an important role in the management of moderate to severe chronic and acute pain. However, serious outcomes such as those listed above may result

when used improperly. This protocol describes the surveillance of abuse, misuse, and death in relation to the ER/LA REMS monitoring. Additional outcomes of interest will include serious adverse events, unintentional therapeutic errors, pediatric unintentional exposure, and adolescent intentional abuse.

3. BACKGROUND

3.1 Description of Prescription Drug Abuse Epidemic in the United States (US)

Prescription drugs, including opioids, provide therapeutic value to millions of Americans. However, prescription drug abuse is the fastest growing drug problem in the United States and has become a national epidemic. Overdoses and deaths involving non-medical prescription drug use, especially opioid analgesics, have risen dramatically over the last decade such that overdose death rates in the US have more than tripled since 1990 [1]. In 2012, an estimated 6.8 million Americans (2.6 percent of the population) reported using prescription drugs non-medically in the previous month. [2] Many factors contribute to this epidemic, including the increasing prevalence of chronic pain in an aging US population, wider acceptance of opioids for treatment of chronic pain, the misperception that these drugs are safe when used outside of medical practice, their relatively low cost, and the increase in potency of some agents.

3.2 Overview of ER/LA REMS Products

The following table lists the generic names, brand names (when applicable), and Sponsors for the ER/LA products included in the REMS [3].

Table 3.2.1 ER/LA REMS Generic and Branded Product Names (as of 3/2014)

Generic Name	Brand Name	Sponsor
Buprenorphine transdermal system	Butrans®	Purdue Pharma
Fentanyl transdermal system		Aveva
Fentanyl extended-release transdermal system		Mallinckrodt
Fentanyl extended-release transdermal system		Mylan Technologies
Fentanyl extended-release transdermal system		Noven
Fentanyl extended-release transdermal system		Par
Fentanyl extended-release transdermal system		Sandoz
Fentanyl transdermal system		Watson
Fentanyl transdermal system	Duragesic®	Janssen Pharmaceuticals
Fentanyl transdermal system		Apotex
Hydrocodone bitartrate extended release capsules	Zohydro®	Zogenix
Hydromorphone hydrochloride extended release caplets	Palladone®*	Rhodes
Hydromorphone hydrochloride extended release tablets	Exalgo®	Mallinckrodt
Methadone hydrochloride oral concentrate		Roxane
Methadone hydrochloride tablets		Mallinckrodt
Methadone hydrochloride tablets	Methadose®	Mallinckrodt
Methadone hydrochloride tablets		The PharmaNetwork
Methadone hydrochloride tablets		Sandoz
Methadone hydrochloride tablets	Dolophine®	Roxane
Methadone hydrochloride tablets		Roxane
Methadone hydrochloride oral solution		Roxane
Methadone hydrochloride oral solution		Vistapharm
Morphine sulfate extended-release capsules	Kadian®	Watson
Morphine sulfate extended-release capsules		Watson
Morphine sulfate extended-release capsules		Par
Morphine sulfate extended-release capsules	Avinza®	Pfizer
Morphine sulfate extended-release capsules		Ranbaxy

Generic Name	Brand Name	Sponsor
Morphine sulfate extended-release capsules		Upshire-Smith
Morphine sulfate controlled-release tablets	MS Contin®	Purdue Pharma
Morphine sulfate extended-release tablets		Mallinckrodt
Morphine sulfate extended-release tablets		Mylan
Morphine sulfate extended-release tablets		Rhodes
Morphine sulfate and naltrexone extended-release capsules	Embeda®*	Pfizer
Oxycodone hydrochloride controlled-release tablets	OxyContin®	Purdue Pharma
*Oxycodone hydrochloride extended-release tablets		Impax
Oxymorphone hydrochloride extended-release tablets		Actavis
Oxymorphone hydrochloride extended-release tablets	Opana ER®	Endo Pharmaceuticals
Oxymorphone hydrochloride extended-release tablets		Impax
Tapentadol extended-release oral tablets	Nucynta ER®	Janssen Pharmaceuticals

*Not currently marketed.

3.3 ER/LA REMS Subgroups

In addition to examining the ER/LA REMS drugs as a group, rates of abuse, misuse, and death compared to the IR opioid and stimulant comparators will be evaluated for the five subgroups denoted below.

- Morphine ER
- Oxymorphone ER
- Methadone
- Fentanyl and buprenorphine transdermal delivery systems
- Other ER opioid group (i.e., oxycodone ER, hydromorphone ER, tapentadol ER, and hydrocodone ER)

4. OBJECTIVES

The fifth assessment of the REMS is to conduct surveillance for abuse, misuse, overdose, addiction, and death and to evaluate if the REMS meets its surveillance goals, and if it does not, to modify it appropriately based on the metrics. Briefly, therefore, the overall surveillance objective is to evaluate for trends before and after the shared REMS is implemented to

collectively assess for changes in abuse, misuse, overdose, addiction, and death for different risk groups and settings.

4.1 Study Design

The study design will be unique to each metric and data source. The surveillance metrics that RPC proposes are very similar to the targets for metrics that the FDA outlined in its 2010 Final Report of the Metric Working Group. To consider the assessments proposed by RPC, it is helpful to review the surveillance data by what data are feasible to collect or obtain. ASSESSMENT 5 DATA SOURCES ARE:

- ASSESSMENT 5.2: Intentional exposures among adolescents and adults, including severity and deaths, using nationally-based poison control surveillance data.
- ASSESSMENT 5.3: Unintentional exposures among infants and children, including severity and deaths, using nationally-based poison control surveillance data.

5. DATA SOURCES

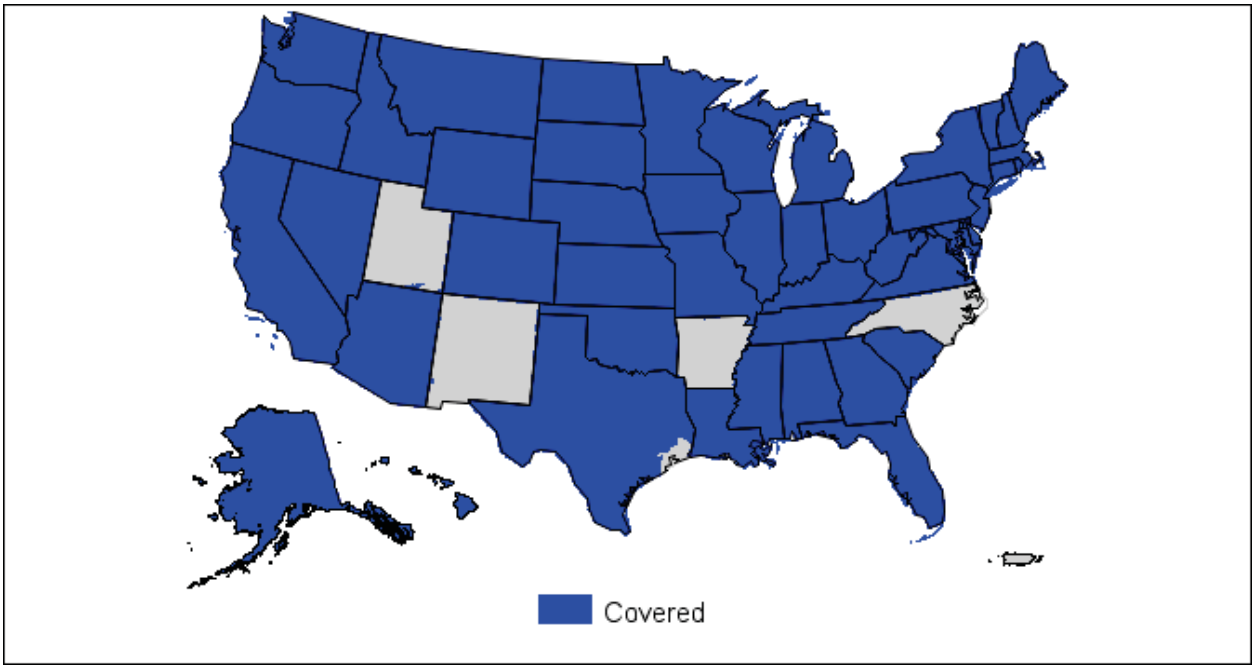
5.1. RADARS® System

The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System provides post-marketing surveillance of prescription medication abuse, misuse, and diversion to pharmaceutical companies, regulatory agencies, and policy making organizations. The RADARS System is comprised of multiple programs which gather data from several unique populations along the spectrum of drug abuse.

5.2. Poison Center Program

The RADARS System Poison Center Program obtains data from individuals within the general population and from healthcare providers who are seeking advice regarding potential toxic exposures, including prescription opioids and prescription stimulants. The objectives of the Poison Center Program are to detect product-specific prescription drug abuse and misuse in near real-time and to identify geographic sites with disproportionately high rates of abuse and misuse. Poison center data collected through the RADARS System provide an estimate of change in intentional abuse, misuse, and deaths associated with these drugs. The Poison Center Program gathers data from 49 regional US Poison Centers in 46 states, including urban, suburban, and rural regions (over 90% of the US population). Investigators at each participating poison center collect data using a nationally standardized electronic health record. In addition to obtaining exposure and substance data, the Poison Center Program collects demographic, clinical effects, treatment, and medical outcomes information. The Poison Center Program was initiated in 2002.

RADARS® System Poison Center Program 2013 Coverage Map



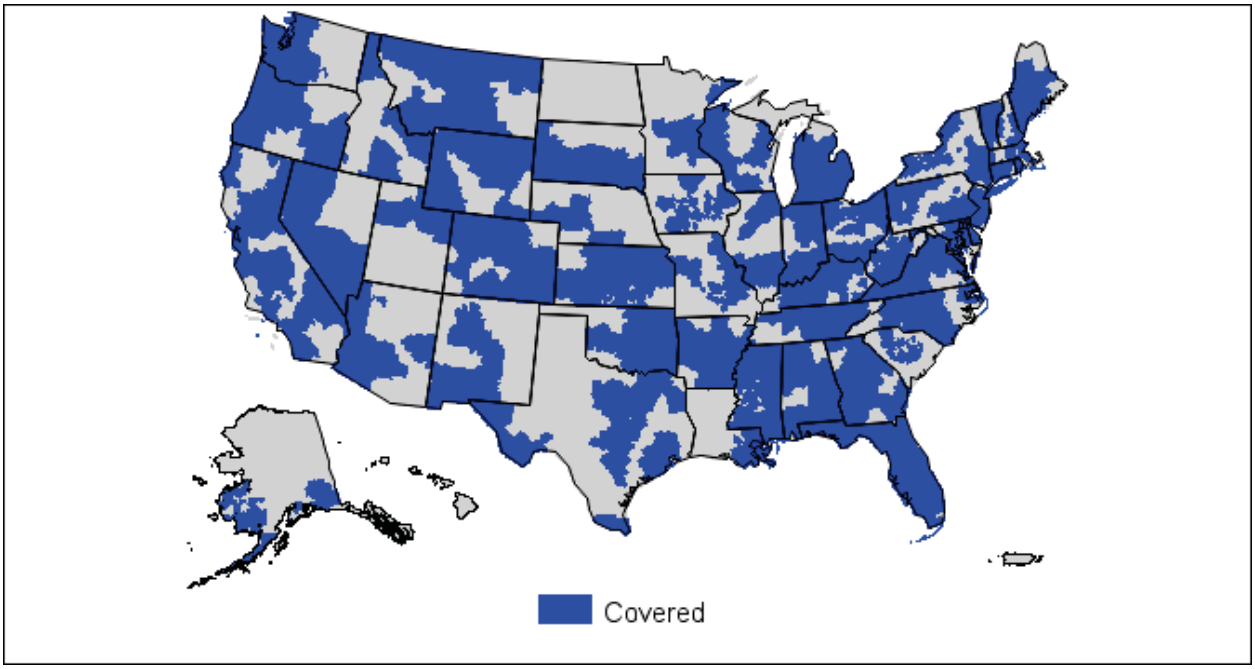
5.3 Treatment Center Programs Combined

The Treatment Center Programs Combined provide data from two distinct RADARS System programs: Opioid Treatment Program and Survey of Key Informants' Patients Program. These two programs use the same core data collection form and complement each other by providing information from patients entering both private and public opioid addiction treatment programs. Patients enrolling in the study are voluntarily recruited and complete a self-administered anonymous questionnaire within the first week of admission. The objectives of these programs are to estimate 1-month prevalence and the injection rate of prescription and illicit opioid and non-opioid drugs among patients admitted to opioid treatment programs. In addition, they seek to determine the patient's drug of choice and the source of the primary drug.

The Opioid Treatment Program involves 77 methadone maintenance treatment programs in both urban and rural areas across 37 states. Formal data collection began in 2005.

The Survey of Key Informants' Patients Program involves 155 substance abuse treatment programs covering 47 states. These primarily private treatment centers are balanced geographically with representation from urban, suburban, and rural centers. The Survey of Key Informants Patients became a RADARS System Program in 2008.

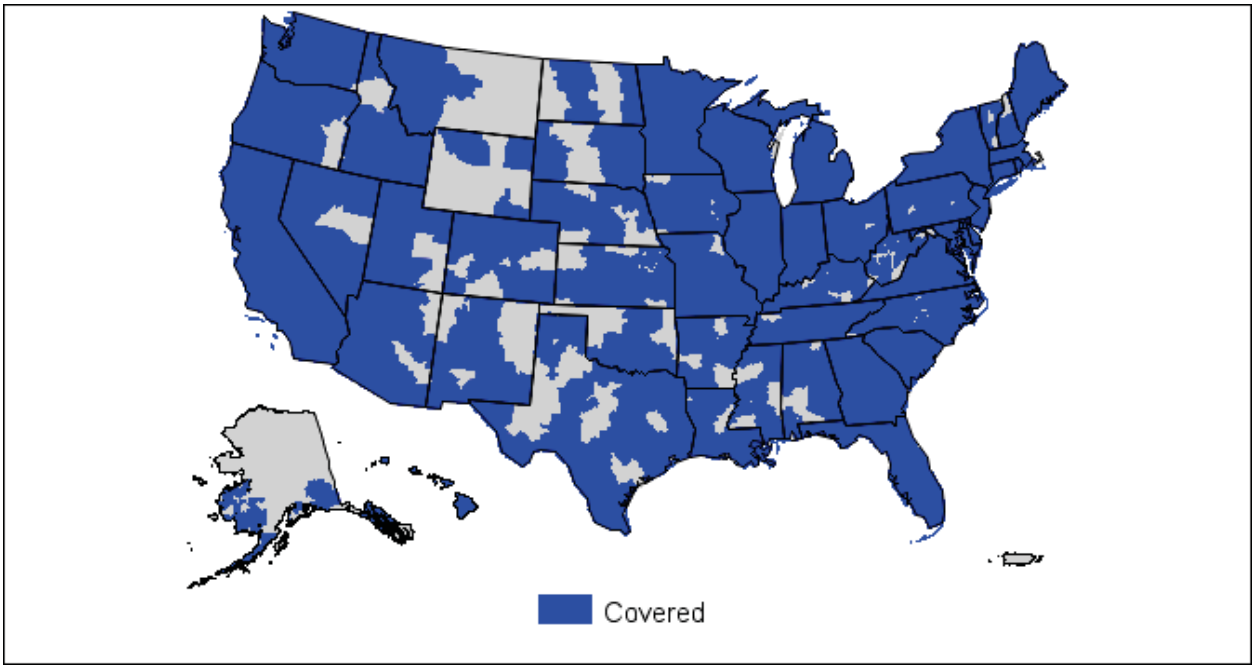
RADARS® System Treatment Center Programs Combined2013 Coverage Map



5.4 College Survey Program

The College Survey Program is an online questionnaire that collects data from self-identified students attending a 2- or 4-year college, university, or technical school at least part-time during the specified sampling period. Data on non-medical use (abuse/misuse) of specific prescription drugs are collected at the completion of the fall and spring academic semesters/quarters and at the end of the summer. The objectives of the College Survey Program are to estimate the scope of non-medical prescription drug use among US college students, determine the drug source, and determine the route of drug administration among these students. A target of 2000 surveys is completed three times per year with enrollment stratified into the four US Census-regions to ensure nationwide distribution of respondents. A nationwide panel company is utilized to identify and target ideal responders. Students are sent an invitation to participate in the study and they receive credits upon completion of the survey. The survey inquires about the non-medical use of prescription drugs by capturing product specific endorsements. Data are national, timely, and drug specific. The College Survey was launched in 2008.

RADARS® System College Survey Program 2013 Coverage Map



5.5 IMS Health Prescription and Dosing Unit Data

IMS Health has been obtaining data on prescription dispensing since 2001. Timely product and geographically specific data are obtained from a sample of roughly 50% of retail pharmacies in the US. IMS Health uses a complex proprietary projection methodology to extrapolate from the observed data to the universe of all retail prescriptions in the US. The proposed study will use estimates from IMS health for total prescriptions dispensed and total dosing units dispensed at the 3-digit ZIP code level for all ER/LA REMS opioids and comparator groups. For a given year-quarter the totals of prescriptions and dosing units in the 3-digit ZIP codes covered by the RADARS System Programs will be computed and these numbers used as the denominators when calculating product availability rates. All rates will be scaled per 1,000 prescriptions or dosing units dispensed.

5.6 US Census

Three-digit ZIP code population data from the 2000 and 2010 US decennial Censuses will be utilized to compute rates of abuse, misuse, and death. For a given year-quarter the total population in the 3-digit ZIP codes covered by the RADARS System Programs will be computed and this number used as the denominator when calculating population rates. All rates will be scaled per 100,000 population.

6. DATA MANAGEMENT

6.1. Poison Center Program Data Management

Participating poison centers have a standard protocol for the management of all cases. The specialists who manage the calls obtain details of the exposure from the caller or the health care provider, and populate standardized fields in the call log database. Investigators at each participating poison center have been trained to use a standardized pre-formatted database to extract all exposure cases regarding the drugs of interest. Each data set includes the standardized fields common to all poison centers with all identifying information removed. Each site coordinator reviews each case and removes all patient identifiers prior to electronic transfer to the RADARS System. To ensure confidentiality, each database is encrypted before the data transfer occurs.

RADARS System staff review these databases for inconsistencies. If inconsistencies are found, the site is notified and asked to rectify the queries. Each case is then reviewed to determine the accuracy of the reason code used. Exposure cases are composed of two categories: *unintentional/other* (resulting from unforeseen or unplanned events, adverse reactions, other, and unknown reasons), and *intentional exposures* (which include suicide, intentional misuse, abuse, intentional unknown, and withdrawal cases). All data are uploaded into a SQL database for summarization and analysis.

6.2. Treatment Center Programs Data Management

6.2.1. Opioid Treatment Program

Participating opioid treatment centers fax completed surveys to the data coordination group on a designated day of the week. Optical character recognition software is used to identify the data within the fax image and all data are exported into an SPSS database. Database quality assurance includes form review and data review within the data recognition software and data edit checking using SPSS. SPSS edit checking is done by flagging inconsistent responses (e.g., letters appearing in ZIP code or duplicate cases in the data). Incoming surveys are manually logged into an Excel spreadsheet to represent the number of surveys faxed from each study site each week. These data are matched against the aggregate count of subjects within site generated by SPSS. The final quarterly SPSS database is then submitted to the RADARS System.

6.2.2. Survey of Key Informants' Patients Program

Each completed questionnaire is logged in the participating Key Informants' site binder, indicating date received. These questionnaires are then submitted to the data coordination group for data entry. All data entry is double-checked and verified for accuracy and quality assurance. Electronic data edit checks are performed to identify inconsistent responses. Quarterly databases are then submitted to the RADARS System.

6.3. College Survey Program Data Management

For each survey launch, the data are downloaded as an Excel file from a secure hosting site once a sample of approximately 2,000 respondents has been obtained. These data are then stored in their raw format on the RADARS System secure server. After the raw data file has been downloaded, the data are then cleaned using validated SAS® software routines, and based on specified criteria, certain respondents are eliminated.

7. METHODS

7.1. Design

RADARS System surveillance data obtained quarterly from July 2010 through December 2016 will be utilized to assess Pre-Implementation to Active Period changes in rates of abuse, misuse, and death.

7.2. Population

The Poison Center Program obtains data from the general population of the US, the Treatment Center Programs obtain data from those entering substance treatment, and the College Survey Program samples from self-identified students attending a 2- or 4- year college, university, of technical school.

7.3. Outcome Variables

Outcome variables include measures of abuse, misuse, serious adverse events, death, unintentional therapeutic errors, pediatric unintentional general exposures, and adolescent abuse. Each outcome is described in the sections below. Table 7.3 summarizes the outcomes measured in each of the RADARS System Programs.

Table 7.3 ER/LA REMS Outcomes by RADARS® System Program

RADARS SYSTEM Program	Abuse	Misuse	Serious Adverse Events	Death	Unintentional Therapeutic Errors	Pediatric Unintentional General Exposures	Adolescent Abuse
Poison Center Program	X	X	X	X	X	X	X
Treatment Center Programs Combined	X						
College Survey Program	X						

7.3.1. Abuse

Measures of abuse will be captured in all three RADARS System Programs included in this protocol: Poison Center Program, Treatment Center Programs Combined, and College Survey Program. In the Poison Center Program, an intentional abuse case is defined as: "An exposure resulting from the 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." [4] In the Treatment Center Programs, abuse will be measured as survey respondent endorsing the use of an ER/LA opioid "to get high" in the past 30 days. Lastly, in the College Survey Program, abuse will be defined as the endorsement of the non-medical use of a drug in the past 90 days.

7.3.2. Misuse

Our working definition of misuse is: the intentional use of a prescription drug in a way other than prescribed or directed by a healthcare provider or the use of an over-the-counter drug in other ways than directed, including: patients intentionally using an over-the-counter or a prescription drug for a different condition than the drug is directed or prescribed for, patients intentionally taking more drug or at a different dosing interval than prescribed, and individuals intentionally using a drug not prescribed for them, though for therapeutic purposes. Misuse will be captured in the Poison Center Program and be defined as those cases with a reason for exposure of intentional misuse, unintentional general and unintentional therapeutic error. In the Poison Center Program, intentional misuse is defined as: "an exposure resulting from the intentional improper or incorrect use of a substance for reasons other than the pursuit of psychotropic effect." [4] Definitions of unintentional therapeutic errors and pediatric unintentional general exposures appear below.

7.3.3. Hospitalization, Major Medical Outcome or Death

In the Poison Center Program any exposure resulting in a major medical outcome, hospitalization, or death will be defined as a serious adverse event.

7.3.4. Death

Death is recorded in the Poison Center Program based upon case follow-up.

7.3.5. Unintentional Therapeutic Errors

Unintentional Therapeutic Errors will be captured in the Poison Center Program. In the Poison Center Program, unintentional therapeutic errors are defined as: "An unintentional deviation from a proper therapeutic regiment that results in the wrong dose, incorrect route of administration, administration to the wrong person, or administration of the wrong substance." [4]

7.3.6. Pediatric Unintentional General Exposures

Pediatric Unintentional General Exposures will be captured in the Poison Center Program and are defined as those cases in children under 6 with a reason code of unintentional general which consists primarily of accidental unsupervised ingestions such as a toddler getting into a grandparent's prescription medicine.

7.3.7. Adolescent Abuse

Adolescent Abuse will be captured in the Poison Center Program and is defined as cases 13-19 years old or with an age code of teen that have a reason for exposure of intentional abuse. This is a subset of all intentional abuse cases noted above.

7.4. Comparators

Two comparator groups are planned: immediate release prescription opioids and prescription stimulants.

7.4.1. Immediate Release (IR) Prescription Opioids

Rates of abuse, misuse, and death for ER/LA opioids will be compared to corresponding rates for prescription IR opioids. This control group will include IR formulations of fentanyl, hydrocodone, hydromorphone, morphine, oxycodone, oxymorphone, and tapentadol. IR formulations for injection will be excluded.

7.4.2. Prescription Stimulants

Although the ER/LA REMS is specifically targeted to ER/LA opioids, some overlap of the education effect may be realized for IR opioids as well. For this reason ER/LA opioid rates will also be compared to rates for prescription stimulants. Prescription stimulants will consist of methylphenidates and prescription amphetamines.

7.5. Denominators

Three denominators that will be considered are population, number of prescriptions dispensed, and number of dosing units dispensed. The population denominator will be considered primary.

Exploratory analyses will be conducted using the ratio of total units dispensed per 3-digit ZIP code covered by the RADARS System divided by the corresponding total number of prescriptions dispensed. This will give a measure of average prescription size. Analysis will be conducted to determine if average prescription sizes are decreasing in the Active Period. If significant differences in the average prescription size are smaller in the Active Period compared to the Pre-Implementation period then only analyses on population and number of dosing units dispensed will be conducted.

7.5.1 Population

The population estimates were obtained by extrapolating using data from the 2000 and 2010 US censuses at the 3-digit ZIP code level for each quarter. Data will be summed across those 3-digit ZIP codes in areas covered by a particular RADARS System Program.

7.5.2 Prescriptions Dispensed

Detailed data on projected number of prescriptions dispensed by drug, formulation, and 3-digit ZIP code are purchased from IMS Health. Data will then be summed to determine the total number of prescriptions dispensed separately for ER/LA REMS products, IR prescription

opioids, and prescription stimulants across 3-digit ZIP codes covered by a particular RADARS System Program.

7.5.3 Dosing Units Dispensed

Detailed data on projected number of dosing units dispensed by drug, formulation, and 3-digit ZIP code are also purchased from IMS Health. Data will then be summed to determine the total number of prescriptions dispensed for all ER/LA REMS products, IR prescription opioids, and prescription stimulants across 3-digit ZIP codes covered by the RADARS System Program.

7.6. Analysis

Poisson regression will be used to compare changes in rates of abuse, misuse, overdose, and death over time within the ER/LA opioid group to changes in rates among the comparator groups.

Time will be divided into three periods: Pre-Implementation (third quarter 2010 through second quarter 2012), Transition (third quarter 2012 through second quarter 2013), and Active Period (third quarter 2013 forward). Depending on the number of quarters of data available in the Active Period at the time of each report, one or two different methods of analysis will be applied to the data: the means model and the spline model. In the means model, mean outcome rates will be compared across the three periods. In addition, for later reports a gradual progressive change in the trends over time will be compared using a spline model. Each of these modeling approaches is further detailed below.

For both the mean and spline models, drug product will be categorized as an ER/LA REMS opioid or comparator (IR opioid or stimulants). The total number of cases mentioning one or more ER/LA REMS opioid or comparator in the 3-digit ZIP codes covered by the RADARS System each quarter will be computed and used as the dependent variable in the Poisson regression models. The denominator of the rates will enter the Poisson model as an offset variable. A drug group specific variance structure will be fit, thus allowing for different variances in the ER/LA REMS opioid group versus the comparator.

For the means model, the Poisson regression model will include fixed effects for the period by drug group effect which will be used to determine if:

1. There are changes in the Pre-Implementation to Active Period means.

2. The Active Period to Pre-Implementation changes in means in the ER/LA REMS group differs from the changes in means for the comparator group.

In addition to examining the ER/LA REMS drugs as a group, rates of abuse, misuse, overdose, and death compared to the IR opioid and stimulant comparators will be evaluated for the five subgroups denoted below.

- Morphine ER
- Oxymorphone ER
- Methadone
- Fentanyl and buprenorphine transdermal delivery systems

- Other ER opioid group (i.e., oxycodone ER, hydromorphone ER, tapentadol ER, and hydrocodone ER)

For the spline model two periods will be evaluated: the Pre-Implementation Period and the combined Transition and Active Period (Post-Implementation period). The Poisson regression model will include a continuously scaled effect for quarter number, where quarter zero corresponds with the beginning of the Transition Period. The model will include a drug group effect allowing for difference in intercepts for the two drug groups and a drug group by period by quarter number effect allowing for differences in the slopes for the Pre-Implementation and Post-Implementation periods for both drug groups. The model will be used to test if:

1. The slopes for the two periods in the ER/LA REMS drug group differ.
2. The changes in slopes for the ER/LA REMS group differs from the change in slopes for the comparator group.

In addition to examining the ER/LA REMS drugs as a group, rates of abuse, misuse, intentional exposure, and death compared to the IR opioid and stimulant comparators will be evaluated for the five subgroups denoted below.

- Morphine ER
- Oxymorphone ER
- Methadone
- Fentanyl and buprenorphine transdermal delivery systems
- Other ER opioid group (i.e., oxycodone ER, hydromorphone ER, tapentadol ER, and hydrocodone ER)

Secondary analyses will be conducted to determine if the mean number of dosing units per prescriptions dispensed differs across time for the ER/LA REMS drug group. If the REMS education intervention is effective then health care professionals may dispense fewer dosing units per prescription. As with the primary analysis, time will be categorized into three periods and changes in mean dosing units per prescriptions dispensed over time will be compared for the ER/LA opioid group and for the comparison group using a log linear model separately for pills, patches, and solution as dosing units are of different magnitudes across these three strata. The model will include a fixed indicator variable for period.

8. LIMITATIONS

More cautious prescribing in the ER/LA REMS may carry over to the IR opioid class, resulting in no difference between the ER/LA opioid group and the IR opioid comparator group. Also, total reports of exposures to US Poison Centers have been decreasing in the past three years; thus, a decline in ER/LA opioid without a corresponding difference in at least one control group will not be conclusive. Further, each of the programs is based on self-reported information which increases the likelihood of ambiguous answers and incomplete data.

9. OFFSETTING STRENGTHS

The RADARS System data are drug- and formulation-specific allowing us to identify IR versus ER/LA product groups. The data will be available for analysis within 12 weeks of each calendar quarter conclusion, permitting identification of trends in near real-time. An additional strength is the large catchment area covered. Cases can arise from large metropolitan areas as well as rural populations and thus provide results that are more broadly applicable than those from a smaller geographic region. The joint use of RADARS System multiple detection programs allows for the assessment of trends by various populations and in different settings to enhance the generalizability of the data. Comprehensive results from independent programs provide better understanding of the trends of interest.

10. HUMAN SUBJECT CONSIDERATION

This study is part of the research being conducted under the protocols for the three RADARS System programs. Protocols for each program have already been reviewed and approved by IRBs as described below. The approvals do not limit data analysis. Further, the work in this protocol involves no interaction with human subjects. A separate IRB review of this protocol is therefore not necessary.

Poison Center Program

The Poison Center Program study protocol was last reviewed and received approval from the Colorado Multiple Institutional Review Board (COMIRB) on 13 March 2012. In addition, the study protocol was reviewed and approved by the IRB of each participating poison center.

Treatment Center Program

The Opioid Treatment Program study protocol was last reviewed and received expedited approval from the IRB of the Principal Investigator, National Development and Research Institutes Inc. on 16 February 2012. The Survey of Key Informants' Patients Program study protocol was last reviewed and received expedited approval from the IRB of Washington University in St. Louis, the home institution of the Principal Investigator, on 6 June 2012.

College Survey Program

The College Survey Program study protocol was last reviewed and approved by COMIRB on 24 April 2012.

11. REFERENCES

1. National Vital Statistics System. Drug overdose death rates by state. 2008.

2. Substance Abuse and Mental Health Services Administration, Results from the 2012 National Survey on Drug Use and Health: Summary of National Findings, NSDUH Series H-46, HHS Publication No. (SMA) 13-4795. Rockville, MD: Substance Abuse and Mental Health Services Administration, 2013.

3. http://www.er-la-opioidrems.com/IwgUI/rems/products.action

4. American Association of Poison Control Centers National Poison Data System Reference Manual, June 2007.

Appendix E - RADARS Full Report

RADARS® System Report

Extended Release/Long Acting (ER/LA) Risk Evaluation and Mitigation Strategy (REMS) FDA Report #3 Third Quarter 2010 through Fourth Quarter 2013

DENVER HEALTH
Level One Care for ALL

RMPDC
ROCKY MOUNTAIN POISON & DRUG CENTER
Saving Lives with Answers

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Appendix F - Inflexxion Protocol

Title: REMS assessment and surveillance study to evaluate the impact of extended-release/long-acting (ER/LA) opioid analgesics class REMS on abuse among those in substance abuse treatment

Date: May 14, 2014

TABLE OF CONTENTS

1. PROTOCOL SYNOPSIS

Table 1.

Rationale	In 2012, the FDA approved a class-wide extended-release (ER) and long-acting (LA) opioid analgesics risk evaluation and mitigation strategy (REMS). One component of this REMS is assessment and evaluation of the effects of implementing mitigation strategies aimed at both prescriber and patient-related education regarding the benefits and risks of opioid analgesics.
Objectives	The objective of this annual study is to monitor and evaluate patterns of abuse of ER/LA opioids, overall, as well as by compounds/subgroups and in comparison to immediate-release (IR) opioids as a group and benzodiazepines among a sentinel population of adults assessed for substance use problems for treatment planning.
Data sources	NAVIPPRO Addiction Severity Index-Multimedia Version (ASI-MV) NAVIPPRO Comprehensive Health Assessment for Teens (CHAT)
Design	A cross-sectional observational surveillance study for ASI-MV Descriptive analyses for CHAT
Population	Male and female adults aged 18 years and older (ASI-MV) and adolescents (14 to 18 years of age) being assessed for substance abuse problem severity and treatment planning.
Primary outcomes	Past 30-day abuse of specified ER/LA opioid analgesics and source of the drug reported as abused in the past 30 days.
Study Period	Current study submission for Year One: July 2010 – December 2013: o Pre-REMS implementation period: July 2010 – June 2012 o REMS implementation period: July 2012 – June 2013 o Active Period: July 2013 – December 2013
Annual report date	Current study submission date for Year One: • Inflexxion to REMS Program Companies (RPC) Subteam: May 14, 2014 • RPC to FDA: July 9, 2014

2. BACKGROUND AND RATIONALE

In April 2011, the U.S. FDA determined that a class-wide risk evaluation and mitigation strategy (REMS) was required of all manufacturers of extended-release/long-acting (ER/LA) opioid analgesics to support efforts to address the national problem of prescription opioid abuse. The class-wide REMS was approved by the FDA on July 9, 2012 and is being jointly implemented by pharmaceutical companies that manufacture both brand and generic formulations of ER/LA opioids (the REMS Program Companies or RPC). As part of the REMS, all ER/LA opioid analgesic companies must provide: (1) education for prescribers of

these medications through accredited continuing education (CE) activities supported by the companies, and (2) information that prescribers can use when counseling patients about the risks and benefits of ER/LA opioid analgesic use. The shared REMS education initiative (referred to in this document as "the REMS intervention") is based on the FDA Blueprint document and expected to reflect Elements to Assure Safe Use (ETASU)[1].

One component of the REMS is assessment and evaluation of the effects of implementing the mitigation strategies. The fifth REMS assessment includes monitoring for misuse, abuse, overdose, addiction, and death and stipulates that adjustment in REMS strategies be taken based on the findings of these metrics. Surveillance monitoring of these metrics among specific populations will provide an important outcome measure of whether the REMS is having the intended effect of reducing the public health burden of morbidity and mortality. Along with other metrics such as 1) prescriber and patient knowledge and awareness based on surveys and 2) measures of prescribing practices, surveillance data will be monitored to see if any trends are developing (positive or negative) that will inform whether the shared REMS needs to be modified.

The FDA has indicated that surveillance should include information on changes in misuse, abuse, overdose, addiction, and death for different risk groups, for example, teens and chronic abusers, as well as different settings such as emergency rooms, addiction treatment centers, and poison control call centers. Drug safety databases that are used to assess safety risks for drugs in other therapeutic classes are alone not sufficient for the surveillance of opioids, as they are focused on the use of drugs by patients. An important risk associated with this class of products is misuse and abuse by non-patients. Therefore, surveillance databases that capture information on misuse and abuse and abuse-related outcomes in non-patients is necessary.

Given that individuals in treatment for substance use disorders constitute a population at high risk for abuse and addiction of prescription opioids, the RPC Metric Subteam reviewed sources of surveillance data that are feasible to collect or obtain and proposed that ASSESSMENT 5 data sources include:

> ASSESSMENT 5.4: Rates of individuals in substance abuse treatment programs abusing ER/LA opioids, as well as source of acquiring the ER/LA opioids, as compared to comparator IR opioids and benzodiazepines using the national surveillance systems among substance treatment seekers.

This protocol directly addresses this goal and outlines specifications for surveillance data that specifically address this high-risk population. Two of Inflexxion's proprietary data streams within the National Addictions Vigilance Intervention and Prevention Program (NAVIPPRO®)—the ASI-MV® and CHAT®—will be used to examine the impact of the REMS intervention as a response to objective 4 of assessment 5 outlined by the RPC Metric Subteam.

3. OBJECTIVES

The fifth assessment of the REMS intends to conduct surveillance for misuse, abuse, overdose, addiction, and death and to evaluate if the REMS meets its surveillance goals, and if it does not, to modify it appropriately based on the metrics. Briefly, therefore, the overall surveillance

objective is to evaluate for trends in abuse of ER/LA opioids before and after the shared REMS intervention is implemented to collectively assess for changes in misuse, abuse, overdose, addiction, and death for different risk groups and settings. The present protocol addresses a high-risk sample of individuals being evaluated for treatment planning and triage for substance use disorders.

The main objective of this study is to monitor and evaluate patterns of abuse of ER/LA opioids among a sentinel population of adults assessed for substance use problems for treatment planning. To better understand ER/LA opioid abuse patterns, secondary analyses will examine the ER/LA opioids by compounds (subgroups). Secondary objectives will also compare abuse of ER/LA opioids as a group to immediate-release opioids as a group and benzodiazepines. Tertiary analyses will assess abuse patterns of ER/LA as a group and at the compound/subgroup level over time as well as source of procurement among those individuals reporting past 30-day abuse of ER/LA opioids. The primary, secondary, and tertiary objectives are described below (Section 3.1. through 3.3 and Table 2). The approach for conducting analyses related to each objective is delineated in the Methods section of this protocol. Details regarding the study population, the study period, and definitions for target and comparator opioids, source of procurement categories, and study denominators are provided in the methods section of this protocol.

3.1. Primary Objective:

The primary objective for this study is to estimate changes in population-based (i.e., all unique ASI-MV assessments) prevalence of past 30-day abuse of ER/LA products as a group across a pre-REMS period (baseline), REMS implementation (time 1) and continuing active REMS phase (time 2).

3.2. Secondary Objectives

Three secondary objectives will be evaluated for this study:

1. To estimate changes in population-based prevalence of past 30-day abuse at the compound (or subgroup)-level for the ER/LA opioid group across pre-REMS (baseline), REMS implementation (time 1) and continuing active REMS phase (time 2).
2. To compare changes in estimates of population-based prevalence of ER/LA products as a group with IR opioids as a group across pre-REMS (baseline), REMS implementation (time 1) and continuing active REMS phase (time 2).
3. To compare changes in estimates of population-based prevalence of ER/LA products as a group with benzodiazepines (as captured by the ASI-MV) as a group across pre-REMS (baseline), REMS implementation (time 1) and continuing active REMS phase (time 2).

3.3. Tertiary Objectives:

Two tertiary objectives will be evaluated for this study:

1. To examine changes in the proportion of the source of drug for ER/LA prescription opioids as a group and at the compound (or subgroup) level across pre-REMS

(baseline), REMS implementation (time 1) and continuing active REMS phase (time 2).

2. To examine quarterly trend for population-based (i.e., all unique ASI-MV assessments) prevalence of past 30-day abuse and source of drug among ER/LA opioid abusers across all quarters of the study period.

Table 2. Summary of numerators, denominators and time period comparisons for analyses corresponding to study objectives

Objectives	Comparisons
Primary objective	
1. To estimate changes in population-based prevalence of abuse among all ASI-MV assessments of ER/LA products as a group across pre-REMS (baseline), REMS implementation (time 1) and continuing active REMS phase (time 2).	• Pre-REMS compared to implementation • Pre-REMS compared to active period • Denominator: 1. Per 100 unique patient ASI-MV assessments • Numerator: number of reports of past 30-day abuse of at least one compound within target category: **ER/LA opioids***
Secondary Objectives	
1. To estimate changes in population-based abuse prevalence at the compound (or subgroup)-level for the ER/LA opioid group across baseline (pre-REMS), time1 (REMS implementation) and time 2 (continuing active REMS phase).	• Pre-REMS compared to implementation • Pre-REMS compared to active period • Denominator: 1. Per 100 unique patient ASI-MV assessments • Numerator: number of reports of past 30-day abuse of at least one compound within each category: **ER/LA compound/subgroup level****
2. To compare changes in estimates of population-based abuse prevalence of ER/LA products as a group with IR opioids as a group across baseline (pre-REMS), time1 (REMS implementation) and time 2 (continuing active REMS phase).	• Pre-REMS compared to implementation • Pre-REMS compared to active period • Denominator: 1. Per 100 unique patient ASI-MV assessments • Numerator: number of reports of past 30-day abuse of at least one product within the category: 1. **ER/LA opioids*** 2. **IR opioids as a group****
3. To compare changes in estimates of population-based abuse prevalence of ER/LA products as a group with benzodiazepines (as captured by the ASI-MV) as a group across baseline (pre-REMS), time1 (REMS implementation) and time 2 (continuing active REMS phase).	• Pre-REMS compared to implementation • Pre-REMS compared to active period • Denominator: 1. Per 100 unique patient ASI-MV assessments • Numerator: number of reports of past 30-day abuse of at least one product within the category: 1. **ER/LA opioids*** 2. **Benzodiazepines**
Tertiary objectives	
1. To examine changes in the proportion of the source of drug for ER/LA prescription opioids as a group and at the compound (or subgroup) level across baseline (pre-REMS), time1 (REMS implementation) and time 2 (continuing active REMS phase).	• Pre-REMS compared to implementation • Pre-REMS compared to active period • Denominator(s): 1. Per 100 abusers of ER/LA opioids 2. Per 100 abusers of compound/subgroup of interest • Numerator: Number of reports of source of procurement category for†: **1. ER/LA opioids*** **2. Compound/subgroup level****

Objectives	Comparisons
2. Quarterly trend analyses for population-based (i.e., all unique ASI-MV assessments) prevalence of past 30-day abuse and source of drug among ER/LA opioid abusers across all quarters between July 2010 and December	• Quarterly • Denominator(s): (For ER/LA opioids) Per 100 unique patient ASI-MV assessments (For source) Per 100 abusers of the compound group of interest • Numerator: 1. Number of reports of past 30- day abuse of at least one compound within category: **a. ER/LA opioids*** **b. Compound/subgroup level**** 2. Number of reports of source of procurement for category:† **a. ER/LA opioids***

* Numerator is count of past 30-day abuse for individuals who reported abuse of any (at least one) product defined within the ER/LA opioid group. See Section 6.4 for detail on this definition.

** Numerator is count of past 30-day abuse for individuals who reported abuse of any (at least one) product defined within the comparator opioid group. See Section 6.4 for detail on this definition

† Numerator is source of procurement and denominator is those who indicated abuse of target group of interest (i.e., ER/LA opioid group, ER/LA compound/sub-group). See Section 6.4 for detail on source of procurement categories.

4. DATA SOURCE

NAVIPPRO®

NAVIPPRO is a scientifically-developed, comprehensive, risk management program for prescription opioids, stimulants, and other Schedule II or III therapeutic agents. NAVIPPRO was developed with extensive support from the National Institutes of Health (NIH) and the National Institute on Drug Abuse (NIDA) as well as industry sponsorship. Designed for incorporation into pharmaceutical risk management and REMS programs, the NAVIPPRO system provides real-time, product-specific surveillance information from both proprietary and public data sources in order to monitor emerging trends in substance abuse from various populations. NAVIPPRO also includes proven prevention and intervention-based educational programs that supplement NAVIPPRO's surveillance component to provide a complete and sophisticated risk management solution for pharmaceutical firms in need of a scientifically-based and comprehensive system for monitoring prescription drug use nationwide.

ASI-MV®

The ASI-MV is a proprietary data stream of the NAVIPPRO system that collects data through a computerized interview on substances used and abused by individuals in treatment for substance use disorders. Data are collected from adults within a network of substance abuse treatment centers and other assessment settings using a self-administered and structured computerized interview. The preliminary data cut for the REMS metric Year One study contains assessments from 41 states (including Washington D.C.) in the United States. This computerized version of the ASI interview was built upon a modified version of the Addiction Severity Index (ASI), which is a standard intake assessment designed for use on admission to drug and alcohol

treatment [2] and has demonstrated reliability and validity [3 4]. The assessment asks questions related to patient demographics and drug-abuse experiences.

Specifically, the ASI is a structured clinical interview used to measure the severity of a range of problem areas typically associated with drug and alcohol abuse. The ASI-MV collects individual-level data across a series of domain areas, including medical, employment/support status, alcohol/drug use, legal, family/social status, and psychiatric status and includes product-specific questions on use and abuse of prescription medications. The ASI-MV has demonstrated good reliability (test-retest) along with discriminant validity, tested against other scales measuring the same domains, and criterion validity, tested against the standard, interviewer-administration of the ASI for both English and Spanish [5 6 7].

The ASI-MV assessment captures product-specific data related to past 30 day use and abuse for over 60 brand and generic prescription opioid products, including information on routes of administration used and sources of procurement for each product. Using the decision tree logic that allows the ASI-MV to simulate an interviewer, appropriate respondents are guided to questions about use of pharmaceutical substances using screens with names (trade, generic, and slang names) and pictures of the pharmaceutical products (as an example, see Figure 1 for ASI-MV and Figure 3 for CHAT). Using a mouse, the respondent clicks on the picture(s) of drugs he or she has used, which registers the product-specific data. A pilot test (N = 31 clients) achieved good agreement between the electronic presentation of these questions and an interview (average ICC = .70 and average Kappa = .65). When ICCs and Kappas were low, this was generally due to a low number of respondents directed to this question or the distribution of responses. Exact agreement also was calculated, with an average percent agreement = 93%.

Respondents who are guided to questions about use and abuse of pharmaceutical substances are presented follow-up questions that make specific inquiries for each product on routes of administration and sources of procurement (as an example, see Figure 2 for ASI-MV and Figure 4 for CHAT). When a respondent has completed the assessment locally at the treatment site, individual-level data are de-identified and electronically uploaded to a central server where they are available for analysis (Butler, Budman, et al., 2008). Data are uploaded from the ASI-MV network of sites around the United States in near real-time allowing for timely analysis. These data comprise the dataset upon which the analyses will be conducted. The ASI-MV was developed with support from the National Institute on Drug Abuse (NIDA) (Grant Nos. DA009938, DA013316, DA013848, and DA019716, Principal Investigator: Stephen Butler, PhD) as well as pharmaceutical industry support.

Figure 1. ASI-MV screen for morphine extended-release products

Figure 2. KADIAN source screen in ASI-MV

CHAT®

The Comprehensive Health Assessment for Teens (CHAT) is a computerized behavioral health assessment targeted to adolescents age 18 and younger entering treatment for drug or alcohol abuse. Questions included in the assessment are related to adolescent experiences in five domain areas: self and personality factors, family and peer relations, physical and emotional health, psychological issues, and drug use experiences. CHAT was developed with support from the National Institutes of Health (NIH) and the National Institute on Drug Abuse (NIDA) and has demonstrated validity and reliability as an assessment tool for adolescents in the treatment setting [9].

The CHAT network of participating sites comprises treatment centers and other facilities, such as alternative schools and mental health programs. The assessment collects data on abuse of prescription medications at a product-specific level, including photographs of brand and generic medications and their street names, routes of administration, and sources of procurement. Similar to the ASI-MV, CHAT collects data on the use and abuse of opioids, as well as psychosocial factors related to substance abuse that are specific to this younger population. Also like the ASI-MV, data related to route(s) of administration, source for obtaining the products and geographic location are collected. CHAT monitors the same prescription medications tracked by ASI-MV and began data collection and surveillance in June 2009.

Figure 3. CHAT screen for morphine extended-release products

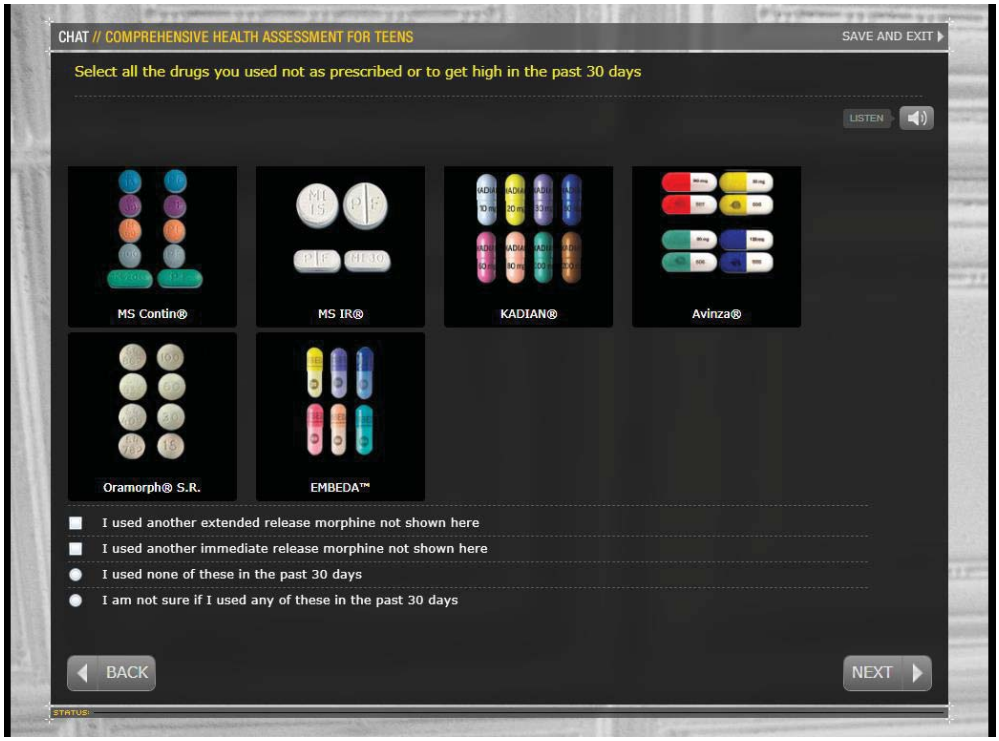
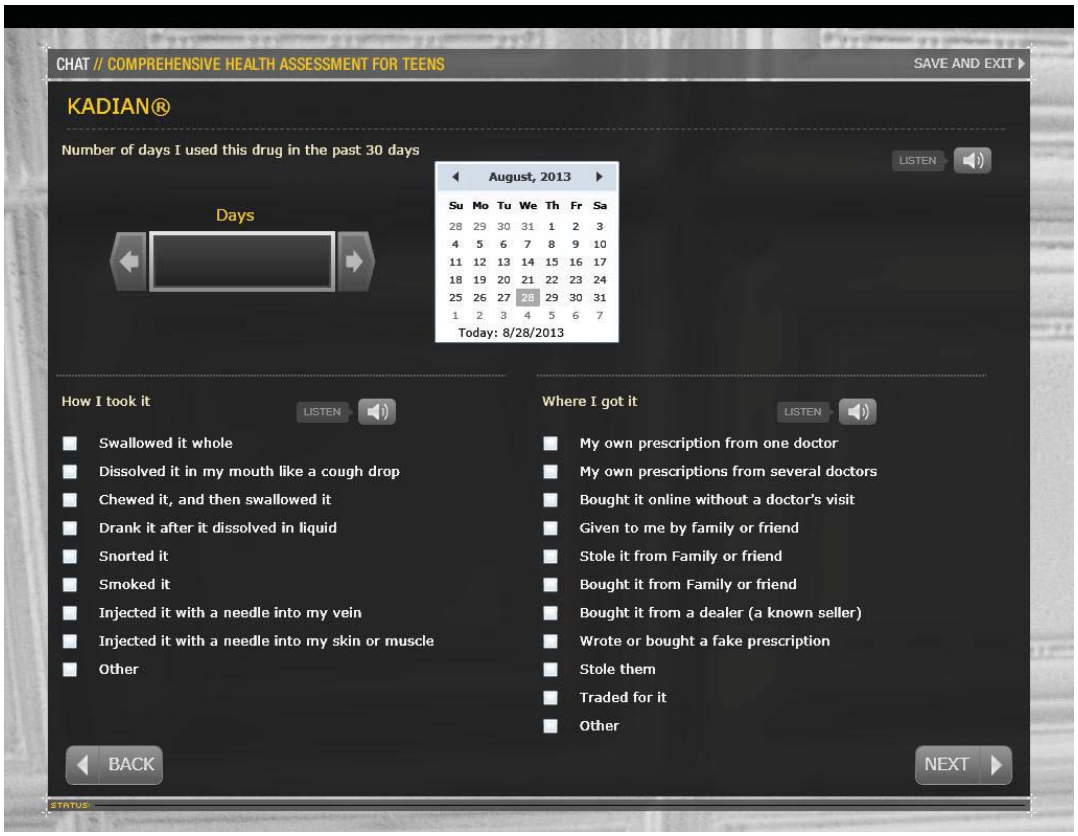


Figure 4. KADIAN source screen for CHAT



5. DATA MANAGEMENT

All procedures and systems regarding data management and electronic data handling for the ASI-MV conform to the Good Clinical Practices guidelines and the FDA Guidance for Industry: Computerized Systems Used in Clinical Trials. ASI-MV and CHAT are similar data collection systems, and data management issues are exactly the same. As previously stated, the ASI-MV and CHAT interview software collects data from individuals as part of the ongoing clinical assessment procedures conducted upon intake at participating sites. Self-reported, individual patient data on drug abuse and other interview question responses are recorded electronically via the ASI-MV interview software program. Once the interview is completed, data transfer over the Internet between the participating facility and Inflexxion are secured, encrypted, and comply with the industry security standards. The data are electronically transmitted from the local source computer at the participating substance abuse treatment site to Inflexxion via automatic upload using a secured Internet connection. The original, raw patient level data are encrypted and stored in a centralized and secured master database at an Inflexxion collocation.

Upon upload, the original patient data collected during the ASI-MV and CHAT interviews are cleaned of any individual-level identifying information (personal health information or PHI) and are assigned a unique identifier, creating a HIPAA compliant patient-level data set (see section below Human Subjects Considerations for further details). With the exception of removal of individual PHI, the original, raw individual-level interview data are not altered or changed upon transmission to the master database.

A data warehousing solution is in place to be used for data analysis and reporting. This model has been designed according to the HIPPA Privacy Rule standards to de-identify all Personal/Protected Health Information (PHI). The data warehousing solution stores the assessment data in a format that can be easily accessed by several analytic tools and data consumers.

Data warehousing of the master database for the ASI-MV and CHAT includes business intelligence tools to extract, transform and load (ETL) data from the secured original data file to a target Data Repository. Standard and pre-defined ETL processes are used to transform the original, raw data from the master data base to standard columns and rows in tabular format in the Data Repository. The Data Repository electronically stores the patient-level data in a tabular format that facilitates reporting and analyses.

A subset of data with interview dates within the range of the defined study period are queried from the Data Repository and downloaded for export to standard statistical and analysis software (i.e., SAS or SPSS) where the data are further cleaned and prepared for analysis. Specifically, the downloaded data file containing variable defined columns for all question responses and individual level rows are exported to standard statistical software applications (i.e., SAS) to subset the data by appropriate required parameters, which includes, for example, date range and selected study variables of interest.

A data manager prepares the subset data by running the data through a standard syntax programming file that labels the data, performs initial transformations and creates composite abuse variables for the drug categories of interest to the study to create a final analytic dataset. Data cleaning and preparation occurs in a stepwise cumulative fashion that creates sequential datasets. Programming syntax and logs are maintained to document all data manipulations and transformations used to create a final dataset for analysis. All subset data files are stored under password protected network locations with access for authorized researchers.

6. METHODS

To address the primary, secondary and tertiary objectives of this study, analyses will be examined among adults being assessed for substance abuse problems and treatment planning within a network of sites administering the ASI-MV located in the United States.

Note that the following sections regarding methods will focus on adults, aged 18 and older being assessed for substance abuse problems and treatment planning within a network of sites administering the ASI-MV located in the United States. CHAT data are provided from clinical sites that use the system for adolescent assessments. Although the CHAT network continues to grow with the addition of new sites over time, this dataset yields a small sample size. Thus, analyses for CHAT data will be descriptive for this study.

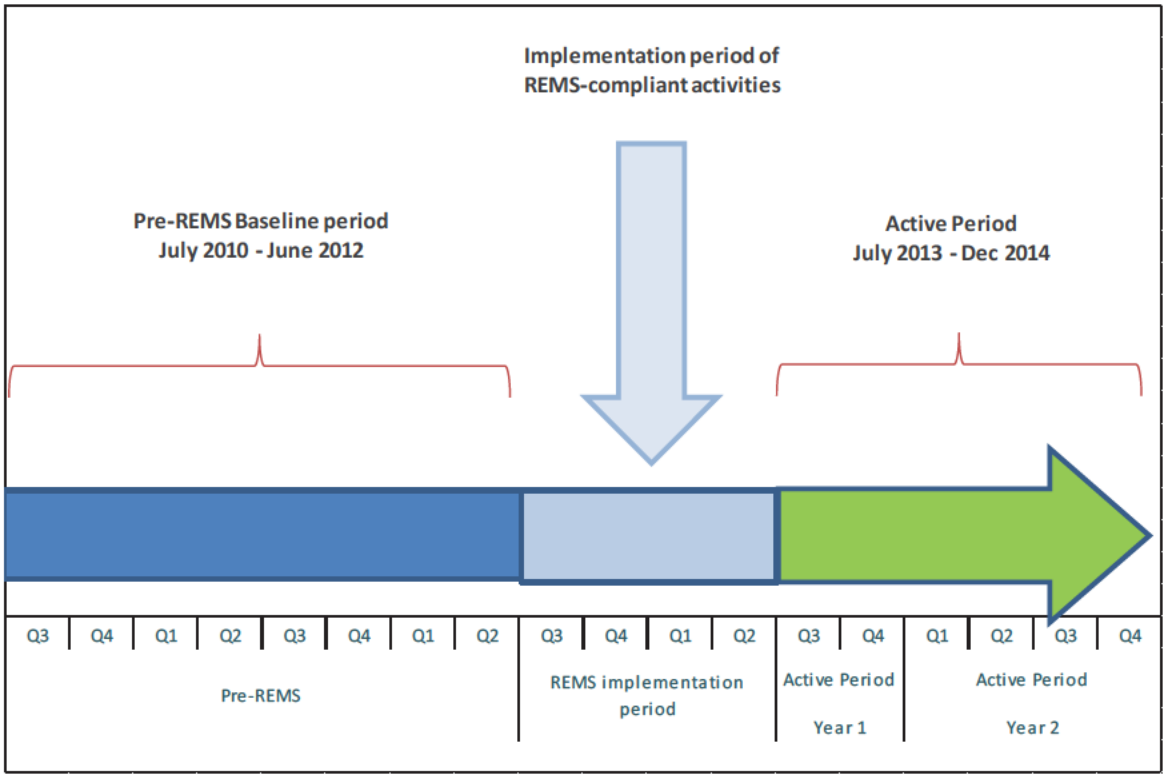
6.1. Study Design

This study can be described as a cross-sectional, observational surveillance study that measures patterns of abuse of ER/LA opioid analgesics over time using data collected by the NAVIPPRO ASI-MV system, which represents a sample of adults assessed for substance abuse treatment within a network of sites administering the Addiction Severity Index Multimedia Version (ASI-MV) located in the United States. The following timeframe definitions will be used to evaluate changes in patterns of abuse, as outlined in the study protocol objectives:

- Pre-REMS implementation period: July 2010 – June 2012
- REMS implementation period: July 2012 – June 2013
- Active Period: July 2013 – December 2013

The primary analyses for this Year One study will compare the prevalence, among all unique ASI-MV respondents, of past 30-day abuse (by any route of administration) for ER/LA opioids as a group during each study time period phase, with the pre-REMS implementation period as the referent category. That is, study outcomes (i.e., past 30-day abuse and source of procurement) will be analyzed during the active period (July 2013 – December 2013) in relation to the pre-REMS implementation period (July 2010 – June 2012) and the REMS implementation period (July 2012 – June 2013) (See Figure 5 for study time periods).

Figure 5. Proposed study timeline



Secondary analyses will examine a number of questions, including past-30-day abuse rates of the ER/LA prescription opioid compounds/subgroups as well as comparisons of the ER/LA opioid group as a whole with IR prescription opioids as a group and benzodiazepines (as captured by the ASI-MV), using the same study time period comparisons as the primary objectives. The compound/subgroup-specific analyses are intended to provide additional context and understanding of changes in past 30-day abuse within the larger ER/LA opioid group over the study time period phases. Tertiary analyses will explore source of procurement of ER/LA prescription opioids as a group and at the compound level to examine any changes in the proportion of the source reported by individuals assessed by the ASI-MV indicating past 30-day abuse of the target opioid group, ER/LA opioids, overall and by compound. An additional tertiary objective is to examine quarterly trends of abuse of ER/LA opioids as a group and at the compound/subgroup level across the study period (i.e., for Year One: July 1, 2010 through December 31, 2013) as well as quarterly trends of source of procurement for ER/LA opioids as a group.

Methodological details regarding all analyses that will be performed to address the primary, secondary and tertiary objectives are provided under the Data Analytic section (section 6.6). The definitions for ER/LA opioids as a group, compound/subgroup ER/LA opioids, IR opioids, benzodiazepines, and specific source categories are delineated in the outcomes variables section of the methods (section 6.4. Outcome Variables). Note that source data are not collected for the combined category containing benzodiazepines (sedatives, tranquilizers, and sleeping pills). Study denominators used for analyses are described in section 6.4.

6.2. Analytic Sample

In regard to file selection criteria for ASI-MV analyses within this study protocol, the study sample will include unique individuals age 18 and over. Duplicate cases will be defined as individuals who had taken an ASI-MV assessment more than once. The ASI-MV contains a HIPAA-compliant unique identifier that allows de-identified tracking of individuals who take the ASI-MV assessment multiple times. Clinically, it can difficult to determine whether a subsequent assessment is the result of a referral to a different level of care, a follow-up assessment for someone still in treatment or other recovery program, or a readmission due to a relapse. While no method completely eliminates these potential confounds, we elected to retain the first assessment of a single patient. Each individual patient represents a unique case line for all analyses. Duplicate cases and those who indicate use of the "fake" drug selection in the ASI-MV will be removed from all analyses.

The ASI-MV is a dynamic system where new sites are added to the network on a regular basis and some attrition or reduction in the number of participating sites exists over time. Data from all ASI-MV sites contributing assessments at any given time throughout this timeframe will provide the data for all study analyses. While data from all ASI-MV sites will be used for all study analyses, a sensitivity analysis will be performed to evaluate any potential impact of geographical variation in the ASI-MV network on abuse estimates for primary study objectives. This sensitivity analysis evaluation will involve the following steps:

1. First, analyses corresponding to the primary study objective will be run on all data after the initial selection criteria has been performed (i.e., criteria regarding age, duplicate cases and reports of the "fake" drug).
2. Secondly, primary analyses will be conducted among a sample of ASI-MV assessments with an additional sample selection criterion for geographic consistency (referred to as "common patient home 3-digit ZIP codes"). The study sample based on common patient home 3-digit ZIP codes will represent ASI-MV assessments submitted from 3-digit ZIP codes that contributed any data (i.e., at least one assessment) to the sample during each phase of the study period (i.e., Pre-REMS implementation period: July 2010 – June 2012; REMS implementation period: July 2012 – June 2013; and the Active Period: July 2013 – December 2013).
3. Results for primary analyses conducted among all data will be compared to results for primary analyses conducted among the common patient 3-digit ZIP code sample. In the event that differences in abuse estimates are similar, remaining analyses will be performed based on all possible data.

A second sensitivity analysis will examine the proportion of individuals reporting past 30-day abuse of any prescription opioid (IR, ER, LA) on the ASI-MV assessment across pre-REMS (baseline), REMS implementation (time 1) and continuing active REMS phase (time 2). The purpose of this sensitivity analysis will be to determine the extent to which the subpopulation of prescription opioid abusers (i.e., any respondent that reports abuse of any prescription opioid) changes across the time periods. Minor changes in abuse would suggest that specific analyses on this subpopulation would not add appreciably to the interpretation of findings intended to reflect on the impact of the REMS program.

6.3. ASI-MV and CHAT Populations

General Characteristics of ASI-MV Database Population

For the current timeframe (July 1, 2010 through December 31, 2013), the ASI-MV database contains a total of 236,598 assessments of patients aged 18 and older (prior to removal of excluded cases). The ASI-MV population includes male and female adults entering substance abuse treatment within a network of participating substance abuse centers located in 41 states. New sites continue to be regularly recruited and added to the network. As shown in Table 3, the ASI-MV population is composed of approximately 64% males and 36% females. Over half of the patient population is Caucasian (58%), approximately 17% is Hispanic/Latino, and 18% is African-American. Of all patients in this ASI-MV dataset, 21.3% (n = 50,109) report past 30-day abuse of any prescription opioid.

Demographic characteristics of the ASI-MV population can be compared with the demographics of the population captured by the Treatment Episode Dataset (TEDS), maintained by SAMHSA, and the United States general population for comparison. Although it is possible to compare the demographic characteristics of the ASI-MV sample in this study to those of the U.S. population, it is not clear that it would be informative beyond a general differentiation between the United States population and the substance abusing clinical population. It is important to note that data collected via the ASI-MV do not necessarily relate to incidence, prevalence, or to increases or decreases in trends of abuse in the general population, including those who abuse but do not seek treatment. A more appropriate comparison would be to the characteristics of those entering treatment in the United States such as in the TEDS. While the TEDS does not represent the total national demand for treatment, it comprises a significant proportion of all admissions to substance abuse treatment as it includes admissions to state-licensed or certified substance abuse treatment centers that receive federal public funding [10]. Specifically, treatment centers within the NAVIPPRO system are not randomly recruited to join the network, therefore; results of the analyses conducted on the patient data collected from these treatment centers may not be generalizable to all patients in substance abuse treatment in the U.S.

As seen in Table 4, the demographic characteristics of patients within the ASI-MV population are comparable to the demographic characteristics of patients sampled in TEDS for 2010 and the latest year for which TEDS data are available, 2011. The two populations are similar with respect to gender, age, and educational characteristics with some noted differences in the racial and employment characteristics between the two populations. The ASI-MV population has a larger proportion of Hispanic individuals as compared to the TEDS population (approximately 19% versus about 13% in 2010 and 2011), whereas the TEDS population has a much larger percentage of individuals who are unemployed (approximately 40%) compared to the ASI-MV population, where about 18 - 19% of individuals report being unemployed. Observed differences in the employment characteristics of the two populations may be related to the fact that the ASI-MV collects data from both private and publicly funded substance abuse treatment centers whereas the TEDS dataset includes only admissions from treatment centers supported by public funds.

Table 3. ASI-MV participant characteristics for 7/1/2010 - 12/31/2013

		All respondents (N = 236,598)		Respondents reporting any past 30-day Rx opioid abuse (n = 50,337)	
Characteristics	**Response**	**n**	**%**	**n**	**%**
Age	Under 24 years	56,670	24.0	12,964	25.8
	25 – 34 years	82,394	34.8	20,090	39.9
	35 – 44 years	49,035	20.7	9,481	18.8
	45 – 54 years	36,139	15.3	6,038	12.0
	55 + years	12,360	5.2	1,764	3.5
Gender	Male	151,385	64.0	26,705	53.1
	Female	85,205	36.0	23,632	46.9
	Missing	8	< 1.0	0	0
Race	Caucasian	138,025	58.3	36,177	71.9
	African American	43,574	18.4	5,391	10.7
	Hispanic/Latino	40,210	17.0	6,789	13.5
	American Indian/Alaskan Native	13,070	5.5	1,697	3.4
	Asian/Pacific Islander	1,713	<1.0	2,821	<1.0
	Unknown/no response	6	<1.0	1	<1.0
Marital status	Married	45,412	19.2	10,056	20.0
	Separated, divorced, widowed	55,672	23.5	11,621	23.1
	Never married	134,957	57.0	28,523	56.7
	Unknown/no response	557	< 1.0	137	<1.0
Employment	Professional	24,594	10.4	5,020	10.0
	Administrative, clerical, sales	30,486	12.9	7,063	14.0
	Skilled or semi-skilled	72,472	30.6	13,849	27.5
	Other manual/unskilled	23,666	10.0	4,911	9.8
	Student	11,548	4.9	2,075	4.1
	Homemaker	11,116	4.7	3,254	6.5
	Did not work for pay in last 3 years	16,928	7.2	3,902	7.8
	Disabled	14,451	6.1	3,892	7.7
	No occupation	30,368	12.8	6,129	12.2
	Unknown/no response	969	< 1.0	242	< 1.0
Criminal justice-required substance abuse treatment*	No	94,564	40.0	30,810	61.2
	Yes	141,553	59.8	19,403	38.5
	Unknown/no response	481	< 1.0	124	<1.0
Chronic medical problem	No	164,612	69.6	29,788	59.2
	Yes	71,450	30.2	20,415	40.6
	Unknown/no response	536	< 1.0	134	< 1.0
Self-reported pain problem	No	158,743	67.1	25,590	50.8
	Yes	77,453	32.7	24,653	49.0
	Unknown/no response	402	< 1.0	94	< 1.0

* "Substance abuse treatment prompted by the criminal justice system" indicates that admission to substance abuse treatment was required or encouraged of the individual by a judge, probation or parole officer, or other criminal justice official.

Table 4. Demographic Characteristics of ASI-MV and Treatment Episode Data Set

		TEDS (2010)	ASI-MV (2010)	TEDS (2011)	ASI-MV (2011)
Characteristics	**Response**	**%**	**%**	**%**	**%**
Age	18-24 years	20.9	25.3	20.2	24.7
	25-34 years	30.1	32.6	30.9	34.1
	35-44 years	22.9	20.8	22.0	20.5
	45-54 years	19.9	15.7	20.1	15.5
	55+ years	6.2	5.0	6.8	5.3
Gender	Male	67.3	64.2	66.4	64.3
	Female	32.7	35.7	33.5	35.7
Race	White	61.4	55.0	61.8	56.2
	African American	20.3	19.7	19.8	18.9
	Hispanic	12.8	19.1	12.7	18.7
	Native American	2.5	5.4	2.4	5.5
	Asian/Pacific Islander	0.1	0.7	.1	.7
	Other/unknown	2.1	0.2	3.2	0
Education Level	Less than High School	31.4	29.5	29.0	28.3
	High School	41.1	41.3	43.8	41.8
	Some College	19.2	23.3	19.9	23.9
	College Degree	5.0	5.6	5.4	5.9
Employment	Full Time	15.6	39.4	15.0	37.3
	Part Time	7.7	21.3	7.3	21.1
	Unemployed	40.4	17.6	40.6	18.8
	Not Working	34.9	21.7	34.4	22.5

Substance Abuse and Mental Health Services Administration (SAMHSA) (2008). Treatment Episode Data Set -- Admissions (TEDS-A), 2010, 2011[Computer file]

General Characteristics of CHAT Database Population

For the current study timeframe (July 1, 2010 through December 31, 2013), a preliminary cut of the CHAT dataset yields 8,825 adolescents who have taken a CHAT assessment. As shown in Table 5, the majority of adolescent respondents were 15 to 18 years of age (79.3%), male (69.1%), and Caucasian (68.4%). Approximately 80% reported usually living with one or both of their biological or adoptive parents. Additionally, the majority of adolescents completing a CHAT assessment indicated current enrollment in school (83.9%), and public school was reported most frequently as the type of school program (61.1%). Thirty-one percent of adolescent respondents reported that they were currently taking a prescribed medication for an emotional, behavioral, or learning problem. A current physical problem or illness was indicated by 27.9%, and 19.4% reported a pain problem.

During the study timeframe, 768 (8.7% of all adolescents assessed by CHAT) indicated having abused a prescription opioid within the past 30-days. Demographically, the sub-population of adolescent prescription opioid abusers was similar to the CHAT network as a whole in that the majority was Caucasian (84.9%), male (59.6%), and between 15 to 18 years of age (86.2%). However, compared with the overall CHAT network, a greater percentage of adolescent respondents who indicated past 30-day prescription opioid abuse were female (40.4% versus 30.9%) and Caucasian (84.9% versus 68.4%). In terms of other participant characteristics, prescription opioid abusers within the CHAT network more frequently indicated a self-reported pain problem (31.6%) as compared to all adolescent assessed by the CHAT (19.4%). Tables 5 and 6 detail the participant characteristics of adolescent respondents within the CHAT network sites during the study timeframe for Year One (July 1, 2010 through December 31, 2013).

Table 5. CHAT participant characteristics (7/1/2010 - 12/31/2013)

	Response	All respondents (N = 8,825)		Respondents reporting past 30-day Rx opioid abuse (n = 768)	
		n	%	n	%
Age	Age distribution				
	Under 10 years	14	< 1.0	0	0.0
	10 - 14 years	1,760	19.9	101	13.2
	15 - 18 years	6,997	79.3	662	86.2
	Over 18 years	53	< 1.0	5	< 1.0
	Unknown/no response	1	< 1.0	0	0.0
Gender	Male	6,095	69.1	458	59.6
	Female	2,728	30.9	310	40.4
	Unknown/no response	1	< 1.0	0	0.0
Race (not mutually exclusive)	Caucasian	6,039	68.4	652	84.9
	African American	1,673	19.0	48	6.3
	American Indian/Alaskan Native	538	6.1	31	4.0
	Asian	110	1.2	8	1.0
	Pacific Islander/Native Hawaiian	45	< 1.0	3	< 1.0
	Hispanic/Latino	1,143	13.0	66	8.6
	Middle Eastern	20	< 1.0	0	0.0
	Other	395	4.5	33	4.3
	Unknown/no response	11	<1.0	1	< 1.0
Usual living situation	One or both biological or adoptive parents	7,081	79.5	608	79.2
	Other relatives	510	5.8	42	5.5
	Legal guardian	505	5.7	46	6.0
	Friends	91	1.0	18	2.3
	Partner or spouse	42	< 1.0	8	1.0
	Foster family	273	3.1	19	2.5
	Alone	22	< 1.0	2	< 1.0
	Other	357	4.0	24	3.1
	Unknown/no response	5	< 1.0	1	< 1.0
Currently enrolled in school	Yes	7,402	83.9	604	78.6
	No	1,422	16.1	164	21.4
	Unknown/no response	1	< 1.0	0	0.0
School program	Public school	5,390	61.1	435	56.6
	Private school	138	1.6	10	1.3
	GED program	199	2.3	23	3.0
	Alternative school or program	1,134	12.8	87	11.3
	Home school	164	1.9	10	1.3
	Technical, trade/beauty, vocational school	57	< 1.0	4	< 1.0
	Treatment or detention center school	162	1.8	21	2.7
	College	64	< 1.0	8	1.0
	Other	89	1.0	5	< 1.0
	Unknown/no response	5	< 1.0	1	< 1.0
	Not asked/not enrolled in school	1,422	16.1	164	21.4

Table 6. Additional CHAT participant characteristics (7/1/2010 - 12/31/2013)

	Response	All respondents (N =8,825)		Respondents reporting past 30-day Rx opioid abuse (n = 768)	
		n	%	n	%
Past 30 days in a controlled environment (jail, substance abuse treatment, etc.)	Yes No Unknown/no response	2,934 5,884 7	33.2 66.7 < 1.0	353 415 0	46.0 54.0 0.0
Currently taking medication for emotional, behavioral, or learning problems.	Yes No Unknown/no response	2,712 6,087 26	30.7 69.0 < 1.0	321 446 1	41.8 58.1 < 1.0
Current physical problems or illnesses	Yes No Unknown/no response	2,460 6,365 0	27.9 72.1 0.0	238 530 0	31.0 69.0 0.0
Current pain problem	Yes No Unknown/no response	1,712 7,094 19	19.4 80.4 < 1.0	243 524 1	31.6 68.2 < 1.0

ASI-MV Site Characteristics and Geographic Representation

As noted, the ASI-MV network collects data from adult patients entering substance abuse treatment throughout the United States. The data are collected from a convenience sample of 756 public and privately funded substance abuse treatment centers located throughout the country in 41 states (Figure 6) and is intended as a sentinel surveillance system. The ASI-MV draws patients from 821 3-digit ZIP codes (Figure 7). The data set is not nationally representative and thus is not intended to be used for estimating national incidence and prevalence rates. As a sentinel population of patients entering treatment for substance abuse, the ASI-MV offers the opportunity to observe patterns and trends in abuse of prescription opioids and other drugs among this population.

It should be noted that the network of treatment sites contained within the ASI-MV system continues to grow, with new participating sites added as time goes on. Although one advantage in this system is that an increase in participating sites allows for more complete geographic coverage, change in participating sites over time presents important challenges since prescription opioid abuse patterns can vary geographically [11]. Thus new sites may represent new geographic areas with different patterns of prescription opioid abuse than sites currently providing data in the database. For the purposes of the present protocol, data for ER/LA opioids and comparators are captured concurrently at any time throughout the time period under investigation.

Figure 6. Location of assessment sites within the ASI-MV Network (7/1/2010 – 12/31/2013)

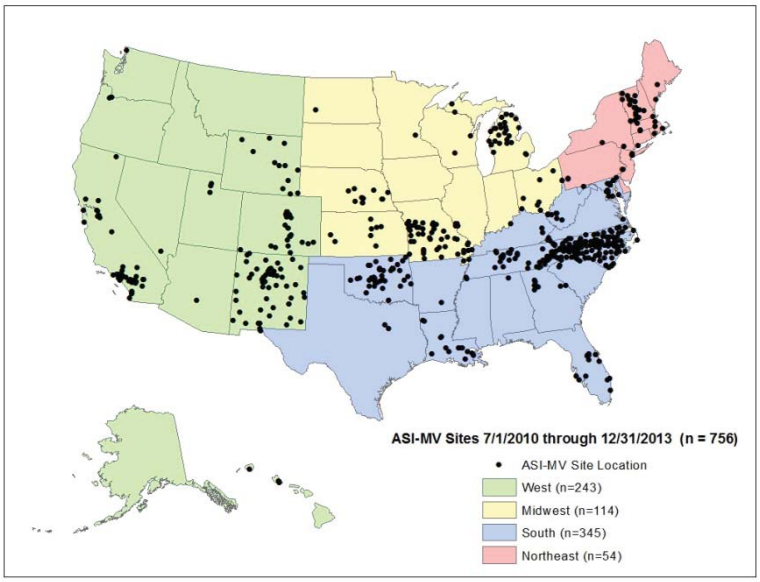
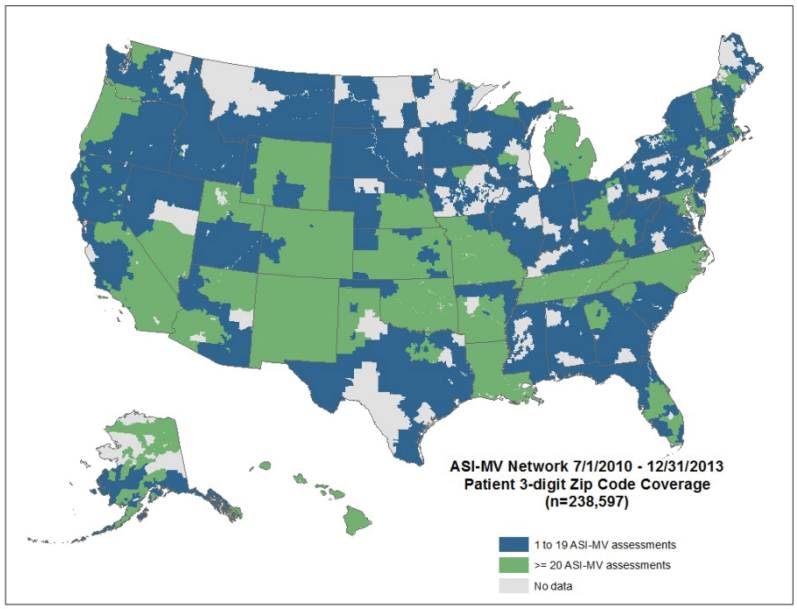


Figure 7. Distribution of assessments by patient 3-digit ZIP code (7/1/2010 – 12/31/2013)



Data collection and surveillance using CHAT began in June 2009 from a limited number of participating adolescent sites. As noted previously, results presented regarding CHAT will be descriptive in nature. This section focuses on the site characteristics and geographic distribution of the ASI-MV network, which provides additional context regarding the analytic study sample, described in section 6.2.

Data Collection Frequency

Data are collected at participating substance abuse treatment centers and assessment locations each time a new patient is admitted for treatment. The data from each individual patient assessment are uploaded in near real-time to a central data center, allowing clinicians from each treatment site to view his or her aggregated patient data in order to detect patterns of drug abuse among their patient population. Note that aggregate, product-specific data are not made available to treatment center personnel. Inflexxion is able to access aggregate, de-identified patient data from all treatment sites via the data center to perform surveillance and analyses. The majority of assessments from sites within the network (85%) are uploaded and available for analysis within the same day. Nearly 90% of all assessments are uploaded within one day with over 95% uploaded within two weeks.

Type of Data Captured

- Demographics
- Geospatial: facility 5-digit ZIP code and patient home 3-digit ZIP code
- Clinical: past 30-day and lifetime substance abuse, substance abuse treatment history, medical information (chronic medical problems, pain problems), psychological information (depression, anxiety, use of prescribed psychiatric medications, etc.), emotional/physical/sexual abuse history
- Health outcome: scores related to severity of alcohol use, drug use, family environment, legal problems, employment problems, and mental health
- Product-specific prescription opioid and prescription stimulant information: past 30-day abuse, number of days abused in the past 30 days, route of administration, and source of procurement.

6.4. Outcome Variables

The primary outcome variables to be used in the analyses in this study are past 30-day abuse and source of procurement of the product.

6.4.1. ER/LA opioids as a group and comparator opioids

For all analyses, the target REMS category will include all extended-release/long-acting brand and generic versions of the opioid products specified by the RPC Metrics Subteam in the document, "Surveillance Monitoring Objectives: ER/LA Opioid Analgesics REMS." Specifically, the ER/LA group includes: extended-release, oral-dosage forms containing: hydrocodone[1], hydromorphone, morphine, oxycodone, oxymorphone, tapentadol, methadone tablets that are indicated for use as analgesics, and a combination of fentanyl and buprenorphine-containing transdermal delivery systems.

[3]Note: The first extended release hydrocodone product, Zohydro ER, received FDA approval in October 2013. As this product was not marketed during the timeframe of this Year One study, data and analyses for extended release hydrocodone will not be included until FDA Report 4.

Compound/subgroup analyses of ER/LA opioids will include:

ER/LA Compounds

- Morphine ER
- Oxymorphone ER
- Methadone

Composite subgroups of ER/LA prescription opioids

- Fentanyl and buprenorphine transdermal delivery systems
- Other ER opioid group (i.e., oxycodone ER, hydromorphone ER, tapentadol ER, and eventually hydrocodone ER)[2]

The specific ASI-MV products comprising the ER/LA opioids category are detailed below in Table 7.

[2] Note: For compound-level analyses, the compound(s) groups that contain a single opioid product will not be provided as an individual category but will be grouped together as other ER/LA opioids.

Table 7. Extended-release (ER)/long acting (LA) opioids

Compounds included in definition	ASI-MV and CHAT monitored products
Morphine ER	• AVINZA® • KADIAN® • MS Contin® • Generic/other morphine ER capsules/tablets
Oxymorphone ER	• Opana ER® • Reformulated Opana ER • Generic/other oxymorphone ER tablets
Methadone	• Methadone brand and generic tablets
Other ER opioid subgroup (i.e., oxycodone ER, hydromorphone ER, tapentadol ER, and hydrocodone ER, once available*)	• Oxycodone ER ○ OxyContin® original and (OC) ○ OxyContin® reformulated (OP) ○ Generic/other oxycodone ER • Hydromorphone ER ○ Exalgo® •Tapentadol ER ○ Nucynta ER® • Hydrocodone ER* ○ Zohydro ER®
Transdermal subgroup (i.e., fentanyl and buprenorphine-containing transdermal delivery systems)	• Duragesic® • Butrans® • Fentanyl patch • Generic/other fentanyl transdermal

* Note: The first extended release hydrocodone product, Zohydro ER, received FDA approval in October 2013. As this product was not marketed during the timeframe of this Year One study, data and analyses for extended release hydrocodone will not be necessary until FDA Report 4.

As a natural corollary to primary analyses which evaluate ER/LA opioids as a group, secondary analyses will compare ER/LA opioids with immediate release (IR) products as a group. The immediate release (IR) category will include immediate release versions of hydromorphone, hydrocodone, morphine, oxymorphone, oxycodone, and tapentadol. A more detailed breakdown of each of the specific products monitored by the ASI-MV for this comparator opioid category is provided in Table 8. In addition, secondary analyses also compare ER/LA opioids and "benzodiazepines." Benzodiazepines represent another class of medications with abuse potential, and may help understand secular trends when evaluating changes in abuse patterns over time. Note that the ASI-MV and CHAT do not collect data for benzodiazepines as a single category. These products are grouped in a general category and will be provided as a combined category of "sedatives, tranquilizers and sleeping pills" (Table 8).

Table 8. Comparator opioids: Immediate-release (IR) oxycodone and benzodiazepines

Compounds included in definition	ASI-MV and CHAT monitored products*
Immediate release(IR) versions of the following: • Hydromorphone • Oxycodone • Morphine • Oxymorphone • Tapentadol • Hydrocodone • Fentanyl	• Dilaudid® • Roxicodone® • Percocet® • Percodan® • Combunox® • OxyIR® • Tylox® • Roxicet® • MSIR® • Opana® • Nucynta® • Lorcet® • Lortab® • Vicodin® • Vicoprofen® • Norco® • Actiq® • Fentora® • Onsolis® • Generic/other hydromorphone • Generic/other oxycodone IR • Generic/other immediate release oxymorphone not shown • Generic IR morphine • Generic/other hydrocodone
Benzodiazepines (As captured by the ASI-MV and CHAT**)	Benzodiazepines, sedatives, tranquilizers and sleeping pills.

*All products are tablets or capsule forms, with the exception of fentanyl products. Injectable versions are excluded.
**The ASI-MV and CHAT do not collect data for benzodiazepines as a single category. These products are grouped in a general category and will be provided as a combined category of sedatives, tranquilizers and sleeping pills.

A few caveats are noted for the comparator opioid products/compounds summarized in Tables 7 and 8. With regard to ER oxymorphone, the reformulated and original versions of Opana ER and generic formulations were each added to the system at various points in time. The ASI-MV interview was updated to include images of the reformulated Opana ER product in April 2012. Additionally, lower and higher dosage strength generic oxymorphone ER versions were added to the ASI-MV system in late 2012 and early

2013, respectively. Thus, ER oxymorphone will include original Opana ER from the baseline period through 2012 and will include Opana ER and generics when available in late 2012 and 2013 forward. In regard to the inclusion of the generic ER oxycodone category within the "other ER opioids" subgroup, note that, prior to the marketing of reformulated OxyContin (pre- REMS intervention period), the ASI-MV screen for ER oxycodone collected data specifically for abuse of original OxyContin, oxycodone ER (manufactured by Endo Pharmaceuticals), oxycodone ER (manufactured Teva Pharmaceuticals), and a category for "other extended-release oxycodone not shown". The first extended release hydrocodone product, Zohydro ER, received FDA approval in October 2013. As this product was not marketed during the timeframe of this Year One study, data and analyses for extended release hydrocodone will not be included until FDA Report 4.

6.4.2. Source of procurement

Tertiary objectives of this study examine source of procurement reported by individuals reporting past 30-day abuse of the ER/LA opioid group and comparator opioid groups. Table 9 presents the ASI-MV and CHAT response options for "source." These response options have been collapsed into four categories deemed relevant to the evaluation of the REMS intervention by the RPC Metric Subteam: own prescription, multiple doctors, family member or friend, and "other," as presented in Table 9.

Table 9. Source of procurement categories

Source of procurement response options available in the ASI-MV and CHAT	Study outcome category for source of procurement
My own prescription from one doctor	Own prescription
My own prescription from several doctors	Multiple doctors
Given to me by family or friend Stole it from family or friend Bought it from family or friend	Family member or friend
Bought it online without a doctor's visit Bought it from a dealer (a known seller) Wrote or bought a fake prescription Stole them Traded for it Other	Other

6.5. Study Denominators

The denominators used for analyses in this study include all unique individuals assessed for treatment by the ASI-MV during the study time period. The rationale for this denominator is that "all unique individuals assessed for treatment by the ASI-MV" is intended to represent the prevalence of past 30-day abuse for a given opioid product among the study sample (i.e., adults entering/assessed for substance abuse treatment). Every individual in this sensitive population of individuals at risk for substance abuse being evaluated by the ASI-MV is allowed the possibility of endorsing past 30-day abuse of any of the more than 60 brand and generic prescription products included in the ASI-MV. This study denominator was determined to provide the best available assessment of relative rates with which individuals evaluated for treatment self-report prescription opioid abuse.

Other denominators were considered and rejected. For example, we considered examination of reported abuse among the subset of individuals reporting abuse of any prescription opioid. While this denominator can be informative, it was determined by the RPC Metric Subteam that this would most likely not be informative in the present context. This is because the numerator (i.e., number of abuse cases) stays the same, so that modifying the denominator by a more-or-less constant (i.e., the proportion of those having abused any prescription opioid), the relative differences between periods would not be impacted. A sensitivity analysis of the prevalence of any prescription opioid abuse is proposed to examine this assumption.

Another important consideration often considered when comparing opioid products on abuse levels is prescribed availability; that is, the extent to which an opioid product is abused is partially dependent on its availability within the community which can be measured through a drug's prescription volume. Prescribed availability of prescription opioids has been shown to be positively related to measures of adverse consequences in the community, including emergency department mentions [12] and past 30-day abuse by individuals evaluated for substance use disorders [13]. Upon discussion with the RPC Metric Subteam, it was determined to exclude this denominator based on the expectation that implementation of the REMS intervention should result in decreased number of prescriptions dispensed. Inclusion of prescription-adjusted analyses in the present study runs the risk of confounding examination of the REMS impact.

Finally, it is important to note that possible threats to validity due to a variety of unaccounted for factors that may explain any differences observed (e.g., prescription drugs monitoring programs, adoption of universal precautions of opioids, etc.). For this reason, comparators are included in the analyses to evaluate and assess whether observed changes are specific to the target category, ER/LA opioids.

6.6. Data Analytic Strategy

The data analytic plan consists of primary, secondary, and tertiary analyses, which are described below in an outline format corresponding to the objectives. While this outline is repetitive in nature, it is intended to help the reader achieve full clarity with respect to the statistical models employed to address each of the objectives within each of the analytic phases. Each analytic approach is associated specifically with the particular study objective to which it applies. In some cases, the same model is appropriate for more than one objective. This is the case for objectives pertaining to the group-level analyses (e.g., ER/LA group, IR opioid group, benzodiazepine group). In other cases, more than one model is proposed for different aspects of a particular objective. All analyses will be conducted using the GLIMMIX procedure in SAS 9.3. The model along with SAS code is provided within each objective. Since each patient-respondent is asked about each prescription opioid during each assessment, there are multiple observations per respondent. These repeated measurements are permitted to be correlated through the residual component of the model which conforms to a GEE-type model.

Since the correlation among repeated measurements on the same subject is accounted for through the variance-covariance matrix in the residual effects (a.k.a. R-side random effects), it will not be shown in the equations presented below. This is because R-side random effects are fit outside of the link function and modeled directly (a.k.a. GEE-type models). The RANDOM _RESIDUAL_ subcommand of the GLIMMIX procedure accounts for within-subject correlation through the R-side random effects. Details regarding the use of the RANDOM _RESIDUAL_ statement to account for R-side random effects in the GLIMMIX procedure are available in the SAS User's Guide (http://support.sas.com/documentation/onlinedoc/stat/131/glimmix.pdf).

6.6.1. Analyses of change in odds of abuse over time

To estimate and compare changes in the odds of abuse between specific drug groups over time (Primary Objective 1, Secondary Objective 2, and Secondary Objective 3.)

A GEE-type logistic regression model will be employed to estimate changes in the odds of abuse for specific drug groups over time. In this model, the fixed effects include a drug-indicator variable (ER/LA product group, IR prescription opioids, and benzodiazepines), a phase indicator variable (pre-REMS phase, REMS implementation phase, and continuing active REMS phase), and the interaction between both effects. Both variables will be treated as categorical. The binary dependent variable is endorsement/no endorsement of abuse in the past 30 days for any of drugs comprising each level of the drug groups (see Tables 7 and 8).

MODEL:

$$abuse_{ij} \sim Bernoulli(\pi_{ij})$$

$$\eta_{ij} = \log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij}$$

where,

- $abuse_{ij}$ is a yes/no response to abuse of the i^{th} drug in the j^{th} phase
- π_{ij} is the probability of observing an abuse response for the i^{th} drug during the j^{th} phase
- $\log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right)$ is the logit link function of π_{ij}
- μ is the overall mean
- α_i is the fixed effect of the i^{th} drug
- β_j is the fixed effect of the j^{th} phase
- $(\alpha\beta)_{ij}$ is the interaction effect between the i^{th} drug and the j^{th} phase

SAS CODE:

```
PROC GLIMMIX DATA=<data file name>;
CLASS drug time subject;
MODEL abuse = drug|time / S LINK = LOGIT DIST = BIN;
RANDOM _RESIDUAL_ / SUBJECT = subject TYPE=CS;
RUN;
```

6.6.2. Analyses of change at the compound/subgroup level

To estimate and compare changes in the odds of abuse between compound/subgroup level groups over time (Secondary Objective 1)

A GEE-type logistic regression model will be employed to estimate and compare changes in the odds of abuse for compound/subgroup-level over time. In this model, the fixed effects include a compound-indicator variable (morphine ER, oxymorphone ER, methadone, transdermal fentanyl and buprenorphine, and the other ER opioid group), and a phase indicator variable (pre-REMS phase, REMS implementation phase, and continuing active REMS phase), and the interaction of both fixed effects. Both variables will be treated as categorical. The binary dependent variable is endorsement/no endorsement of abuse in the past 30 days for any of drugs comprising each level of the compound/subgroup-level groups.

MODEL:

$$abuse_{ij} \sim Bernoulli(\pi_{ij})$$

$$\eta_{ij} = \log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij}$$

where,

- $abuse_{ij}$ is a yes/no response to abuse of the i^{th} compound during the j^{th}
- π_{ij} is the probability of observing an abuse response for the i^{th} compound during the j^{th} phase
- $\log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right)$ is the logit link function of π_{ij}
- μ is the overall mean
- α_i is the fixed effect of the i^{th} compound
- β_j is the fixed effect of the j^{th} phase
- $(\alpha\beta)_{ij}$ is the interaction effect between the i^{th} compound during the j^{th} phase

SAS CODE:

```
PROC GLIMMIX DATA = <data file name>;

CLASS compound time subject;
MODEL abuse = compound|time / S LINK = LOGIT DIST = BIN;
RANDOM _RESIDUAL_ / SUBJECT = subject TYPE=CS;
RUN;
```

6.6.3. Analyses of source of procurement

For analyses of changes in source of procurement over time (Tertiary Objective 1), note that compound/subgroup level analyses are performed in a model separate from group-level (i.e., ER/LA opioids). As such, the description of each analysis is provided separately below.

6.6.3a. Estimate the changes in the source of procurement for ER/LA opioids as a group (Tertiary Objective 1)

Standard logistic regression models will be employed to estimate changes in the odds each source of procurement for those who abuse ER/LA opioids. In this model, the fixed effects include a categorical phase indicator variable (pre-REMS phase, REMS

implementation phase, and continuing active REMS phase). The binary dependent variable for each model is endorsement/no endorsement of each source of procurement in the past 30 days for ER/LA opioids as a group. Since there is only one measurement on each patient (self-report abuse of any ER/LA opioid) being used for this analysis, correlation among repeated measures is not being taken into account.

MODEL:

$$source\_abuse_i \sim Bernoulli(\pi_i)$$

$$\eta_i = \log\left(\frac{\pi_i}{1-\pi_i}\right) = \mu + \beta_i$$

where,

- $source\_abuse_i$ is a yes/no response to abuse of any ER/LA product through a specific source of procurement during the i^{th} phase
- π_i is the probability of observing an abuse response for any ER/LA product through a specific source of procurement during the i^{th} phase
- $\log\left(\frac{\pi_i}{1-\pi_i}\right)$ is the logit link function of π_i
- μ is the overall mean
- β_i is the fixed effect of the i^{th} phase

SAS CODE:

```
PROC GLIMMIX DATA=<data file name>;
BY source;
CLASS time;
MODEL source_abuse = time / S LINK=LOGIT DIST=BIN;
RUN;
```

Note: These analyses will be conducted among abusers of ER/LA opioids and repeated for each source of procurement ("BY source" statement)

6.6.3b. Estimating and comparing the changes in the source of procurement at the compound/subgroup-level (Tertiary Objective 1)

GEE logistic regression models will be employed to estimate changes in the odds of each source of procurement for compound/subgroup level groups over time. In these models,

the fixed effects include a compound/subgroup indicator variable (morphine ER, oxymorphone ER, methadone, transdermal fentanyl and buprenorphine, and the other ER opioid group), phase indicator variable (pre-REMS phase, REMS implementation phase, and continuing active REMS phase), and the two-way interaction. Both variables will be treated as categorical. The binary dependent variable for each model is endorsement/no endorsement of each source of procurement in the past 30 days for any of drugs comprising each level of the drug groups.

MODEL:

$$source\_abuse_{ij} \sim Bernoulli(\pi_{ij})$$

$$\eta_{ij} = \log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \mu + \alpha_i + \beta_j + (\alpha\beta)_{ij}$$

where,

- $source\_abuse_{ij}$ is a yes/no response to abuse of the i^{th} drug (compound/subgroup) through a specific source during the j^{th} phase
- π_{ij} is the probability of observing an abuse response for the i^{th} drug through a specific source during the j^{th} phase
- $log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right)$is the logit link function of π_{ij}
- μ is the overall mean
- α_i is i^{th} fixed effect of the i^{th} drug
- β_j is the fixed effect of the j^{th} phase
- $(\alpha\beta)_{ij}$ is the interaction effect between the i^{th} drug and the j^{th} phase

SAS CODE:

```
PROC GLIMMIX DATA=<data file name>;
BY source;
CLASS compound time subject;
MODEL source_abuse = compound|time / S LINK=LOGIT DIST=BIN;
RANDOM _RESIDUAL_ / SUBJECT = subject TYPE=CS;
RUN;
```

Note: These analyses will be conducted among abusers of the ER/LA compounds/subgroups of opioids and repeated for each source of procurement ("BY source" statement)

6.6.4. Quarterly trend analyses

For trend analyses (Tertiary Objective 2), note that compound/subgroup level analyses are performed in a model separate from group-level (i.e., ER/LA opioids). As such, the description of each analysis is provided separately below.

6.6.4a: Estimating quarterly trends of abuse within each phase for ER/LA opioids as a group (Tertiary Objective 2)

A logistic regression model will be employed to estimate changes in linear trends in abuse for ER/LA opioids as a group across the phases. In this model, the fixed effects include a categorical phase indicator variable (pre-REMS phase, REMS implementation phase, and continuing active REMS phase), time covariate (measured in calendar quarter units), and the interaction of both fixed effects. The binary dependent variable is endorsement/no endorsement of abuse in the past 30 days for any of drugs comprising each level of the drug groups. Since there is only one measurement on each patient (self-report abuse of any ER/LA opioid) being used for this analysis, correlation among repeated measures is not being taken into account.

MODEL:

$$abuse_i \sim Bernoulli(\pi_i)$$

$$\eta_i = \log\left(\frac{\pi_i}{1-\pi_i}\right) = \mu + \alpha_i + \beta_1 x_i + (\delta x)_i$$

where,

- $abuse_i$ is a yes/no response to abuse of an ER/LA product during the i^{th} phase
- π_i is the probability of observing an abuse response of an ER/LA product during the i^{th} phase
- $\log\left(\frac{\pi_i}{1-\pi_i}\right)$ is the logit link function of π_i
- μ is the overall mean
- α_i is the coefficient for the i^{th} phase effect of the intercept
- β_1 is the overall slope
- x_i are the time measurements (in calendar quarter units) during the i^{th} phase

- δ_i is the coefficient of the i^{th} phase effect of the slope

SAS CODE:

```
PROC GLIMMIX DATA=<data file name>;
CLASS time;
MODEL abuse = time|quarter / S LINK=LOGIT DIST=BIN;
RUN;
```

Note: These analyses will be conducted among all ASI-MV respondents.

6.6.4b: Estimating and comparing quarterly trends of abuse within each phase between compound/subgroup level groups (Tertiary Objective 2)

A GEE logistic regression model will be employed to estimate changes in linear trends in abuse for compound/subgroup level groups across the phases. In this model, the fixed effects include a categorical compound/subgroup-indicator variable (morphine ER, oxymorphone ER, methadone, transdermal fentanyl and buprenorphine, and the other ER opioid group), a categorical phase indicator variable (pre-REMS phase, REMS implementation phase, and continuing active REMS phase), a time covariate (measured in calendar quarter units), the two-way interactions, and three-way interaction. The binary dependent variable is endorsement/no endorsement of abuse in the past 30 days for any of drugs comprising each level of the compound/subgroups.

MODEL:

$$abuse_{ij} \sim Bernoulli(\pi_{ij})$$

$$\eta_{ij} = \log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right) = \mu + \alpha_i + \gamma_j + \alpha_i\gamma_j + (\beta_1 + \varphi_i + \delta_j + \varphi_i\delta_j)x_j$$

where,

- $abuse_{ij}$ is a yes/no response to abuse of the i^{th} compound during the j^{th} phase
- π_{ij} is the probability of observing an abuse response for the i^{th} compound during the j^{th} phase
- $\log\left(\frac{\pi_{ij}}{1-\pi_{ij}}\right)$ is the logit link function of π_{ij}
- μ is the overall mean
- α_i is the fixed effect of the i^{th} compound
- γ_j is the fixed effect of the j^{th} phase
- $\alpha_i\gamma_j$ is the fixed effect of the interaction between the i^{th} compound and the j^{th} phase

- β is the overall regression coefficient (slope) for the covariate
- φ_i is the slope effect for the i^{th} compound
- δ_j is the slope effect for the j^{th} phase
- $\varphi_i \delta_j$ is the slope effect of the interaction between the i^{th} compound and the j^{th} phase
- x_j are the time measurements (in calendar quarter units) during the j^{th} phase

SAS CODE:

```
PROC GLIMMIX DATA=<data file name>;
CLASS compound time;
MODEL abuse = compound|time|quarter / S LINK=LOGIT DIST=BIN;
RANDOM _RESIDUAL_ / SUBJECT = subject TYPE=CS;
RUN;
```

Note: These analyses will be conducted among all ASI-MV respondents.

6.6.4c: Estimating quarterly trends of source of procurement for the ER/LA group within each phase between compound/subgroup level groups (Tertiary Objective 2)

A standard logistic regression model will be employed to estimate changes in linear trends in abuse through a specific source for ER/LA opioids as a group across the phases. In this model, the fixed effects include a categorical phase indicator variable (pre-REMS phase, REMS implementation phase, and continuing active REMS phase), time covariate (measured in calendar quarter units), and the interaction of both fixed effects. The binary dependent variable is endorsement/no endorsement of abuse in the past 30 days through a specific source for any of drugs comprising each level of the drug groups.

MODEL:

$$source\_abuse_i \sim Bernoulli(\pi_i)$$

$$\eta_i = \log\left(\frac{\pi_i}{1-\pi_i}\right) = \mu + \alpha_i + \beta_1 x_i + (\delta x)_i$$

where,

- $source\_abuse_i$ is a yes/no response to abuse of an ER/LA product through a specific source during the i^{th} phase
- π_i is the probability of observing an abuse response of an ER/LA product through a specific source during the i^{th} phase
- $\log\left(\frac{\pi_i}{1-\pi_i}\right)$ is the logit link function of π_i
- μ is the overall mean

- α_i is the coefficient for the i^{th} phase effect of the intercept
- β_1 is the overall slope
- x_i are the time measurements (in calendar quarter units) during the i^{th} phase
- δ_i is the coefficient of the i^{th} phase effect of the slope

SAS CODE:

```
PROC GLIMMIX DATA=<data file name>;
BY source;
CLASS time;
MODEL source_abuse = time|quarter / S LINK=LOGIT DIST=BIN;
RUN;
```

Note: These analyses will be conducted among abusers of ER/LA opioids and repeated for each source of procurement ("BY source" statement)

Accounting for other Dependencies via Additional Random Components.

As mentioned previously, where appropriate, the models above account for correlation among repeated measurements on the same patient-respondent. Some relevant dependencies that could be accounted for include (1) within calendar-quarter correlation at the ZIP code level and (2) correlation between quarterly averages within ZIP codes (a.k.a. temporal correlation). The rationale for including R-side random effects to account for within-subject correlation before including additional random components listed above is due to the expected larger correlation among observations within the same person versus higher level correlations. It would advisable to account for the strongest dependency in the dataset to minimize the bias in the parameter estimates, standard errors, and p-values. Given the computational intensiveness of accounting for these other dependencies due to the requirement of (1) integrating over a large number of random effects and (2) availability of current software and hardware, it was infeasible to account for these other random components in the first set of analyses, particularly using data on all ASI-MV respondents collected during the study period. That being said, the other random components mentioned above will be considered in future analyses after the necessary software and hardware have been acquired and careful consideration of the practicality of integrating over the additional number of random effects has been taken into account.

6.6.5. Power considerations

Several factors should be taken into account when considering how to achieve an acceptable level of statistical power associated with the primary objective of this study. The objectives pertain to examining the change in the odds of abuse of ER/LA opioids due to or associated with the REMS intervention. Statistical power in these analyses will involve considerations of: (1) the number of ASI-MV assessments collected (sample size) per time period, (2) number of events (e.g., past 30-day abuse cases of the target drugs) per time period, and (3) effect size due to the intervention (i.e., differences in the

proportion of abuse events between time periods). With respect to the sample size, the ASI-MV draws from a large (although not comprehensive and not representative) geographic area and several hundred treatment sites. During the study period for this Year One analysis (July 2010 through December 2013), preliminary examination of the data suggests an N approaching 200,000 ASI-MV assessments were collected. A total sample size of this magnitude is large and will likely supply adequate power for virtually any statistical test on changes in odds and be able to detect even small effect sizes (e.g., 10% relative change in the odds of abuse). In some cases, it may be determined that analyses are over-powered and findings of significant differences are judged to be not clinically meaningful. Given the expected high levels of power for each statistical analysis, confidence intervals will be provided to assist in determining whether a significant finding is meaningful from a public health perspective at the lower and upper limits of the effect size. In the event non-significant findings are observed, factors affecting the low post-hoc power will be investigated and reported. It should also be noted that the expected effect size of an intervention, in this case, the REMS intervention, is also an important component of statistical power. Thus, for the REMS intervention, it is logical that some, as yet undetermined level of intervention exposure (i.e., proportion of the target population of the intervention having completed the REMS training), may be required for "saturation" to occur, making it reasonable to anticipate a detectable, national impact. It is expected that, as the active period of the REMS intervention increases beyond December 2013, the level of exposure will increase, presumably increasing the potential effect size. Thus, over time, the sample size reflected in the ASI-MV database may more readily detect an impact.

6.6.6. CHAT analyses

As noted at the beginning of this Methods section, due to the current, limited coverage of the CHAT network as well as other factors, such as the relatively few reports of abuse of the ER/LA medications that are the focus of this investigation, CHAT analyses will be descriptive. At this time, the analytic approach for CHAT data will include creating the same outcome abuse variables outlined in section 6.4 for the ASI-MV. Descriptive statistics for demographic variables and the outcome variables by quarter will be reported as counts, and where appropriate, raw proportions. Counts and frequencies for source of procurement data will also be provided. When feasible, appropriate univariate tests of proportions may be applied. Given the limited data, trend analyses will not be provided for CHAT data.

7. LIMITATIONS

The ASI-MV system is intended to provide sentinel surveillance. The system provides important information about trends of abuse, but has yet to achieve national representativeness. Thus, results of analyses on these data cannot be interpreted as nationally representative. Some states have considerable coverage, while data from other states are represented from only a small number of participating treatment centers. Data are collected at 821 patient 3-digit home ZIP codes. Calculation of rates of abuse in the states or other geographical regions with few sites and/or few cases is limited and must be interpreted with caution. The population represented is

not randomly selected. It consists of those who seek or are mandated to treatment for substance abuse and who have access to substance abuse treatment. Thus, this database may have a socioeconomic bias against those who do not have access to such care. It is possible that there are subpopulations or geographically localized areas in the country where individuals are abusing the target drugs in ways that are unique and not consistent with a larger national trend of abuse. The ASI-MV network may miss such unique groups and specific subpopulations. However, if the question of interest pertains to larger trends of abuse patterns associated with the target drugs, it is likely that the saturated populations included here will capture any large trend.

Since treatment centers within the ASI-MV system are not randomly recruited to join the network, data collected from these treatment centers cannot and should not be generalized to all substance abuse treatment centers. Such limitations are inherent in this country's substance abuse landscape, rendering any data stream for this population susceptible to significant limitations.

Another possible limitation is that these data are self-report, which is subject to recall bias. While this is absolutely true, it is unclear what other data source would provide reliable information on product-specific sources of procurement.

8. OFFSETTING STRENGTHS

Despite its limitations, it is important to not lose sight of the strengths of data collected from the ASI-MV data stream. For example, this data stream is designed for active data collection, and as such, is not dependent upon passive, retrospective, and often anecdotal data characteristic of other, commonly used data streams. Secondly, the ASI-MV system yields data in near real time: the majority of patient assessments (85%) are uploaded within the same day. Data are uploaded within two weeks for 95% of all assessments. While representative data are always preferable, when available, the public health importance of near-real time data from a sentinel population of those most involved with substances, such as the ASI-MV data, are likely to reflect use patterns of "early adopters". Thus, the ASI-MV could prove invaluable for estimating emerging trends in drug abuse indicators [15],[16]. Evaluation of the impact of a REMS initiative on specific product abuse rates and sources of procurement requires prospectively collected data on these variables at the product-specific and patient-specific level. To our knowledge, the ASI-MV is the only existing data stream that systematically collects product-specific source of procurement for each product endorsed by a respondent. Finally, the broad distribution of treatment sites in the ASI-MV network yields a sample that is similar in some respects to other, more comprehensive data streams. For instance, the demographic characteristics of patients within the ASI-MV data set are comparable to patients in the Treatment Episode Data Set (see Table 4), suggesting that the ASI-MV data may be tapping a sample that is generally reflective of the larger population of substance abuse treatment centers.

As noted in the Limitations section, the reliability and validity of self-report from substance abuse clients has been questioned. This concern usually reflects the observed phenomena of "denial" and the consistent under-reporting of consumption in general population surveys. However, research and reviews continue to support the reliability and validity of self-report of patients entering treatment [17,18, 19, 20, 21, 22]. Although such literature generally supports the validity of self-report, it should be acknowledged that a few studies have found self-reported use to under-report drug use [23, 24]. A further consideration is that individuals in this particular patient

population have an acknowledged difficulty with substance abuse—a difficulty that has developed to the degree of necessitating treatment—and thus they may have less motivation to minimize or deny their drug use in comparison with people who are not in treatment. In addition to the general support for the validity of self-reported substance use in the treatment setting, there is evidence that reporting via computer self-administration is as valid as reporting to a live interviewer. Where discrepancies exist, computer self-administration tends to elicit reports of more, rather than fewer, psychosocial and substance use problems[25]. Finally, the ASI-MV uses a methodology for questioning respondents about use/abuse of particular prescription medications that is similar to methods employed by the NSDUH survey[26]. NSDUH utilizes pictures of prescription products, names, slang and so forth as well as other widely accepted methodological practices for increasing the accuracy of self-reports, such as audio computer-assisted self-interviewing (as does the ASI-MV). Examinations of these NSDUH methods have shown that they reduce reporting bias[27] in general populations. Furthermore, the ASI-MV assessment presents respondents with a "fake" prescription opioid product to gauge the extent to which respondents may be responding haphazardly or otherwise not reporting honestly. A few respondents (.01% of all respondents) endorse use/abuse of this "drug." These few respondents are removed prior to analyses. Finally, given the data requested by the RPC Metric Subteam, self-report is the only method for obtaining information about specific products used/abuse or specific sources of those products.

9. HUMAN SUBJECT CONSIDERATION

The work proposed here is exempt from the IRB policy. Specifically, this protocol cites use of data from existing databases (ASI-MV and CHAT) that collect data during the course of ongoing clinical work at treatment facilities within the NAVIPPRO network. Therefore, the ASI-MV and CHAT datasets qualify for exemption as an existing limited dataset in which subjects cannot be identified. Review by the New England Institutional Review Board (NEIRB) has determined that surveillance activities using data from the NAVIPPRO ASI-MV and CHAT data streams does not meet the HIPAA definition of research and is therefore exempt (ASI-MV exemption: NEIRB #11-212, 7/8/2011) (CHAT exemption: NEIRB# 11-252, 8/11/2011).

The ASI-MV and CHAT databases consist of de-identified client data collected under a Business Associate Agreement and Limited Data Set Use Agreement with participating treatment facilities around the country. Exemption is claimed under conditions specified under the Code of Federal Regulations, Title 45, Part 46, Revised June 23, 2005, Effective June 23, 2005, Subpart A--Basic HHS Policy for Protection of Human Research Subjects (available on the OHRP website at http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.htm). The research proposed here meets or exceeds this exclusion requirement.

Finally, the ASI-MV and CHAT upload processes utilize an algorithm which assigns each case a unique, 128-character identifier that is a concatenation of data entered by patients and are unlikely to change (e.g., gender, year of birth, mother's name, etc. Using cryptographic techniques, the identifier is converted into a unique linking code at upload and is maintained in the dataset but no longer reveals any elements of the personally identifying information. The nature of the ID permits identification of an individual who completes the ASI-MV or CHAT assessment at different times and even at different locations. Testing of a similar system with census data found an unduplicated rate of 99.845%[28]. The unique ID retains patient privacy

while permitting longitudinal tracking of patients within and across assessment sites and elimination of duplicate patients in appropriate analyses. Only anonymous, de-identified information is contained in the ASI-MV database. Utilization of any patient data will comply with all federal, state, and local laws, including, but not limited to, HIPAA.

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Appendix G - Inflexxion Report

Title: REMS assessment and surveillance study to evaluate the impact of extended-release/long-acting (ER/LA) opioid analgesics class REMS on abuse among those in substance abuse treatment

Date: May 14, 2014
Revised: May 30, 2014

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Appendix H - IMS Protocol

Protocol for ER/LA Opioid Analgesic REMS Assessments Utilizing a National Prescription Database:

- Assessment #6: Drug utilization study of trends in prescriptions for class REMS ER/LA opioids and comparator products

- Assessment #7: Evaluation of changes in prescribing behavior of ER/LA opioid prescribers

- Assessment #8: Monitoring patterns of prescribing to identify changes in access to ER/LA opioid analgesics

UPDATE

Date: May 1, 2014

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1. PROTOCOL SYNOPSIS

Rationale	In April 2011, the U.S. Food and Drug Administration (FDA) determined that a class-wide risk evaluation and mitigation strategy (REMS) for all extended-release (ER) and long-acting (LA) opioid medications is necessary to support national efforts to address the prescription drug abuse epidemic and to ensure that the benefits continue to outweigh the risks associated with use of these products. Specifically, the goal of this ER/LA Opioid Analgesics REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes include addiction, unintentional overdose, and death. In the interest of public health and to minimize the burden on the healthcare delivery system from having multiple unique REMS programs, pharmaceutical companies subject to this REMS (the REMS Program Companies, or "RPC") joined together to implement this REMS for all ER/LA opioid drug products. The RPC is implementing this REMS as part of national efforts to address the epidemic of prescription drug abuse in the United States. The ER/LA Opioid Analgesics REMS provides a structure for all of the companies of the RPC to efficiently implement the FDA-mandated risk evaluation and mitigation activities across all ER/LA opioid analgesic products in a uniform and integrated manner. The REMS was approved by FDA on July 9th, 2012 (http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm).
Objectives & Approach	The RPC is responsible for the execution of the FDA-approved plan to assess / evaluate effects of the ER/LA Opioid Analgesics REMS. While this plan includes 10 specific Assessments, this document focuses on three (3) of them, which are identified by the FDA as Assessments 6-8. 1. Assessment 6: Evaluation of drug utilization patterns 2. Assessment 7: Evaluation of changes in prescribing behavior 3. Assessment 8: Evaluation of changes in access to ER/LA Opioid Analgesics Assessment 6: Drug Utilization Patterns A drug utilization study will be performed to describe trends in the number of prescriptions and patients for class REMS ER/LA opioids and comparator products. The specific objectives of the Drug Utilization Study are: 1. To estimate trends by month in the number of prescriptions for a one-year period before, and each month after, the implementation of the REMS 2. To compare average number of prescriptions per 3 month period in the 2 years before as compared to the same measure in transition implementation period and post period 3. To compare the trends in prescribing, both number of prescriptions and patients, by prescriber specialty

	These trends and changes over time will be estimated for the following groups of opioids: • All ER/LA opioids included in the class REMS versus immediate-release (IR) opioids not in the class • Immediate- versus extended-release formulations of each drug substance • Each product in the ER/LA opioid class 4. Show switches (absolute and rates of switching) from ER/LA opioids to comparator analgesics with introduction of REMS. Assessment 7: Changes in Prescribing Behavior A study will be performed to evaluate changes in prescribing behavior of prescribers. 1. For products that are indicated for use in opioid-tolerant patients only (ie, fentanyl transdermal patches and extended-release hydromorphone pills),describe trends in the proportion of prescriptions for these products to opioid-non-tolerant patients in the year preceding the availability of REMS-compliant CE courses and compare the proportion of prescriptions to opioid non-tolerant patients pre- versus post-REMS CE course availability 2. For products whose labels indicate that higher dosage strengths should only be used in opioid-tolerant patients, describe trends in the proportion of prescriptions prescribed to opioid non-tolerant patients with a high starting dosage strength; compare the proportion of prescriptions for such products that are prescribed to opioid non-tolerant patients with a high starting dosage strength pre- versus post-REMS CE course availability 3. Describe trends in the proportion of prescriptions for ER/LA opioids prescribed to patients that have early refills of prescriptions and compare this proportion pre- versus post-REMS CE course availability. 4. To compare the concomitant use of benzodiazepines with ER/LA opioids before and after REMS implementation. Assessment 8: Changes in Access Changes in prescribing will be compared in prescribers from specialties whose prescribing is hypothesized to be relatively unaffected by the REMS (such as oncologists and hospice providers) versus those for whom the REMS could have greater impact on prescribing (eg, dentists). This will be conducted using the methodology described for Assessment #6 (Utilization patterns) above.
Data sources	This study will be based on two IMS data sources: • National Prescription Audit™ • LifeLink™ patient-level longitudinal prescription (LRx) database

2. RATIONALE

In April 2011, the U.S. Food and Drug Administration (FDA) determined that a class-wide risk evaluation and mitigation strategy (REMS) for all extended-release (ER) and long-acting (LA) opioid medications was necessary to support national efforts to address the epidemic of abuse of prescription drugs and to ensure that the benefits continue to outweigh the risks associated with use of these products. Specifically, the goal of this ER/LA Opioid Analgesics REMS is to reduce serious adverse outcomes resulting from inappropriate prescribing, misuse, and abuse of ER/LA opioid analgesics while maintaining patient access to pain medications. Adverse outcomes include addiction, unintentional overdose, and death.

3. BACKGROUND

In the interest of public health and to minimize the burden on the healthcare delivery system from having multiple unique REMS programs, pharmaceutical companies subject to this REMS (the REMS Program Companies, or "RPC") joined together to implement this REMS for all ER/LA opioid drug products. The RPC is implementing this REMS as part of national efforts to address the epidemic of prescription drug abuse in the United States. . The ER/LA Opioid Analgesics REMS provides a structure for all of the companies of the RPC to efficiently implement risk evaluation and mitigation activities across all ER/LA opioid analgesics in a uniform manner. The REMS was approved by FDA July 9th, 2012 (http://www.fda.gov/drugs/drugsafety/informationbydrugclass/ucm163647.htm).

4. OBJECTIVES

The RPC is responsible for the implementation of the FDA-approved plan to assess / evaluate effects of the ER/LA Opioid Analgesics REMS. While this plan includes 10 specific Assessments, this protocol focuses on three (3) of them, which are identified by the FDA as Assessments 6-8.

- Assessment 6: Evaluation of drug utilization patterns
- Assessment 7: Evaluation of changes in prescribing behavior
- Assessment 8: Evaluation of changes in access to ER/LA Opioid Analgesics

5. DATA SOURCES

These Assessments will be based on two IMS Health data sources:

IMS Health, National Prescription Audit™ (NPA™)

The IMS National Prescription Audit™ is the industry standard for measuring the outflow of prescriptions from retail pharmacies, mail service houses, or long-term care facilities into the hands of consumers. For this study, IMS will report on Retail channel, which tracks the volume of pharmaceutical prescriptions dispensed through Chain Store Pharmacies, Independent Store Pharmacies, and Food Store Pharmacies. Data are projected to National estimates.

IMS Health, LifeLink™ patient-level longitudinal prescription (LRx) database

The IMS LRx database consists of patient de-identified longitudinal prescription data from a sample of the IMS Health retail and mail order prescription universe (NPA). Data are collected for the LRx database via direct data feeds from retail (pharmacy chains, food stores, independents and mass merchandisers) and mail service pharmacies included in the IMS Health data supplier panel. All data loaded into the LRx database are encrypted using a proprietary encryption algorithm to de-identify and assign each patient a unique patient ID, which ensures HIPAA compliance. Encrypted patient IDs allow IMS to account for patient travel across data suppliers within the sample without losing visibility to the patient.

The database provides robust coverage of the retail prescription universe, with approximately 65% of all retail prescriptions filled in the U.S. captured within the database. Over 150 million unique de-identified patients are contained within the database along with prescribing information for over one million prescribers. Relationships with LRx data suppliers are broader than the longitudinal prescription data alone as they encompass core IMS prescription services such as NPA and Xponent, resulting in a very stable data supply for the database. The database contains IMS prescriber IDs and zip codes for each transaction, allowing for accurate prescriber-level and sub-national reporting of patient-level data metrics.

6. ANALYSIS PLAN—Assessment 6: Evaluation of Drug Utilization Patterns

1. *Study design*

   A retrospective cohort study that will utilize a repeated cross-sectional design to estimate the number of prescriptions of (or number of unique individuals prescribed) a specific drug or group of drugs in each specified time period: a 24-month pre period, a 12-month implementation period, and a 6-month post period.

   The analyses will include and report on patient activity before and after REMS implementation, spanning a 42-month period, July 2010 through December 2013.

   Selection Periods:

   - Pre Period: July 2010 – June 2012
   - Transition implementation Period: July 2012 – June 2013
   - Post Period: July 2013 – December 2013

   Note that the above post period will be utilized for the 2014 report. Additional months will be added for reports in subsequent years.
   For this study, results will be aggregated. One analysis will measure trends over time in monthly number of prescriptions. Another analysis will measure the average number of prescriptions per quarter in the pre, transition implementation, and post-period.

   Changes in prescriptions for ER/LA opioids included in the class REMS will be assessed relative to changes in comparator drug groups.

   Prescription and patient counts will be projected to the national level based on the LRx prescription sample with projection factors derived from the prescriptions in LRx relative to NPA TRx.

2. *Inclusion Criteria*

   Subjects filling a prescription for a product of interest (Appendix 1) during the specified time period will be included. Subjects receiving study products (ER/LA opioids included in the class REMS) will all be reported at the individual generic strength level. Subjects

receiving comparator products will be grouped into three product groups and reported at the product group level.

i. Definition of study and comparator products

- REMS ER/LA Opioid Analgesics
  - Extended-release, oral-dosage forms containing: Hydrocodone, Hydromorphone, Morphine, Oxycodone, Oxymorphone, Tapentadol
  - Fentanyl and buprenorphine-containing transdermal delivery systems
  - Methadone tablets and solutions that are indicated for use as analgesics
- Comparator Products
  - Other opioid analgesics not covered by the class REMS for ER/LA opioids; reported at the individual market level – not individual product level, including oral forms.
  - Prescription Nonsteroidal Anti-Inflammatory Drug (NSAID), celecoxib, as an "analgesic control" group. Celecoxib was selected as the only NSAID comparator because all celecoxib strengths require prescriptions. This is not the case with many other NSAIDs, which do not require prescriptions or do not require prescriptions for some strengths. As a result, data would therefore not be available in IMS or other claims databases. In addition, just as with the ER/LA opioid analgesics, celecoxib is more likely to be used for longer term pain due to its lower risk of gastrointestinal bleeding as compared to other NSAIDs that are generally more often used for acute pain than chronic pain.
  - Benzodiazepines as an "abuse control" group since this class of prescription drugs is subject to abuse; reported at the individual market level – not individual product level

ii. Patient Cohort

For each reporting month, patients who filled at least one Rx in the market of interested will be selected in the analysis. Patient will be indexed on their first prescription by product in the reporting month.

All patients will need to meet the following eligibility requirements to be included in the cohort:

- Constant Store Panel: IMS requires that the pharmacies used by each patient consistently supply data to the LRx database for the entire study window
- Patient Start Date: IMS also requires that each patient had activity in the LRx database (for any market) prior to the study period.

These eligibility criteria are necessary to control for complete patient history in the LRx database. The use of the "constant store panel" and "patient start date" are standard practices for ensuring continuous eligibility in custom LRx projects.

3. Objectives

i. To estimate trends by month in the number of prescriptions for a one-year period before, and each month after, the implementation of the REMS

ii. To compare average number of prescriptions per 3 month period in the 2 years before as compared to the same measure in transition implementation period and post period

iii. To compare the trends in prescribing, both number of prescriptions and patients, by prescriber specialty.

These trends and changes over time will be estimated for the following groups of opioids:

- All ER/LA opioids included in the class REMS versus immediate-release (IR)opioids not in the class
- Immediate- versus extended-release formulations of each drug substance
- Each product in the ER/LA opioid class

A corresponding set of analyses will be carried out based on number of unique individuals prescribed ER/LA opioids and comparator drugs.

Additional Patient Criteria
None.

Outcomes
1. Monthly prescription volumes
2. Monthly patient volumes
3. Average prescription volumes per quarter in the 3 study periods
4. Average patient volumes per quarter in the 3 study periods
5. Monthly volume of prescriptions for each prescribing specialty
6. Monthly volume of patients for each prescribing specialty
7. Pre-post changes in average quarterly number of prescriptions/prescribers as a % change, and a difference in % change relative to comparator drug groups

Statistical Analysis
Measurements of changes in prescribing before, during the transition implementation period, and after REMS implementation will be preformed. The average percent changes in volumes from the pre-period, transition period, and post periods, and 95%CI will be calculated. The statistical significance of these changes will be estimated by T-test. P values less than 0.05 will be considered significant. SAS 9.2 (Cary, NC) will be used to perform statistical tests for significance. The distribution of prescriptions across products will be calculated. These analyses will be stratified by categories of patient age group, gender, pay type and prescriber specialty group. The same analyses will be conducted for both ER/LA opioids and comparator groups so changes in prescribing can be compared and assessed across REMS and comparator products. An analysis of variance will be performed to assess whether the changes in prescription volumes from before and after REMS initiation are different for opioids included in class REMS vs opioids not included in the class REMS (IR opioids) and vs benzodiazepines.

iv. Show switches (absolute and rates of switching) from ER/LA opioids to comparator analgesics with introduction of REMS.

Additional Patient Criteria
For this objective, we will use a subset of patients who have switched prescriptions from a REMS product to one in a different product group. Switching is defined as filling a different product prescription in the previous 3 months relative to the current prescription.

Outcomes
1. Monthly volume of patients who switch from REMS products to other product groups
2. Monthly volume of patients who switch between REMS products, by product
3. Rates of switching by REMS products

Statistical Analysis
Measurements of changes in prescribing before, during the transition implementation period, and after REMS implementation will be preformed. The average percent changes in volumes from the pre-period, transition period, and post periods, and 95%CI will be calculated. The statistical significance of these changes will be estimated by T-test. P values less than 0.05 will be considered significant. SAS 9.2 (Cary, NC) will be used to perform statistical tests for significance. The distribution of prescriptions across products will be calculated. These analyses will be stratified by categories of patient age group, gender, pay type and prescriber specialty group. The same analyses will be conducted for both ER/LA opioids and comparator groups so changes in prescribing can be compared and assessed across REMS and comparator products. An analysis of variance will be performed to assess whether the changes in prescription volumes from before and after REMS initiation are different for opioids included in class REMS vs opioids not included in the class REMS (IR opioids) and vs benzodiazepines.

7. ANALYSIS PLAN—Assessment 7: Evaluation of Changes In Prescribing Behavior

1. Study design

A retrospective cohort study that will utilize a repeated cross-sectional design to estimate the number of prescriptions of (or number of unique individuals prescribed) a specific drug or group of drugs in each specified time period: a 24-month pre period, a 12-month implementation period, and a 6-month post period.

We will define outcomes measures that are both proxy measures of inattentive or problematic prescribing practices by prescribers or ER/LA opioids and are feasible to measure in the available data systems. Three such prescribing outcome measures are:

- Whether products that are indicated for use only in opioid-tolerant patients (i.e., fentanyl transdermal patches and extended-release hydromorphone pills) are prescribed to non-opioid tolerant/opioid-naïve patients

- Whether products whose labels indicate that higher dosage strengths should only be used in opioid-tolerant patients are prescribed with a high starting dose in non-opioid tolerant/opioid-naïve patients, and

- Whether the number of patients prescribed ER/LA opioids who receive an early refill for an opioid prescription changes

The analyses will include and report on patient activity before and after REMS implementation, spanning a 42-month period, July 2010 through December 2013.

Selection Periods:

- Pre Period: July 2010 – June 2012
- Transition Implementation Period: July 2012 – June 2013
- Post Period: July 2013 – December 2013

Note that the above post period will be utilized for the 2014 report. Additional months will be added for reports in subsequent years.
For this study, results will be aggregated and reported at the month and quarter levels.

Changes in prescriptions for ER/LA opioids included in the class REMS will be assessed relative to changes in comparator drug groups.

Prescription and patient counts will be projected to the national level based on the LRx prescription sample with projection factors derived from the prescriptions in LRx relative to NPA TRx.

2. *Inclusion Criteria*

Subjects filling a prescription for a product of interest (Appendix 1) during the specified time period will be included. Subjects receiving study products (ER/LA opioids included in the class REMS) will all be reported at the individual generic strength level. Subjects receiving comparator products will be grouped into three product groups and reported at the product group level.

i. <u>Definition of study and comparator products</u>

- REMS ER/LA Opioid Analgesics, reported at the strength level:
  - Extended-release, oral-dosage forms containing: Hydrocodone, Hydromorphone, Morphine, Oxycodone, Oxymorphone, Tapentadol
  - Fentanyl and buprenorphine-containing transdermal delivery systems
  - Methadone tablets and solutions that are indicated for use as analgesics
- Comparator Products
  - IR opioids reported at the individual market level – not individual product level, including oral forms.
  - Benzodiazepines as an "abuse control" group; reported at the individual market level – not individual product level

ii. Patient Cohort

For each reporting month, patients who filled at least one Rx in the market of interested will be selected in the analysis. Patient will be indexed on their first prescription by product in the reporting month.

All patients will need to meet the following eligibility requirements to be included in the cohort:

- Constant Store Panel: IMS requires that the pharmacies used by each patient consistently supply data to the LRx database for the entire study window
- Patient Start Date: IMS also requires that each patient had activity in the LRx database (for any market) prior to the study period.

These eligibility criteria are necessary to control for complete patient history in the LRx database. The use of the "constant store panel" and "patient start date" are standard practices for ensuring continuous eligibility in custom LRx projects.

3. Objectives

i. For products that are indicated for use in opioid-tolerant patients only (ie, fentanyl transdermal patches and extended-release hydromorphone pills),describe trends in the proportion of prescriptions for these products to opioid-non-tolerant patients in the year preceding the availability of REMS-compliant CE courses and compare the proportion of prescriptions to opioid non-tolerant patients pre- versus post-REMS CE course availability

Additional Patient Criteria

For this objective, we will use a subset of patients who have filled prescriptions for products that are indicated for use only in opioid-tolerant patients. These are:

- Fentanyl Transdermal patches
- Extended-release hydromorphone pills

We will then determine if those prescriptions are being filled by opioid-tolerant patients or non-opioid tolerant patients.
Non-opioid tolerant is defined as an individual who has not received an opioid for 6 months.

Outcomes

1. Monthly volume of prescriptions in opioid-tolerant patients
2. Monthly volume of prescriptions in non-opioid tolerant patients
3. Monthly proportion of patients that are non-opioid tolerant

Statistical Analysis

Measurements of changes in prescribing before, during the transition implementation period, and after REMS implementation will be preformed. The average percent changes in volumes from the pre-period, transition period, and post periods, and 95%CI will be calculated. The statistical significance of these changes will be estimated by T-test. P values less than 0.05 will be considered significant. SAS 9.2 (Cary, NC) will be used to perform statistical tests for

significance. The distribution of prescriptions across products will be calculated. These analyses will be stratified by categories of patient age group, gender, pay type and prescriber specialty group. The same analyses will be conducted for both ER/LA opioids and comparator groups so changes in prescribing can be compared and assessed across REMS and comparator products. An analysis of variance will be performed to assess whether the changes in prescription volumes from before and after REMS initiation are different for opioids included in class REMS vs opioids not included in the class REMS (IR opioids) and vs benzodiazepines.

ii. For products whose labels indicate that higher dosage strengths should only be used in opioid-tolerant patients, describe trends in the proportion of prescriptions prescribed to opioid non-tolerant patients with a high starting dosage strength; compare the proportion of prescriptions for such products that are prescribed to opioid non-tolerant patients with a high starting dosage strength pre- versus post-REMS CE course availability

Additional Patient Criteria

For this objective, we will use a subset of patients who have filled prescriptions for products whose labels indicate that higher dosage strengths should only be used in opioid-tolerant patients. For example, from the Duragesic label, "DURAGESIC should ONLY be used in patients who are already receiving opioid therapy, who have demonstrated opioid tolerance, and who require a total daily dose at least equivalent to DURAGESIC 25mcg/hr."

As a secondary analysis, we will assess the subject of using a morphine equivalent threshold for all ER/LA products. The 24 month assessment report will not include this secondary analysis due to time and programming constraints, but we will provide this in the 36 month assessment report. We will define the level of starting dose based on a morphine equivalent of greater than 60mg per day. The justification for this level is based on the definition of opioid tolerance in ER/LA opioid product labels. This analysis will not calculate actual daily dose. Daily dose will be imputed based on the dosage strength units dispensed. For example, a patient who receives a prescription for 30mg ER morphine tablets who did not have a prior opioid prescription would be considered acceptable, whereas a patient who receives a prescription for 40mg ER morphine tablets would be considered starting on too high a dose. This assumes the standard dose of ER morphine is twice daily.

Non-opioid tolerant is defined as an individual who has not received an opioid for 6 months. For the purposes of this study this term is used synonymously with opioid naïve.

Outcomes

1. Monthly volume of high-starting dose prescriptions in opioid-tolerant patients
2. Monthly volume of high starting dose prescriptions in non-opioid tolerant patients

3. Proportion of non-opioid tolerant patients that have high-starting dose prescriptions

Statistical Analysis
Measurements of changes in prescribing before, during the transition implementation period, and after REMS implementation will be preformed. The average percent changes in volumes from the pre-period, transition period, and post periods, and 95%CI will be calculated. The statistical significance of these changes will be estimated by T-test. P values less than 0.05 will be considered significant. SAS 9.2 (Cary, NC) will be used to perform statistical tests for significance. The distribution of prescriptions across products will be calculated. These analyses will be stratified by categories of patient age group, gender, pay type and prescriber specialty group. The same analyses will be conducted for both ER/LA opioids and comparator groups so changes in prescribing can be compared and assessed across REMS and comparator products. An analysis of variance will be performed to assess whether the changes in prescription volumes from before and after REMS initiation are different for opioids included in class REMS vs opioids not included in the class REMS (IR opioids) and vs benzodiazepines.

iii. Describe trends in the proportion of prescriptions for ER/LA opioids prescribed to patients that have early refills of prescriptions and compare this proportion pre- versus post-REMS CE course availability.

Additional Patient Criteria
For this objective we will denote which new-to-therapy patients have early refills. Early refills is defined as 2 consecutive prescriptions for the same individual and the same drug with the number of days between prescriptions >15% lower than the number of days of supply in the first prescription.

Previously published studies have uses a threshold for early refills of 10%, but the published studies have reported that patients may frequently get refills 3 days early on a 30-day prescription within the course of usual clinical practice

Note: Data for this objective will not be projected.

O**utcomes**
1. Volume of early refills by monthly patient cohort
2. Volume of normal refills by monthly patient cohort
3. Proportion of patients receiving early refills
4. Early refill rate by monthly patient cohort

Statistical Analysis
Measurements of changes in prescribing before, during the transition implementation period, and after REMS implementation will be preformed. The average percent changes in volumes from the pre-period, transition period, and

post periods, and 95%CI will be calculated. The statistical significance of these changes will be estimated by T-test. P values less than 0.05 will be considered significant. SAS 9.2 (Cary, NC) will be used to perform statistical tests for significance. The distribution of prescriptions across products will be calculated. These analyses will be stratified by categories of patient age group, gender, pay type and prescriber specialty group. The same analyses will be conducted for both ER/LA opioids and comparator groups so changes in prescribing can be compared and assessed across REMS and comparator products. An analysis of variance will be performed to assess whether the changes in prescription volumes from before and after REMS initiation are different for opioids included in class REMS vs opioids not included in the class REMS (IR opioids) and vs benzodiazepines.

iv. To compare the concomitant use of benzodiazepines with ER/LA opioids before and after REMS implementation.

Additional Patient Criteria
For this objective, we will use a subset of patients who are using a REMS product and a product in the Benzodiazepine group concomitantly. Concomitant use is defined as filling a Benzodiazepine prescription in the previous 3 months.

Outcomes
1. Monthly volume of patients who are using a REMS product and a Benzodiazepine concomitantly

Statistical Analysis
Measurements of changes in prescribing before, during the transition implementation period, and after REMS implementation will be preformed. The average percent changes in volumes from the pre-period, transition period, and post periods, and 95%CI will be calculated. The statistical significance of these changes will be estimated by T-test. P values less than 0.05 will be considered significant. SAS 9.2 (Cary, NC) will be used to perform statistical tests for significance. The distribution of prescriptions across products will be calculated. These analyses will be stratified by categories of patient age group, gender, pay type and prescriber specialty group. The same analyses will be conducted for both ER/LA opioids and comparator groups so changes in prescribing can be compared and assessed across REMS and comparator products. An analysis of variance will be performed to assess whether the changes in prescription volumes from before and after REMS initiation are different for opioids included in class REMS vs opioids not included in the class REMS (IR opioids) and vs benzodiazepines.

8. ANALYSIS PLAN—Assessment 8: Evaluation of Changes In Access To ER/LA Opioid Analgesics

1. Study design

A retrospective cohort study that will utilize a repeated cross-sectional design to estimate the number of prescriptions of (or number of unique individuals prescribed) a specific drug or group of drugs in each specified time period: a 24-month pre period, a 12-month implementation period, and a 6-month post period.

Changes in prescribing will be compared in prescribers from specialties whose prescribing is hypothesized to be relatively unaffected by the REMS (such as oncologists and hospice providers) versus those for whom the REMS could have greater impact on prescribing (e.g., dentists).

The analyses will include and report on patient activity before and after REMS implementation, spanning a 42-month period, July 2010 through December 2013.

Selection Periods:

- Pre Period: July 2010 – June 2012
- Implementation Period: July 2012 – June 2013
- Post Period: July 2013 – December 2013

Note that the above post period will be utilized for the 2014 report. Additional months will be added for reports in subsequent years.
For this study, results will be aggregated and reported at the month and quarter levels.

Changes in prescriptions for ER/LA opioids included in the class REMS will be assessed relative to changes in comparator drug groups.

Prescription and patient counts will be projected to the national level based on the LRx prescription sample with projection factors derived from the prescriptions in LRx relative to NPA TRx.

2. Inclusion Criteria

Subjects filling a prescription for a product of interest (Appendix 1) during the specified time period will be included. Subjects receiving study products (ER/LA opioids included in the class REMS) will all be reported at the individual generic strength level. Subjects receiving comparator products will be grouped into three product groups and reported at the product group level.

i. <u>Definition of study and comparator products</u>

- REMS ER/LA Opioid Analgesics, reported at the strength level:
  - Extended-release, oral-dosage forms containing: Hydrocodone, Hydromorphone, Morphine, Oxycodone, Oxymorphone, Tapentadol
  - Fentanyl and buprenorphine-containing transdermal delivery systems
  - Methadone tablets and solutions that are indicated for use as analgesics
- Comparator Products
  - Other opioid analgesics not covered by the class REMS for ER/LA opioids; reported at the individual market level – not individual product level, including oral forms.

- Prescription Nonsteroidal Anti-Inflammatory Drug (NSAID), celecoxib, as an "analgesic control" group. Celecoxib was selected as the only NSAID comparator because all celecoxib strengths require prescriptions. This is not the case with many other NSAIDs, which do not require prescriptions or do not require prescriptions for some strengths. As a result, data would therefore not be available in IMS or other claims databases. In addition, just as with the ER/LA opioid analgesics, celecoxib is more likely to be used for longer term pain due to its lower risk of gastrointestinal bleeding as compared to other NSAIDs.
- Benzodiazepines as an "abuse control" group; reported at the individual market level – not individual product level

ii. Patient Cohort

For each reporting month, patients who filled at least one Rx in the market of interested will be selected in the analysis. Patient will be indexed on their first prescription by product in the reporting month.

All patients will need to meet the following eligibility requirements to be included in the cohort:

- Constant Store Panel: IMS requires that the pharmacies used by each patient consistently supply data to the LRx database for the entire study window
- Patient Start Date: IMS also requires that each patient had activity in the LRx database (for any market) prior to the study period.

These eligibility criteria are necessary to control for complete patient history in the LRx database. The use of the "constant store panel" and "patient start date" are standard practices for ensuring continuous eligibility in custom LRx projects.

3. Objectives

i. Changes in prescribing will be compared in prescribers from specialties whose prescribing is hypothesized to be relatively unaffected by the REMS (such as oncologists and hospice providers) versus those for whom the REMS could have greater impact on prescribing (eg, dentists).

Additional Patient Criteria

For this objective we will segment prescriptions from prescribing specialties (Appendix 2) that are hypothesized to be relatively unaffected by the REMS and those for whom the REMS could have greater impact on prescribing.

Specialties (Appendix 2) that are hypothesized to be relatively unaffected by the REMS:

1. Dentists
2. Pediatricians
3. Non-clinical specialties (Medical genetics, Nuclear medicine, Pathology, Radiology, except interventional)

Specialties for which the REMS could have greater impact on prescribing:

1. Oncologists
2. Hospice care
3. Palliative care
4. Neurologists
5. Rheumatologists
6. Anesthesiology
7. Physical Medicine and Rehabilitation

The 24 month assessment report will not be able to break out specialties into the categories above, due to restrictions in methodology. For the 24 month report, we will analyze according to the specialty groups found in the appendix of this document. The 36 month assessment report will provide the specialty breakouts described above.

Outcomes

1. Monthly volume of prescriptions from specialties hypothesized to be relatively unaffected by the REMS
2. Monthly volume of prescriptions from specialties hypothesized to be more affected by the REMS

Statistical Analysis

Measurements of changes in prescribing before, during the transition implementation period, and after REMS implementation will be preformed. The average percent changes in volumes from the pre-period, transition period, and post periods, and 95%CI will be calculated. The statistical significance of these changes will be estimated by T-test. P values less than 0.05 will be considered significant. SAS 9.2 (Cary, NC) will be used to perform statistical tests for significance. The distribution of prescriptions across products will be calculated. These analyses will be stratified by categories of patient age group, gender, pay type and prescriber specialty group. The same analyses will be conducted for both ER/LA opioids and comparator groups so changes in prescribing can be compared and assessed across REMS and comparator products. An analysis of variance will be performed to assess whether the changes in prescription volumes from before and after REMS initiation are different for opioids included in class REMS vs opioids not included in the class REMS (IR opioids) and vs benzodiazepines.

9. HUMAN SUBJECT CONSIDERATION

This study will comply with all applicable laws, regulations, and guidance regarding patient protection including patient privacy.

This is a database study; no individual patients will be identified or enrolled. IMS Health has established Health Insurance Portability and Accountability Act (HIPAA)-compliant operating policies and procedures for extracting, translating, loading, and removing all personal health information (de-identifying) prior to depositing data in the IMS Health databases. The chance that any patient's identity would be revealed is exceedingly small. This is the only known risk to

individuals contained in the database. No direct benefits to individuals will be realized. The investigators do not intend to pursue review of the protocol by an ethical review board.

APPENDIX 1: PRODUCT LIST

The tables below outline the products that will be included in the analysis:

- Product Group denotes the product group and method of action.
- Generic Name denotes the generic name of each product included.
- Dosage Form Code lists the code for each product form that is included in our analysis.

REMS ER/LA Opioid Analgesics

PRODUCT GROUP	GENERIC NAME	DOSAGE FORM CODE
BUPRENORPHINE-TD	BUPRENORPHINE	PTWK
FENTANYL-TD	FENTANYL	PT72
HYDROCODONE ER	HYDROCODONE BITARTRATE	CP12
HYDROMORPHONE-LA	HYDROMORPHONE HCL	CP24, T24A
METHADONE	METHADONE HCL	CONC, SOLN, TABS, TBSO
MORPHINE-LA	MORPHINE SULFATE	CP24, TB12, TBCR
	MORPHINE SULFATE BEADS	CP24
	MORPHINE-NALTREXONE	CPCR
OXYCODONE-LA	OXYCODONE HCL	T12A, TB12
	OXYMORPHONE HCL	T12A, TB12
TAPENTADOL-LA	TAPENTADOL HCL	TB12

Comparator Products

Other Opioid Analgesics

Note: We have removed injectable and IV forms of other opioids per request from the FDA, SOLN below refers to oral or nasal solution forms.

PRODUCT GROUP	GENERIC NAME	DOSAGE FORM CODE
OTHER OPIOIDS	FENTANYL	LIQD
	FENTANYL CITRATE	FILM, LPOP, SOLN, SUBL, TABS
	HYDROCODONE-ACETAMINOPHEN	CAPS, LIQD, SOLN, TABS
	HYDROCODONE-IBUPROFEN	TABS
	HYDROMORPHONE HCL	LIQD, SUPP, TABS,
	MORPHINE SULFATE	SOLN, SUPP, TABS
	OXYCODONE HCL	CAPS, CONC, SOLN, TABA, TABS
	OXYMORPHONE HCL	SUPP, TABS
	TAPENTADOL HCL	TABS

Prescription NSAIDs

PRODUCT GROUP	GENERIC NAME	DOSAGE FORM CODE
NSAIDs	CELECOXIB	CAPS

Benzodiazepines

PRODUCT GROUP	GENERIC NAME	DOSAGE FORM CODE
BENZODIAZEPINES	ALPRAZOLAM	CONC, TABS, TB24, TBDP
	CHLORDIAZEPOXIDE HCL	CAPS, SOLR
	CLORAZEPATE DIPOTASSIUM	TABS, TB24
	DIAZEPAM	CONC, DEVI, SOLN, TABS
	HALAZEPAM	TABS
	LORAZEPAM	CONC, SOLN, TABS
	OXAZEPAM	CAPS, TABS

APPENDIX 2: PRESCRIBER SPECIALTY LIST

Prescribers will be grouped by specialty and reported on as follows:

Pain

APM	PAIN MEDICINE (ANESTHESIOLOGY)
PMD	PAIN MEDICINE
PME	PAIN MANAGEMENT
PMN	PAIN MEDICINE (NEUROLOGY)
PMR	PAIN MEDICINE (PHYSICAL MEDICINE & REHABILITATION)
PPN	PAIN MEDICINE (PSYCHIATRY)

PCP

GP	GENERAL PRACTICE
GPM	GENERAL PREVENTIVE MEDICINE
FM	FAMILY MEDICINE
FP	FAMILY PRACTICE
FPG	GERIATRIC MEDICINE (FAMILY MEDICINE)
IM	INTERNAL MEDICINE
IMA	INTERNAL MEDICINE/ANESTHESIOLOGY
IMG	GERIATRIC MEDICINE (INTERNAL MEDICINE)
IPM	INTERNAL MEDICINE/PREVENTIVE MEDICINE

Dentist

DGP	DENTIST
DNAN	DENTISTRY/ANESTHESIOLOGY
DNED	DENTISTRY/ENDODONTICS
DNOR	DENTISTRY/ORTHODONTICS
DNPD	DENTISTRY/PEDODONTICS
DNPO	DENTISTRY/PROSTHODONTICS
DNPR	DENTISTRY/PERIODONTICS
OMF	ORAL & MAXILLOFACIAL SURGERY

Surgery

CCS	SURGICAL CRITICAL CARE (SURGERY)

CDS	CARDIOVASCULAR SURGERY
CFS	CRANIOFACIAL SURGERY
CHS	CONGENITAL CARDIAC SURGERY (THORACIC SURGERY)
CRS	COLON & RECTAL SURGERY
CTS	CARDIOTHORACIC SURGERY
DS	DERMATOLOGIC SURGERY
ENR	ENDOVASCULAR SURGICAL NEURORADIOLOGY (NEUROLOGY)
ES	ENDOVASCULAR SURGICAL NEURORADIOLOGY (NEUROLOGICAL SURGERY)
ESN	ENDOVASCULAR SURGICAL NEURORADIOLOGY (RADIOLOGY)
FPR	FEMALE PELVIC MEDICINE & RECONSTRUCTIVE SURGERY
FPS	FACIAL PLASTIC SURGERY
GS	GENERAL SURGERY
HNS	HEAD & NECK SURGERY
HPS	HOSPICE & PALLIATIVE MEDICINE (SURGERY)
HS	HAND SURGERY
HSO	HAND SURGERY (ORTHOPEDICS)
HSP	HAND SURGERY (PLASTIC SURGERY)
HSS	HAND SURGERY (SURGERY)
NCC	CRITICAL CARE MEDICINE (NEUROLOGICAL SURGERY)
NS	NEUROLOGICAL SURGERY
NSP	PEDIATRIC SURGERY (NEUROLOGY)
OMF	ORAL & MAXILLOFACIAL SURGERY
ORS	ORTHOPEDIC SURGERY
OSM	SPORTS MEDICINE (ORTHOPEDIC SURGERY)
OSS	ORTHOPEDIC SURGERY OF THE SPINE
PCS	PEDIATRIC CARDIOTHORACIC SURGERY
PDS	PEDIATRIC SURGERY
PS	PLASTIC SURGERY
PSH	PLASTIC SURGERY WITHIN THE HEAD & NECK
PSO	PLASTIC SURGERY WITHIN THE HEAD & NECK (OTOLARYNGOLOGY)
PSP	PLASTIC SURGERY WITHIN THE HEAD & NECK
SO	SURGICAL ONCOLOGY
SPS	SURGERY/PLASTIC SURGERY
TRS	TRAUMA SURGERY
TS	THORACIC SURGERY
TTS	TRANSPLANT SURGERY
UPR	FEMALE PELVIC MEDICINE & RECONSTRUCTIVE SURGERY (UROLOGY)
VS	VASCULAR SURGERY

Emergency Medicine

CCE	CRITICAL CARE MEDICINE (EMERGENCY MEDICINE)
EFM	EMERGENCY MEDICINE/FAMILY MEDICINE
EM	EMERGENCY MEDICINE
EMP	PEDIATRICS/EMERGENCY MEDICINE
EMS	EMERGENCY MEDICAL SERVICES
EMSP	EMERGENCY MEDICAL SERVICES (OTHER)
ESM	SPORTS MEDICINE (EMERGENCY MEDICINE)
ETX	MEDICAL TOXICOLOGY (EMERGENCY MEDICINE)

HPE	HOSPICE & PALLIATIVE MEDICINE (EMERGENCY MEDICINE)
MEM	INTERNAL MEDICINE/EMERGENCY MEDICINE
PE	PEDIATRIC EMERGENCY MEDICINE
PEM	PEDIATRIC EMERGENCY MEDICINE (PEDIATRICS)

Oncology

GO	GYNECOLOGICAL ONCOLOGY
HO	HEMATOLOGY/ONCOLOGY
OMO	MUSCULOSKELETAL ONCOLOGY
ON	MEDICAL ONCOLOGY
PHO	PEDIATRIC HEMATOLOGY/ONCOLOGY
RO	RADIATION ONCOLOGY

Hospice and Palliative Medicine

HPA	HOSPICE & PALLIATIVE MEDICINE (ANESTHESIOLOGY)
HPD	HOSPICE & PALLIATIVE MEDICINE (RADIOLOGY)
HPF	HOSPICE & PALLIATIVE MEDICINE (FAMILY MEDICINE)
HPI	HOSPICE & PALLIATIVE MEDICINE (INTERNAL MEDICINE)
HPM	HOSPICE & PALLIATIVE MEDICINE
HPN	HOSPICE & PALLIATIVE MEDICINE (PSYCHIATRY & NEUROLOGY)
HPO	HOSPICE & PALLIATIVE MEDICINE (OBSTETRICS & GYNECOLOGY)
HPP	HOSPICE & PALLIATIVE MEDICINE (PEDIATRICS)
HPR	HOSPICE & PALLIATIVE MEDICINE (PHYSICAL MEDICINE & REHABILITATION)
PLM	PALLIATIVE MEDICINE

All Other: all other specialty codes not listed above.
Our analysis will break out the top 10 other specialties based on total prescriptions for ER/LA Opioid products of interest during the entire study period.

Appendix I - DRRP Letter 3

Prescriber Letter #3

FDA-Required REMS Program for Serious Drug Risks

Subject:	**Risk Evaluation and Mitigation Strategy (REMS) for all extended-release/long-acting opioid analgesic drug products due to their risks of misuse, abuse, addiction, and overdose**

Dear **DEA**-Registered Prescriber:

You are receiving this letter because you recently registered with DEA to prescribe Schedule II or III drugs. The purpose of this letter is to inform you about a Risk Evaluation and Mitigation Strategy (REMS) that has been required by the U.S. Food and Drug Administration (FDA) for all extended-release and long-acting (ER/LA) opioid analgesic drug products.

ER/LA opioid analgesics are used for the management of chronic moderate-to-severe pain in the U.S., and can be safe and effective in appropriately selected patients when used as directed. However, opioid analgesics are also associated with serious risks and are at the center of a major public health crisis of increased misuse, abuse, addiction, overdose, and death.

FDA determined that a REMS was necessary to ensure that the benefits of ER/LA opioid analgesics continue to outweigh their risks of adverse outcomes (addiction, unintentional overdose, and death) resulting from inappropriate prescribing, abuse, and misuse. A REMS is a strategy to manage a known or potential serious risk associated with a drug product. In the interest of public health and to minimize the burden on the healthcare delivery system of having multiple unique REMS programs, the pharmaceutical companies subject to this REMS have joined together to implement the REMS for all ER/LA opioid analgesic drug products.

The ER/LA Opioid Analgesic REMS has three principal components:

a) prescriber training on all ER/LA opioid analgesics,
b) a *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD), and
c) a unique Medication Guide for each ER/LA opioid analgesic drug product.

The branded and generic drug products subject to this REMS include *all*:

- extended-release, oral-dosage forms containing
  - hydromorphone,
  - morphine,
  - oxycodone,
  - oxymorphone, or
  - tapentadol;
- fentanyl and buprenorphine-containing transdermal delivery systems; *and*
- methadone tablets and solutions that are indicated for use as analgesics.

Prescriber Action

Under the REMS, you are **strongly encouraged** to do **all** of the following:

- **Train (Educate Yourself) -** Complete REMS-compliant training on the ER/LA opioid analgesics offered by an accredited provider of continuing education (CE) for your discipline. *REMS-compliant training* will: (a) be delivered by accredited CE providers; (b) cover all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"); (c) include a post-course knowledge assessment; and (d) be subject to independent audit of content and compliance with applicable accrediting standards.

- **Counsel Your Patients –** Discuss the safe use, serious risks, storage, and disposal of ER/LA opioid analgesics with patients and their caregivers every time you prescribe these medicines. Use the enclosed *Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics* (PCD) to facilitate these discussions.

- **Emphasize Patient and Caregiver Understanding of the Medication Guide -** Stress to patients and their caregivers the importance of reading the Medication Guide that they will receive from their pharmacist every time an ER/LA opioid analgesic is dispensed to them, as information may have changed.

- **Consider Using Other Tools -** In addition to the PCD, there are other publicly available tools to improve patient, household and community safety when using ER/LA opioid analgesics, as well as compliance with conditions of treatment, including Patient-Prescriber Agreements (PPAs) and risk assessment instruments.

REMS-compliant Training Programs

REMS-compliant training is a critical component of the ER/LA Opioid Analgesics REMS program. REMS-compliant training will focus on the safe prescribing of ER/LA opioid analgesics. The FDA developed core messages to be communicated to prescribers in the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics ("FDA Blueprint"), which is being used by accredited CE providers to develop the REMS-compliant training courses. The Blueprint is available at http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM277916.pdf

REMS-compliant training for prescribers includes both general and product-specific drug information, as well as information on weighing the benefits and risks of opioid therapy, appropriate patient selection, managing and monitoring patients, and counseling patients on the safe use of these drugs. In addition, the education will include information on how to recognize evidence of, and the potential for, opioid misuse, abuse, addiction, and overdose. REMS-compliant training may also be offered by academic institutions or learned societies independent of REMS-related funding. We encourage you to successfully complete REMS-compliant training from an accredited CE provider to improve your ability to prescribe these medications more safely.

For a listing of available REMS-compliant training offered by accredited CE providers under the REMS, visit www.ER-LA-opioidREMS.com.

The Patient Counseling Document on Extended-Release/Long-Acting Opioid Analgesics (PCD)

Enclosed with this letter is the Patient Counseling Document that was developed under the REMS for ER/LA opioid analgesics and designed to assist you in having important conversations with patients for whom you select an ER/LA opioid analgesic. It contains important safety information common to the drug products subject to this REMS, and includes space for you to write additional information to help your patients use their ER/LA opioid analgesic safely. The PCD should be provided to the patient or their caregiver at the time of prescribing. Patients and their caregivers should be counseled on:

- the importance of taking these medicines exactly as you prescribe them,
- the need to store ER/LA opioid analgesics safely and securely – out of the reach of children, pets, and household members– to avoid risks from unintended exposure,
- the importance of not sharing these medications, even if someone has the same symptoms as the patient, *and*
- the proper methods of disposal of unneeded ER/LA opioid analgesics.

You can re-order or print additional copies of the PCD from www.ER-LA-opioidREMS.com.

Adverse Event Reporting

To report all suspected adverse reactions associated with the use of the ER/LA opioid analgesics, contact:

- the pharmaceutical company that markets the specific product, or
- the FDA MedWatch program:
  - by phone at 1-800-FDA-1088 (1-800-332-1088) or
  - online at www.fda.gov/medwatch/report.htm

More information about this REMS can be obtained at: www.ER-LA-opioidREMS.com or by calling the ER/LA Opioid Analgesic REMS Call Center at 1-800-503-0784.

Sincerely,

The ER/LA Opioid Analgesic REMS Companies

Appendix J – PCD

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics

Patient Name:

The DOs and DON'Ts of Extended-Release / Long - Acting Opioid Analgesics

DO:

- Read the **Medication Guide**
- Take your medicine exactly as prescribed
- Store your medicine away from children and in a safe place
- Flush unused medicine down the toilet
- Call your healthcare provider for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

Call 911 or your local emergency service right away if:

- You take too much medicine
- You have trouble breathing, or shortness of breath
- A child has taken this medicine

Talk to your healthcare provider:

- If the dose you are taking does not control your pain
- About any side effects you may be having
- About all the medicines you take, including over-the-counter medicines, vitamins, and dietary supplements

DON'T:

- **Do not** give your medicine to others
- **Do not** take medicine unless it was prescribed for you
- **Do not** stop taking your medicine without talking to your healthcare provider
- **Do not** break, chew, crush, dissolve, or inject your medicine. If you cannot swallow your medicine whole, talk to your healthcare provider.
- **Do not** drink alcohol while taking this medicine

For additional information on your medicine go to: **dailymed.nlm.nih.gov**

Patient Counseling Document on Extended-Release / Long-Acting Opioid Analgesics

Patient Name:

Patient Specific Information

Take this card with you every time you see your healthcare provider and tell him/her:

- Your complete medical and family history, including any history of substance abuse or mental illness
- The cause, severity, and nature of your pain
- Your treatment goals
- All the medicines you take, including over-the-counter (non-prescription) medicines, vitamins, and dietary supplements
- Any side effects you may be having

Take your opioid pain medicine exactly as prescribed by your healthcare provider.

Documento de orientación al paciente sobre medicamentos narcóticos para el dolor, también llamados analgésicos opiáceos *(opioid analgesics en inglés),* de liberación extendida y/o acción prolongada

Nombre del paciente:

LO QUE DEBE HACER y NO DEBE HACER con los medicamentos narcóticos para el dolor, también llamados analgésicos opiáceos *(opioid analgesics en inglés),* de liberación extendida y/o acción prolongada

LO QUE DEBE HACER:

- Lea la **Guía del Medicamento**
- Use su medicina siguiendo exactamente las instrucciones de como ha sido indicada
- Guarde su medicina fuera del alcance de los niños y en un lugar seguro
- Arroje la medicina que le ha sobrado en el servicio sanitario/el inodoro/la taza del baño y vacíelo para asegurarse que no queden residuos de la medicina en el mismo
- En caso de reacciones a su medicina, comuníquese inmediatamente con su médico o proveedor de salud. Usted tiene la opción de reportar reacciones a su medicina a la FDA al 1-800-FDA-1088

Llame inmediatamente al 911 o a su centro/servicio local de emergencia, si:

- Tomó demasiada medicina
- Siente dificultad al respirar o siente que le falta el aire
- Un niño ha tomado la medicina

Hable con su médico o proveedor de salud:

- Si la dosis recetada no controla su dolor
- Sobre cualquier reacción que tenga a su medicina
- Acerca de todas las medicinas que está tomando, incluyendo medicinas sin receta médica, vitaminas y suplementos nutricionales

LO QUE NO DEBE HACER:

- **No** debe dar su medicina a otras personas
- **No** debe tomar medicinas a menos que se las hayan recetado específicamente a usted
- **No** debe dejar de tomar su medicina sin antes consultar con su médico o proveedor de salud
- **No** debe moler/triturar, quebrar, disolver, masticar, ni inyectar su medicina. Si usted no puede tragar/ingerir su medicina entera, comuníquese con su médico o proveedor de salud
- **No** debe tomar bebidas alcohólicas mientras esté tomando esta medicina

Para obtener información adicional sobre su medicina, visite:
dailymed.nlm.nih.gov

Documento de orientación al paciente sobre medicamentos narcóticos para el dolor, también llamados analgésicos opiáceos (opioid analgesics en inglés), de liberación extendida y/o acción prolongada

Nombre del paciente:

Información específica del paciente

Lleve estas instrucciones cada vez que visite a su médico o proveedor de salud e infórmele:

- Su historia médica completa y la de su familia, incluyendo cualquier antecedente de abuso de sustancias o enfermedades de salud mental
- La causa, los síntomas y el grado de severidad de su dolor
- Los resultados que espera de su tratamiento
- Acerca de todas las medicinas que está tomando, incluyendo medicinas sin receta médica, vitaminas y suplementos nutricionales
- Sobre cualquier reacción que usted está teniendo a su medicina

Tome sus medicamentos narcóticos para el dolor, también llamados analgésicos opiáceos *(opioid analgesics en inglés),* de liberación extendida y/o acción prolongada exactamente como han sido indicados por su médico o proveedor de salud

Appendix K - Glossary

Appendix A: Glossary

Accredited provider	An institution or organization that is accredited to provide certified continuing education activities for licensed health care professionals [a]
Ashfield Healthcare	REMS Call Center/IVR Vendor
Call Center Subteam	The team responsible for selection and oversight of the vendor operating the centralized Call Center for the ER/LA Opioid Analgesics REMS, including development and ongoing operations.
Cenveo	PCD Portal Vendor
Certified continuing education activity	An educational event or intervention offered by an accredited provider to licensed health care professionals that is based upon identified needs, has a purpose or objectives, and is evaluated to assure the needs are met[a]
CE Outcomes	CE Data Aggregation Reporting Vendor
Continuing Active REMS Phase	Time period from July 2013- December 2013
Continuing Education Subteam	The team responsible for design and implementation of CE activities for the REMS Program (eg, grant management system, review process).
Dentist	Dental public health, endodontics, general dentistry, oral and maxillofacial pathology, oral and maxillofacial radiology, oral and maxillofacial surgery, orthodontics and dentofacial orthopedics, pediatric dentistry, periodontics and prosthodontics[b]
ER/LA Opioid Analgesic prescriber	An individual clinician who is registered with the DEA, eligible to prescribe schedule 2 and 3 drugs, and has written at least one ER/LA opioid script in the past year[b]
Extended-Release/Long-Acting (ER/LA) Opioid Analgesics	Certain opioid drug products indicated for use as analgesics that comprise two distinct subsets – those products that have a duration of action that is inherently, or pharmacologically, longer-acting than most other opioid analgesic drug substances, and those products embodying modified-release formulations that are specifically designed to provide a longer duration of action than immediate-release formulations containing the same opioid drug substances. The long-acting/extended-release opioid analgesics currently include a) extended-release, solid, oral dosage forms containing hydromorphone, morphine, oxycodone, tapentadol, and oxymorphone, plus the fentanyl-containing and buprenorphine-containing transdermal delivery systems (collectively, the modified-release formulations that are pharmaceutically-long-acting opioid analgesics), and b) methadone tablets or liquid, which are not formulated in extended-release dosage forms (collectively, the pharmacologically-long-acting opioid analgesics)[a]

FDA Blueprint	A document entitled, "FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioid Analgesics," approved as part of this REMS that contains core messages to be conveyed to prescribers in the training about the risks and appropriate prescribing practices for the safe use of ER/LA opioids[a]
HealthCore	Vendor reposible for Assessment Element 4
IMS Health	Vendor who contributed to Assessment Elements 6, 7, and 8
Inflexxion	Vendor who contributed to Assessment Element 5
McKesson	REMS Website Vendor
MedBiquitous	REMS CE Data Collection Standards Vendor
Metrics Subteam	The team responsible for designing and implementing the metrics Assessment Reports in accordance with FDA requirements.
NDA/ANDA holder	A pharmaceutical company that has authorization to market a drug product that is subject to the ER/LA Opioid Analgesics REMS[a]
Non-pain specialist	A specialist or subspecialist that does not specialize in the evaluation and treatment of patient pain[b]
Pain specialist	A specialist whose practice predominately involves the evaluation and treatment of patient pain[b]
PDRN	REMS Communication Vendor
Polaris	GMS Portal Vendor CE Data Aggregation System Vendor
Practice type	A description of the clinician's practice by broad category [b]
Pre-REMS Period	Time period from July 2010-June 2012
Prescriber	A licensed healthcare professional that is authorized to write prescriptions for medications or medical devices. Prescribers are required to be registered with the federal Drug Enforcement Administration to write prescriptions for medicines containing controlled substances. In some jurisdictions, a separate registration with a state controlled substances authority is also required for prescribing those medicines.[a]
Prescribers successfully completing	FDA REMS defined ER/LA opioid prescribers that have completed all components of an educational activity and met the education provider's criteria for passing. Components of an education al activity include instruction, assessment of learning, and potentially evaluation Profession: Professions inclusive of all those eligible to prescribe

	ER/LA opioids- physicians, advanced practice nurse, pharmacists, dentist, optometrist, physician assistant, podiatrist, other.[b]
Primary care	A clinician serving as a first contact and providing continuing care to the patient. Primary care clinicians may coordinate specialist care for the patient.[b]
Profession	Professions inclusive of all those eligible to prescribe ER/LA opioids- physicians, advanced practice nurse, pharmacists, dentist, optometrist, physician assistant, podiatrist, other [(b)]
Related activities	Activity is related to the REMS regulation but does not meet all requirements set out for CE activities by the REMS regulation[c]
REMS-Launch Period	Time period from June 2012-June 2013
REMS Program Companies (RPC)	Companies with approved ANDAs/NDAs for ER/LA opioid analgesics. The RPC is the program's governing body with overall responsibility for supervision and direction of the program. The consortium of NDA/ANDA holders of branded and generic long-acting and extended-release opioid analgesic drug products that was formed for the express purpose of creating a single shared REMS for those products[a]
RPC-supported REMS-compliant training	Training will be considered "REMS-compliant training" if 1) it, for training provided by CE providers, is offered by an accredited provider to licensed prescribers, 2) it includes all elements of the FDA Blueprint for Prescriber Education for Extended-Release and Long-Acting Opioids ("FDA Blueprint"), 3) it includes a post-course knowledge assessment of all of the sections of the FDA Blueprint, and 4) it is subject to independent audit to confirm that conditions of the REMS training have been met.[a]
RMPDC	Vendor who contributed to Assessment Element 5
RPC Oversight Committee	An appointed number of RPC member companies selected by the entire RPC responsible for day-to-day operations of the ER/LA Opioid Analgesics REMS.
Sponsor	A term used by the continuing education community to refer to accredited providers of certified continuing education activities[a]

Successfully completing	Completing all components of an educational activity and meeting the education provider's criteria for passing. Components of an educational activity include instruction, assessment of learning, and potentially evaluation[b]
UBC	Vendor responsible for the following: Assessment report development Surveillance Monitoring – NSDUH and MTF (Assessment Element 5) Prescribers perception to barriers of access survey vendor
Technology Subteam	The team responsible for providing oversight and subject-matter expertise on the ER/LA Opioid Analgesics REMS Website and other technology related items, eg Call Center, metrics database
Title	The title of the CE activity[c]

Sources:

(a) Extended-Release and Long-Acting Opioid Analgesics Risk Evaluation and Mitigation Strategy (REMS) Supporting Document

(b) Medical Education Metrics definition- MedBiquitous website http://www.medbiq.org/mems/definitions

(c) Medical Education Metrics Implementation Guidelines for REMS CE Data Exchange 4/26/13