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Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology Review of Final Sponsor Reports and FDA Evaluations for ER/LA PMRs 3033-3, 3033-4, and 3033-5

Date:	November 13, 2019
Primary Reviewer:	Cynthia Kornegay, Ph.D. Epidemiologist, Division of Epidemiology II (DEPI II)
Team Leader:	Tamra Meyer, Ph.D., M.P.H. Epidemiology Team Lead, DEPI II
Associate Office Director:	Judy Staffa, Ph.D., R.Ph. Associate Director for Public Health Initiatives Office of Surveillance and Epidemiology
Subject:	Summary assessment of final reports and FDA evaluations for ER/LA PMRs 3033-3, 3033-4, and 3033-5
Drug Name(s):	extended-release and long-acting opioid analgesic products
Application Type/Number(s):	multiple
Applicant/Sponsor(s):	multiple
OSE RCM #:	
PMR #:	3033-3, 3033-4, 3033-5

Table of Contents

Abbreviations

AUDADIS-IV	Alcohol Use Disorder and Associated Disabilities Interview Schedule-IV
BPI-SF	Brief Pain Inventory – Short Form
DoD	Department of Defense
DSM	American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders
EMR	electronic medical record
ER/LA	extended release/long-acting
FDA	Food and Drug Administration
ID	identification
LCA	latent class analysis
LEAD	Longitudinal Expert All-Data
MOS SF-36	Medical Outcomes Study: 36-Item Short Form Health Survey Instrument
MTMM	Multi-Trait Multimethod Matrix
OPC	Opioid PMR Consortium
PDUQp	Prescription Drug Use Questionnaire-Patient Version
PMR	post-marketing requirement
POMAQ	Prescription Opioids Misuse and Abuse Questionnaire
POTQ V2	Prescription Opioid Therapy Questionnaire
PRISM	Psychiatric Research Interview for Substance and Mental Disorders
PRO	patient-reported outcomes
SCID-I	Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Substance Use Disorders Module
SDRS-5	Socially Desirable Response Set 5-Item Survey
SR-MAD	Self-Report Misuse, Abuse, and Diversion of Prescription Opioids
SUD	substance use disorder

1 EXECUTIVE SUMMARY

In September 2013, the Food and Drug Administration required all extended-release/long-acting (ER/LA) opioid analgesic sponsors to conduct a suite of post-marketing required studies (PMRs) to assess the risks of abuse, misuse, addiction, overdose and death associated with the long-term use of ER/LA opioid analgesics for chronic pain. These studies were designed in close communication with Agency scientists. Based on the eventual study designs and stakeholder feedback from the "Postmarketing Requirements for the Class-Wide Extended-Release/ Long-Acting Opioid Analgesics Public Meeting" in May 2014, the ER/LA opioid analgesic sponsors were released from the original PMRs and issued revised PMR studies, ER/LA PMR's 3033-1 through 3033-11.

Three of the Agency's required studies (3033-3, 3033-4, and 3033-5; formerly 2065-2a, b, and c) involve developing and validating instruments to measure misuse, abuse, and addiction of opioid analgesics among patients with chronic pain. These validated instruments are expected to be used to assess misuse, abuse, and addiction in studies 3033-1 and 3033-9.

The sponsors developed two instruments to evaluate these outcomes, the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) and the Psychiatric Research Interview for Substance and Mental Disorders (PRISM-5-Op). These questionnaires were validated in three studies: ER/LA PMRs 3033-3 and 3033-4 for the POMAQ, and ER/LA PMR 3033-5 for the PRISM.

ER/LA PMR 3033-3 assessed the face validity and comprehension of the POMAQ. ER/LA PMR's 3033-4 and 3033-5 were quantitative content validation evaluations of the POMAQ and PRISM-5-Op, respectively. In addition to the POMAQ and PRISM responses, additional surveys were used to assess pain, general health, and specific aspects of opioid analgesic use, misuse, and abuse, as well as other addictive behaviors. Urine and hair samples were collected for the POMAQ validation, specifically to assess the agreement between what patients admitted to taking and what drugs were actually present in their bodies. For both studies, the patient information collected was also analyzed by two independent experts, and their responses compared to the survey results. FDA evaluated the results of these studies using the framework described in "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims".

Both the sponsor group and the FDA evaluators found that the POMAQ and PRISM-5-Op were valid and reliable measures of misuse, abuse, and addiction behaviors, respectively. The strengths of the studies were that the instruments were tailored to the needs of the ER/LA PMR studies, and they were comprehensively assessed within a clearly described framework. FDA evaluators did find that the complicated scoring algorithms for both surveys likely lowered the agreement between the expert evaluation results and the surveys. In addition, since the POMAQ is a cross-sectional tool that is being used to assess a condition that is diagnosed over time, repeated surveys are recommended for the best estimates of the prevalence of misuse and abuse.

In summary, the goal of these three studies was to provide validated, consistent, operationalized outcome definitions of misuse, abuse, and addiction for the ER/LA PMR study series. **The POMAQ and PRISM-5-Op both demonstrated the ability to ascertain misuse, abuse, and SUD/addiction at an acceptable level for the ER/LA PMR studies, and fulfilled ER/LA PMRs 3033-3, 4, and 5.** These instruments will be used in ER/LA PMR 3033-1, a prospective cohort study investigating the risks of misuse, abuse, and addiction in a cohort or patients prescribed opioid analgesics for chronic pain. FDA also expects that these instruments can form the basis of future studies in the arena of misuse and abuse research and hopes that the validation work started by the OPC can be extended to other appropriate populations of patients with pain conditions.

2 INTRODUCTION

On September 8, 2013, the Food and Drug Administration (FDA) required all extended-release/long-acting (ER/LA) opioid analgesic sponsors (Opioid PMR Consortium, OPC) to conduct a suite of post-marketing studies to assess the risks of abuse, misuse, addiction, overdose and death associated with the long-term use of ER/LA opioid analgesics for chronic pain [Post-Marketing Requirements (PMRs) 2065-1, 2065-2, 2065-3, 2065-4, and 2065-5, each with sub-studies]. Based on stakeholder feedback at the "Postmarketing
Requirements for the Class-Wide Extended-Release/ Long-Acting Opioid Analgesics Public Meeting" in May of 2014, ER/LA opioid analgesic sponsors were released from the original PMRs and issued revised PMRs (sent on February 4th, 2016), with new timelines (PMRs 3033-1 through 3033-11).

Three of the Agency's required studies (3033-3, 3033-4, and 3033-5; formerly 2065-2a, b, and c) involve developing and validating instruments to measure misuse, abuse, and addiction of opioid analgesics among patients with chronic pain. These validated instruments are expected to be used to assess misuse, abuse, and addiction in studies 3033-1 and 3033-9.

To partially fulfill this post-marketing requirement, the OPC chose to modify two existing instruments: the first is the Self-report Misuse, Abuse and Diversion of Prescription (Rx) Opioids questionnaire (SR-MAD). The SR-MAD was originally developed with the intent of capturing opioid analgesic tampering practices, and modifications were made following input from an Agency-led observational studies workgroup to enhance the clarity of the questions, and to include additional questions regarding misuse and abuse behaviors. The new, modified questionnaire has been renamed the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). The POMAQ includes 19 items and is designed to assess current and past patient behaviors related to prescription opioid analgesic misuse and abuse.

The OPC conducted two separate studies: 3033-3 (qualitative) and 3033-4 (quantitative) to validate the POMAQ. The objective of the first study was to qualitatively evaluate patient understanding and ensure the content validity of the POMAQ among adults with chronic moderate to severe pain, including patients who were known to abuse and those known not to abuse opioid analgesics, those known to abuse other known substances, and those not using opioid analgesics. The objective of the second study was to quantitatively assess the validity and reliability of the POMAQ. This analysis collected information from several questionnaires, hair and urine samples, and patient medical records. This information was used to verify and confirm patient's responses to POMAQ questions, assess the reliability of patient answers, and to compare the POMAQ outcomes to those arrived at by experts in the addiction and pain fields.

The second modified instrument selected is the Psychiatric Research Interview for Substance and Mental Disorders (PRISM). The PRISM is a diagnostic interview for conditions described in the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorders (DSM). The validity of the instrument had been previously established in the literature. For the ER/LA PMR's, the PRISM was updated for DSM-5 criteria and customized for patients on chronic opioid analgesic therapy (Op). The objective of ER/LA PMR 3033-5 was to determine if this new version of the PRISM (PRISM-5-Op) was still valid when used in a population of patients on chronic opioid analgesic therapy at high- and low-risk of developing a substance use or addiction disorder.

Both surveys were assessed for content validity according to the framework described in the 2009 Agency Guidance for Industry, Patient Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims (PRO guidance). This guidance emphasizes the importance of conducting qualitative research throughout the process of instrument development to ensure that the content of the measure is consistent with patients' experiences and to ensure that the questions are interpreted as intended and asked in a manner understood by patients.

2.1 REGULATORY HISTORY

In 2013, the OPC was required to conduct multiple studies to better understand the risks associated with long-term opioid analgesic therapy for the treatment of chronic pain. Two of the studies required the sponsors to validate a measure of abuse and misuse of prescription opioid analgesics that could be used in other required studies.

The original post-marketing study 2065-2 requirements were described as follows:
"Develop and validate measures of the following opioid-related adverse events: misuse, abuse, addiction, overdose and death (based on DHHS definition, or any agreed-upon definition), which will be used to inform the design and analysis for PMR # 2065-1 and any future post-marketing safety studies and clinical trials to assess these risks. This can be achieved by conducting an instrument development study or a validation study of an algorithm based on secondary data sources."

During the protocol development process, the OPC and the FDA agreed to address this question with three studies – 2065-2a (qualitative), 2065-2a (quantitative), and 2065-2b. The first two studies assessed the validity of the POMAQ, while the third investigated the PRISM-5-Op.

Because all of the questions in the original PMR required multiple investigations to fully address, in 2015 FDA revised the ER/LA PMRs to enable each study to be tracked individually, and a release and reissue letter was sent to the OPC on February 4, 2016. The revised and reissued post-marketing requirements are as follows:

3033-3 A prospective observational study designed to assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Patient understanding of the concepts of misuse and abuse will also be obtained.

3033-4 An observational study to evaluate the validity and reproducibility of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ), which will be used to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.

3033-5 An observational study to validate measures of prescription opioid Substance Use Disorder and addiction in patients who have received or are receiving opioid analgesics for chronic pain.

3 REVIEW METHODS AND MATERIALS

This review summarizes the protocol, final report, and FDA assessments of ER/LA PMR studies 3033-3, 3033-4, and 3033-5.

The sponsor submitted the following documents for ER/LA PMR 3033-3:

- Observational Study 2A (Qualitative Protocol): A Qualitative Study to Assess the Content Validity of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) (Dec 2014)
- Observational Study 2A: Final Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) Clinician Interview Report (Jun 2015)
- Observational Study 2A (Qualitative): Report on A Qualitative Study to Assess the Content Validity of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ): Qualitative Report of Cognitive Interviews (Dec 2015)

The FDA reviews for study ER/LA PMR 3033-3 study are:

- Review of Final Observational Study 2A (Qualitative Protocol) (C. Lee, Sep 2014)
- Epidemiology: Final Study Report – Study 3 (3033-3), ER/LA Opioid Post-Market Required Study (A. Secora, Apr 2017)

Note that the final protocol was submitted by the sponsors after FDA's review to provide the opportunity for them to incorporate FDA's suggestions.

The sponsor submitted the following documents related to ER/LA PMR Study 3033-4:

- Observational Study 2A (Quantitative Protocol): A Quantitative Study to Assess the Construct Validity of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) (Nov 2015)
- Observational Study 2A: Protocol for the Validation Substudy of the Study 2A (3033-4) POMAQ Validation Study (Apr 2017)
- Observational Study 2A (Quantitative) – 3033-4: Final Report Part 1: Descriptive Report on a Quantitative Study to Assess the Construct Validity of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) (Jun 2017)
- Observational Study 2A (Quantitative) – 3033-4: Final Report on a Quantitative Study to Assess the Construct Validity of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) (Nov 2017)
- Observational Study 2A (Quantitative) – 3033-4: Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) Validation Substudy 2 Report (May 2018)

The FDA reviews related to ER/LA PMR 3033-4 are:

- "Evaluate draft submittal of proposed survey instrument to address ER/LA Post Marketing Requirement (PMR) #2 (Validation of Misuse, Abuse, Addiction, Overdose, and Death)" (A. Trachtenberg, Jul 2014)
- Review of Final Observational Study 2A (Quantitative Protocol), "A Quantitative Study to Assess the Construct Validity of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ)" (C. Lee, Nov 2014)
- Final Study Report (Part 1) – Study 3033-4, ER/LA opioid analgesic post-market required study (A. Secora, Aug 2017)
- Assessment of Extended Release/Long-Acting PMR Studies 3033-3, 3033-4, 3033-5 Final Study Reports Designed to Validate the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) and Psychiatric Research Interview for Substance and Mental Disorders - DSM-5 Version for Opioid Use Disorders (PRISM-5-OP) Survey Instruments (A. Trachtenberg, Dec 2018)
- Clinical Outcome Assessment (COA) review for POMAQ/misuse and abuse behaviors of opioid (W. Chen, Dec 2018)
- Final Report on a Quantitative Study to assess the Construct Validity of the prescription Opioid Misuse and Abuse Questionnaire (POMAQ) (C. Lee, Nov 2018)

The summary of ER/LA PMR 3033-5 includes the following sponsor submissions:

- Draft protocol "Validation of PRISM-5-OP, Measure of addiction to prescription opioid medication" (Aug 2014)
- Final protocol "Validation of PRISM-5-OP, Measure of addiction to prescription opioid medication" (Apr 2015)
- ER/LA opioid post-marketing requirement observational study #3033-5 (Study 2b), "Validation of PRISM-5-OP, Measure of addiction to prescription opioid medication", Final Report (Oct 2017)

The following FDA documents will also be summarized:

- Protocol review of Study # 2065-2b, "Validation of PRISM-5-OP, Measure of addiction to prescription opioid medication" (C. Lee, Sep 2014)
- Assessment of Extended Release/Long-Acting PMR Studies 3033-3, 3033-4, 3033-5 Final Study Reports Designed to Validate the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) and Psychiatric Research Interview for Substance and Mental Disorders - DSM-5 Version for Opioid Use Disorders (PRISM-5-OP) Survey Instruments (A. Trachtenberg, Dec 2018)

3.1 VALIDITY ASSESSMENT

Content, construct, and criterion validity are all important when designing a survey instrument or questionnaire. Content validity is the extent to which an instrument measures the concept of interest, while construct validity determines if relationships among items, domains, and concepts conform to a priori hypotheses concerning logical relationships that should exist with other measures or characteristics of patients and patient groups. Criterion validity measures the degree to which the survey results predict or relate to real-life outcomes of interest. These concepts are closely related, and the process of assessing content validity includes evaluating construct and criterion validity as well.

3.1.1 Content Validity

For surveys and questionnaires, content and construct are the main types of validity of concern to the Agency. FDA's "Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims"[1] (PRO Guidance) describes the Agency's current thinking about and approaches to examining content validity in patient surveys. Specifically, content validity is assessed using several different pieces of information:

- Item generation – was the source of questions in a population with the condition of interest, and did it include a wide array of patients?
- Data collection – were adequate quality controls in place, and are data collected through different methods (e.g., written vs. telephone) comparable?
- Recall period – what is the rationale for the selected period, and is it appropriate?
- Response options – are they consistent with the purpose and intended use of the instrument?
- Instrument Format, Instructions, and Training – are the procedures and processes implemented and followed consistently throughout instrument development?
- Patient understanding – do patients understand the questions and instructions in the survey?
- Item and domain scoring – were individual items scored appropriately, and, for a multi-item score, does the scoring algorithm create an appropriate summary score?
- Respondent and administrator burden – does completing the survey place undue physical, emotional, or cognitive strain on respondents? Does it require excessive administrator attention for proper survey completion?

While the evaluation of content validity is qualitative in nature, a key part of the process is that an expert panel rates and judges the match between survey questions and the domain of interest (in this case, misuse or abuse).

3.1.2 Face Validity

Face validity attempts to answer the question of whether survey questions look like they measure what they are supposed to measure. Although it is similar to content validity, it is considered a more superficial measure. While content validity requires explaining the theoretical underpinnings and

[1] Available at "https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims"

background of a survey, face validity does not. As such, although it may be simpler to measure, it is not equivalent to content validity.

3.1.3 Comparative Validity

Study 3033-5 introduces the term comparative validity as an objective. Although it is not explicitly defined, the description is very similar to the content validity analyses being conducted in study 3033-4. Since the content validity of the PRISM-5 has been previously examined, the purpose of this study will be to ensure that changes made for the ER/LA PMR studies (PRISM-5-OP) did not adversely affect the validity, and that the diagnoses based on the survey are reflected in the patient's medical records.

4 RESULTS

4.1 ER/LA PMR 3033-3

Table 1. Protocol Summary

Parameters	Description
Rationale	The Food and Drug Administration (FDA) has requested, as part of a post-marketing requirement (PMR) for new drug application (NDA) holders of extended release/long-acting (ER/LA) opioid analgesics, to conduct a study to develop and validate a measure of the opioid-related adverse events of misuse and abuse among patients with chronic pain prescribed long-term opioid analgesic therapy. This measure will be used to assess misuse and abuse in PMR Study 2065-1A and PMR Study 2065-4B. Currently, no tool exists to meet this need except for the Self-report Misuse, Abuse and Diversion of Prescription (Rx) Opioids questionnaire (SR-MAD) which has undergone several rounds of prior content validation. The SR-MAD has been modified to meet the needs of PMR Studies 2065-1A and 2065-4B and has been renamed the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). This study will seek to further develop and validate the POMAQ using the *Food and Drug Administration (FDA) Guidance for Industry, Patient- Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (FDA 2009) as a reference for conducting qualitative research throughout the process of instrument development to ensure the content validity of a measure and to evaluate the comprehensibility of included questions. This qualitative study to evaluate content validity will be conducted prior to the quantitative study to evaluate construct validity.
Objectives	To assess the content validity and patient interpretation of the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). Concept elicitation regarding patient thoughts on what misuse and abuse are will also be obtained.
Data Source	Interviews with patients with chronic pain: those with a history or currently using prescription opioid analgesics as part of their pain treatment, and those with no history of opioid analgesic use. Data will also be collected from patients via completion of self-report measures including the Brief Pain Inventory- Short Form (BPI-SF) and a sociodemographic form.
Design	A cross-sectional, one-time qualitative interview. After providing informed consent, participants will complete one study visit. During the in-person visit, participants will complete the POMAQ via the internet using a computer and then undergo a one-on-one cognitive interview using a semi-structured interview guide to evaluate their understanding of the POMAQ. Participants will complete the BPI-SF and a sociodemographic form upon the completion of the interview.

Population	Approximately 28 to 40 participants, 18 years of age or older who have chronic moderate to severe pain, will take part in this study. There will be four groups of participants: • Group 1 will be at least 7 participants who are currently taking opioid analgesics and have a past history of or current known opioid analgesic abuse; • Group 2 will be at least 7 participants who are currently taking opioid analgesics, do not have a history of opioid analgesic abuse, but have history of other substance abuse (e.g., alcohol, benzodiazepines); • Group 3 will be at least 7 participants who are currently taking opioid analgesics and do not have a history of opioid analgesic abuse or other substance abuse (e.g., alcohol, benzodiazepines); and • Group 4 will be at least 7 participants who are not on opioid analgesic therapy (defined as having no prior or current chronic opioid analgesic use).
Recruitment	Participants will be recruited from approximately three to five clinical sites.
General Inclusion Criteria	1. Age ≥ 18 years; 2. Patients who, based on the Site Investigator's clinical judgment, have chronic moderate to severe pain; 3. Willing to provide written informed consent; 4. Able to participate in a one-on-one interview; and 5. Able to read, speak, and understand English and complete all study assessments.
Group 1: Specific Inclusion Criteria for Patients Known to Abuse Opioids	1. Patient meets all general inclusion criteria; 2. Patient is currently on an opioid analgesic prescribed by a physician, defined as taking a daily dose for at least 7 days prior to screening; 3. Patient has any of the following within the past 5 years: a. past and/or current diagnosis of opioid analgesic abuse or opioid use disorder (as assessed by Diagnostic and Statistical Manual of Mental Disorders-IV-Text Revised [DSM-IV-TR] or DSM-5); or b. was/is participating in, and/or is seeking treatment for opioid abuse or opioid use disorder.

Group 2: Specific Inclusion Criteria for Patients Known to Abuse Other Substances	1. Patient meets all general inclusion criteria; 2. Patient is currently on an opioid analgesic prescribed by a physician, defined as taking a daily dose for at least 7 days prior to screening; 3. Patient has no history of or current opioid abuse or opioid use disorder 4. Patient has any of the following within the past 5 years: a. History of, or is currently diagnosed and/or exhibiting signs or symptoms of substance abuse or substance use disorder (as defined by DSM-IV-TR or DSM-5 criteria) for substances other than opioids; b. Was/is participating in, and or seeking treatment for substance abuse or substance use disorder for substances other than opioids (e.g., alcohol, benzodiazepines).
Group 3: Specific Inclusion Criteria for Patients Known Not to Abuse Opioids	1. Patient meets all general inclusion criteria; 2. Patient is currently on an opioid analgesic prescribed by a physician, defined as taking a daily dose for at least 7 days prior to screening; 3. Patient meets all of the following: a. No history of or current substance abuse or substance use disorder including opioid abuse and opioid use disorder (as defined by DSM-IV-TR or DSM-5 criteria); b. No history of or current diagnosis and/or exhibiting signs or symptoms of abuse or substance use disorder including opioid abuse or opioid use disorder (as defined by DSM-IV-TR or DSM-5 criteria); c. No history or currently seeking treatment for substance abuse or use disorder including opioid abuse or opioid use disorder (as defined by DSM-IV-TR or DSM-5 criteria).
Group 4: Specific Inclusion Criteria for Patients Not on Opioid Therapy	1. Patient meets all general inclusion criteria; 2. Patient has no known history of past chronic use (> 3 consecutive months) of opioids and no use within the past year; 3. Patient meets all of the following criteria: a. No history of or current substance abuse or substance use disorder including opioid abuse or opioid use disorder (as defined by DSM-IV-TR or DSM-5 criteria); b. No history of or current diagnosis and/or exhibiting signs or symptoms of substance abuse or substance use disorder including opioid abuse or opioid use disorder (as defined by DSM- IV-TR or DSM-5 criteria); c. No history of or seeking treatment for substance abuse or substance use disorder including opioid abuse or opioid use disorder (as defined by DSM-IV-TR or DSM-5 criteria).

Exclusion Criteria for all three groups	1. Cognitive, psychiatric or other impairment based on the Site Investigator's clinical judgment that would interfere with participating in a one-on-one discussion 2. Terminal illness with life expectancy < 6 months.
Primary outcomes	Evidence of content validity from patients regarding 1. the interpretation of POMAQ items, 2. ease of completion, 3. the comprehensiveness of instrument, and 4. the appropriateness of the format, response scales, and recall period
Analysis	Content analysis of the POMAQ interview transcripts and descriptive statistics of the BPI-SF and sociodemographic questions
Study Period (Estimated)	January 2015 – March 2015
Final report due (Estimated)	May, 2015

4.1.1 FDA Protocol Comments:

Although misuse, abuse, and diversion are not typical patient-reported outcomes, the methods being employed to assess them are very similar. As a result, studies 3033-3 and 3033-4 were evaluated using the PRO Guidance as a framework. The reviewer concluded that as designed, the protocol did not address content validity, but instead assessed face validity.

A major reason for this conclusion was that the protocol did not provide much of the documentation needed to assess content validation, including the theoretical framework, expert panel opinions, and a description of the training and administration processes. In addition, the reviewer did not believe that the targeted 20 individuals represented a sufficient cross-section to adequately test survey responses.

Although these questions and comments were submitted to the OPC prior to receipt of the final protocol, they were not able to fully respond within that document. Instead, the OPC stated that much of the requested documentation, including an expert panel assessment, would be done in ER/LA PMR 3033-4 (quantitative). Since this part of the examination did need to precede the quantitative assessment, FDA agreed to let the study proceed.

4.1.2 Results Summary

A total of 56 individuals were enrolled in the study, 54 of whom completed the POMAQ as well as the supplementary surveys (BPI-SF[2], sociodemographic form). Forty-eight percent of individuals completed the backwards and forwards cognitive interviews (N=27 for each direction), while 21% (N=12) completed the full cognitive interview. Of note, the OPC discovered during the study that the full cognitive interview was too burdensome for most patients. To compensate, they alternated the cognitive interviews to start at either the beginning (forward) or end (backward) to increase the number of responses for each question. Figure 1 and Table 2 describe the distribution of the study population across the four groups.

Figure 1. Study 3033-3 population distribution.

[2] See Appendix A for descriptions of additional questionnaires used in the ER/LA PMR investigations.

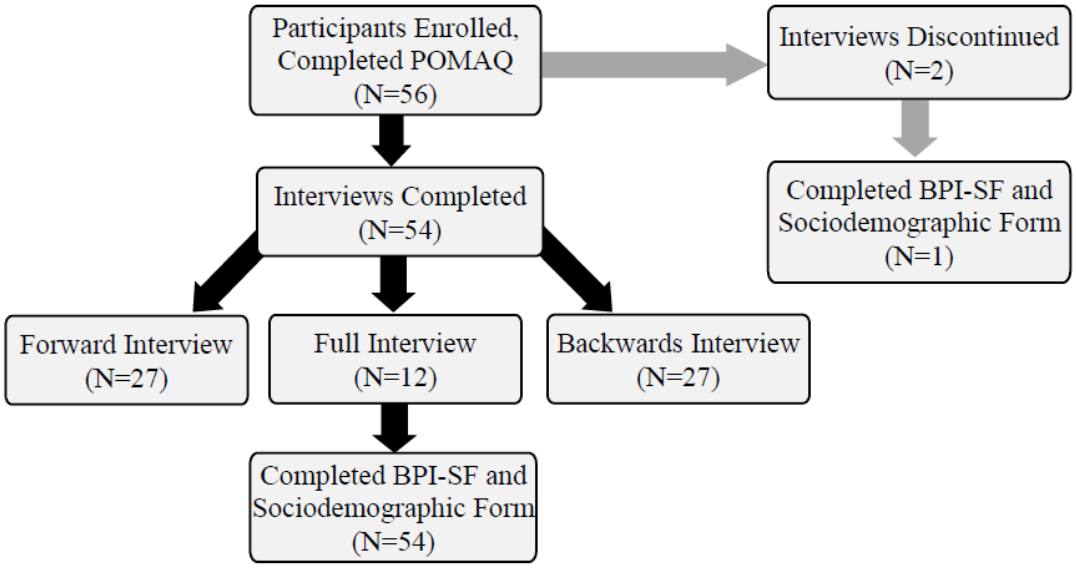


Table 2. Study 3033-3 opioid analgesic use groups.

Group	Total Interviews	Number Forward Interviews	Number Backward Interviews	Number Full Interviews
Opioid Abuse	15	5	10	4
Other Substance Abuse	15	8	7	1
No Opioid Abuse	14	7	7	3
No Opioid Use	10	7	3	4
Total	***54 (96%)***	***27 (48%)***	***27 (48%)***	***12 (21%)***

* 56 patients completed the POMAQ survey, however only 54 participated in the qualitative interviews. Given the complexity and length of the interview and the patient population, the interview approach was modified after the first set of patient interviews (No Opioid Abuse and No Opioid Use groups).

Table 3 summarizes selected sociodemographic and selected clinical characteristics of the survey population. Participants were predominantly female (N=32, 57.1%), with a mean age of 48.7 years (± 12.3 years). Most participants were White, on disability, and had completed some college. Except for those not on opioid analgesic therapy, most participants were on Medicare. Within that group, most participants had private health insurance.

Table 3. Selected sociodemographic and clinical characteristics of survey population.

Characteristic	Total (N=56)	Group 1: Opioid Abuse (N=16)	Group 2: Other Substance Abuse (N=15)	Group 3: No Opioid Abuse (N=15)	Group 4: No Opioid Use (N=10)
Age (Mean ± SD)	48.7 ± 12.3 (N=55)	46.3 ± 10.5 (N=15)	50.6 ± 12.1	48.3 ± 11.1	50.0 ± 17.3
Gender (n, % male)	24 (42.9%)	6 (37.5%)	8 (53.3%)	5 (33.3%)	5 (50.0%)
Race (n, %)	N=55	N=15			
White	44 (80.0%)	12 (80.0%)	10 (66.7%)	13 (86.7%)	9 (90.0%)

Characteristic	Total (N=56)	Group 1: Opioid Abuse (N=16)	Group 2: Other Substance Abuse (N=15)	Group 3: No Opioid Abuse (N=15)	Group 4: No Opioid Use (N=10)
African American	5 (9.1%)	2 (13.3%)	2 (13.3%)	1 (6.7%)	0 (0.0%)
Other	6 (10.9%)	1 (6.7%)	3 (20.0%)	1 (6.7%)	1 (10.0%)
Employment Status (n, %)	N=55	N=15			
Employed (full or part time)	18 (32.8%)	5 (33.4%)	4 (26.6%)	4 (26.7%)	5 (50.0%)
Unemployed	3 (5.5%)	1 (6.7%)	0 (0.0%)	1 (6.7%)	1 (10.0%)
Disabled	24 (43.6%)	7 (46.7%)	9 (60.0%)	8 (53.3%)	0 (0.0%)
Other[1]	10 (18.2%)	2 (13.4%)	2 (13.4%)	2 (13.4%)	4 (40.0%)
Education (n, %)	N=55	N=15			
Elementary/primary school	3 (5.5%)	0 (0.0%)	1 (6.7%)	0 (0.0%)	2 (20.0%)
Secondary/high school	13 (23.6%)	6 (40.0%)	4 (26.7%)	3 (20.0%)	0 (0.0%)
Trade school/some college	27 (49.1%)	7 (46.7%)	8 (53.3%)	8 (53.4%)	4 (40.0%)
College degree	12 (21.8%)	2 (13.3%)	2 (13.3%)	4 (26.7%)	4 (40.0%)
Health Insurance (n, %)[2]					
Private health insurance	18 (32.7%)	3 (20.0%)	5 (33.3%)	5 (33.3%)	5 (50.0%)
Medicare	24 (43.6%)	7 (46.7%)	9 (60.0%)	7 (46.7%)	1 (10.0%)
Medicaid	12 (21.8%)	6 (40.0%)	3 (20.0%)	1 (6.7%)	2 (20.0%)
State sponsored plan	4 (7.3%)	4 (26.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Other[3]	7 (12.7%)	0 (0.0%)	1 (6.7%)	4 (26.7%)	2 (20.0%)
Years of Pain (Mean ± SD)	11.2 ± 8.2	11.9 ± 8.6	13.5 ± 8.8	10.9 ± 8.2	7.1 ± 5.6
Years Treated by Physician (Mean ± SD)	9.3 ± 7.4	7.6 ± 5.1	12.3 ± 9.1	10.6 ± 8.0	5.3 ± 4.5
Years on Pain Medication (Mean ± SD)	5.7 ± 4.9	4.4 ± 3.7	7.4 ± 5.2	6.6 ± 4.8	4.3 ± 5.9

Adapted from Tables 3 and 4 of sponsor's final report
[1]Includes self-employed homemaker, student, retired, other
[2]Responses are not mutually exclusive
[3]Respondents did not supply adequate information to categorize insurance coverage

Based on the analyses conducted in this study, the OPC concluded that the POMAQ was generally well understood. Several minor wording changes were suggested to clarify the available responses and to clarify some of the drug names that were specifically mentioned in the survey. While most participants were comfortable completing the survey via computer, a few (N=3) participants were either not computer savvy or expressed concerns about internet security. Of note, although participants stated that they answered the survey questions honestly, several (N=18) did not think that other individuals would be honest.

The FDA review concluded that while the study did address face validity and general understanding of the POMAQ, the protocol did not address content validity, nor was it responsive to FDA's requests for additional background information. As a result, although the study was considered complete, the PMR could not be marked as fulfilled until the subsequent quantitative investigation was finished.

4.2 ER/LA PMR 3033-4

Table 4. Protocol Synopsis

Parameters	Description
Rationale	The Food and Drug Administration (FDA) has requested, as part of a Post-marketing requirement (PMR) for new drug application (NDA) holders of extended release/long-acting (ER/LA) opioid analgesics, to conduct a study to develop and validate a measure of the opioid-related adverse events of misuse and abuse among patients with chronic pain prescribed long-term opioid analgesic therapy. This measure will be used to assess misuse and abuse in PMR Study 2065-1A and PMR Study 2065-4B. To date, no tool currently exists to address the needs of the PMR except for the Self-Report Misuse, Abuse and Diversion of Prescription (Rx) Opioids questionnaire (SR-MAD) which has undergone several rounds of content validation but requires further validation. The SR-MAD has been substantially modified to meet the needs of PMR Studies 2065-1A and 2065-4B and has been renamed the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ). The POMAQ will undergo content validation via qualitative interviews (Protocol 2065-2A [Qualitative]) prior to use in this validation study (Protocol 2065-2A [Quantitative]). This quantitative study will seek to further develop and validate the POMAQ following the general tenets according to the *Food and Drug Administration (FDA) Guidance for Industry, Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (FDA 2009) which emphasizes the importance of conducting sound psychometric evaluation of patient-reported instruments through quantitative research methods. However, it should be noted that the POMAQ is not a typical PRO measure capturing a specific latent construct and the specified analytic approach to the POMAQ reflects this difference in theoretical frameworks.
Objectives	The objective of this study is to evaluate the validity and reproducibility of the POMAQ to identify opioid abuse and misuse behaviors among participants who have chronic pain which requires long-term opioid analgesic use.
Data Source	Data will be collected from self-reported patient measures, clinical interviews, lab tests, and electronic medical records (EMR).

Design	This is a cross-sectional validation study with a test-retest substudy. Patients will be recruited from within the Department of Defense (DoD)/TriCare health system by a site coordinator. The site coordinator will introduce the study to potential participants identified from clinic databases either in-person during a scheduled visit or by phone. If the patient is interested, written informed consent will be obtained at an in-clinic visit. Upon obtaining consent, participants will be provided with a welcome kit that includes study information and directions to complete a battery of questionnaires online via a secure website on their own time and at a location of their choice. Patients will be provided with a unique identification (ID) in the welcome packet that will allow them access to the survey. Participants will have 5 days to complete the survey. The site coordinator will receive automated messages for participants who have not completed the survey by day 3 and the coordinator will call participants reminding them to complete the survey. The unique ID will also link their responses to their EMR at the end of the study. During the initial in-clinic visit, study participants will be asked to provide a urine sample, which will be processed by the site coordinator and sent to a central lab for analysis. Participants will also be invited to provide a hair sample but opting out of providing a hair sample would not exclude them from participation in the study. After the participant has completed the internet-based questionnaires, the patient will participate in a telephone interview with a mental health expert to ascertain misuse and abuse. Approximately 25% of the participants will be randomly selected using a 1:4 randomized block design to participate in a test-retest administration of the POMAQ. Randomization will be performed at the time of assignment of unique patient ID. If selected, the participants will be sent an email invitation to participate in a second administration of the POMAQ online in a secure environment of their choosing within 7 to 10 days after the initial administration.
Population	Approximately 800 participants aged ≥18 years from within the DoD/TriCare health system with chronic (≥3 months) pain treated with opioid analgesics will take part in this study with the goal to recruit at least 100 patients for each diagnosis (i.e., 100 participants diagnosed with opioid misuse and 100 diagnosed with opioid abuse). Participants known to abuse opioids will not be excluded from this study.
Recruitment	Patients will be recruited using the Department of Defense (DoD)/TriCare health system and database by a site coordinator. The goal will be to recruit non-active service members (family members, dependents, retirees). No active-duty service members will be included.

Inclusion Criteria	1. Age ≥18 years; 2. Diagnosed chronic (≥3 months) pain condition which requires long- term treatment with opioid analgesics; 3. Willingness to provide written informed consent; 4. Willingness to provide a urine sample during in-clinic visit; and 5. Able to participate in and complete an Internet-based survey and a telephone interview in English.
Exclusion Criteria	1. Cognitive or other impairment based on the Principal Investigator's judgment that would interfere with the ability of a participant to complete the validation study; 2. Terminal illness with life expectancy <6 months; or 3. Currently an active-duty service member of the military.
Outcome Assessments (See Appendix A for Questionnaire descriptions)	• Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) • Brief Pain Inventory-Short Form (BPI-SF) • Sociodemographic Questionnaire • Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) Substance Use Disorders Module • Prescription Drug Use Questionnaire-Patient Version (PDUQp) • Prescription Opioid Therapy Questionnaire (POTQ V2) • Urine Toxicology Screening for Non-prescribed or Illicit Opioids • Socially Desirable Response Set 5-Item Survey (SDRS-5) • Medical Outcomes Study: 36-Item Short Form Health Survey Instrument (MOS SF-36) • Electronic Medical records (EMR) for current visit and prior 12 months • If applicable, hair sampling for toxicology screening

Analysis	Descriptive statistics will be used to describe the patient sample and POMAQ item analysis. The initial analytical approach will be to describe the frequency of responses to each question and examine the prevalence of each behavior (e.g., overuse, tampering, doctor shopping, etc.). Each behavior will then be validated following a priori developed algorithms against the relevant ancillary measure(s). This validation process will utilize objective (e.g., EMR) data and subjective data (e.g., PDUQp) to assess the ability of the POMAQ to capture each specific behavior. Once the specific behaviors have been validated, the behaviors will then be coded as misuse, abuse, or misuse and abuse, depending upon the intentionality of the responses based on the draft scoring algorithm and conceptual framework. We will then seek to identify behavior classes or groupings using cluster analysis and/or latent class analysis (LCA). The associations identified by the cluster analysis or LCA will provide the means to assess which misuse or abuse behaviors may group together and which occur in isolation. The identified behavior clusters will be reviewed by clinical experts who will confirm the validity of the clusters. If relevant, the clusters can then be validated in a manner similar to the individual question algorithms against the standardized questionnaires as needed to confirm the reliability and validity of identifying cases of misuse and/or abuse. After the clusters have been identified, gradients of severity may be evaluated with potential scoring algorithms derived to assess patient risk. Logistic regressions may or may not be used during this process depending upon the specific behavior and outcome.
Study Period	Dates are estimated as the Qualitative study (Protocol 2065-2A [Qualitative]) study must be completed prior to start of Quantitative study. First patient in anticipated January 6, 2016, last patient in June 30, 2016.
Final Report Date	November 15, 2016

4.2.1 FDA Protocol Comments

Table 4 summarizes the protocol for the quantitative content validation study. This protocol reflects several suggestions made by FDA after reviewing an earlier draft, specifically that the study be a primary, not a secondary data analysis and that hair as well as urine samples would be requested from participants. In addition, FDA made POMAQ wording suggestions to clarify the intent of the respondent (e.g., instead of asking how many times a patient saw the doctor for pain in the past three months, asking about how many different doctors were seen for pain) and to ensure that the survey did not make assumptions concerning how participants were abusing drugs (e.g., not assuming that any opioid taken sublingually, even if prescribed that way, was an indication of abuse).

The final protocol was again reviewed by FDA, particularly to ensure that the OPC was following the methodology recommended in the PRO Guidance. While there were some elements added, such as the proposed LCA, overall the protocol was still inadequate to properly assess content validation. In response, FDA provided extensive comments outlining the expected analyses and metrics that would be required to

assess the POMAQ using the PRO framework. After further discussions between the Agency and the sponsor group, they agreed to provide the requested information. To accommodate FDA's requests, the sponsor group submitted an "initial" final report describing the POMAQ study population used to establish validity of the POMAQ and completed two additional sub-studies: one that had two independent experts categorize patient responses into misuse, abuse, or neither using only POMAQ information, and a second that asked two independent experts to categorize patient responses using all available information other than the POMAQ responses.

4.2.2 Results Summary

Final Report, Part 1

A total of 3,263 individuals were screened for the study. Fifteen hundred eighty-eight patients declined, leaving 938 individuals who agreed to participate. Figure 2 provides a graphical representation of the study population. Eight hundred nine participants completed the POMAQ; 364 of those respondents were also asked to do a retest of the POMAQ, which 166 (45.6%) completed. Of the 938 patients that were invited, 889 (94.8%) provided a urine sample, while 433 (46.1%) provided a hair sample. Approximately 90% of individuals who provided urine or hair samples also completed the POMAQ.

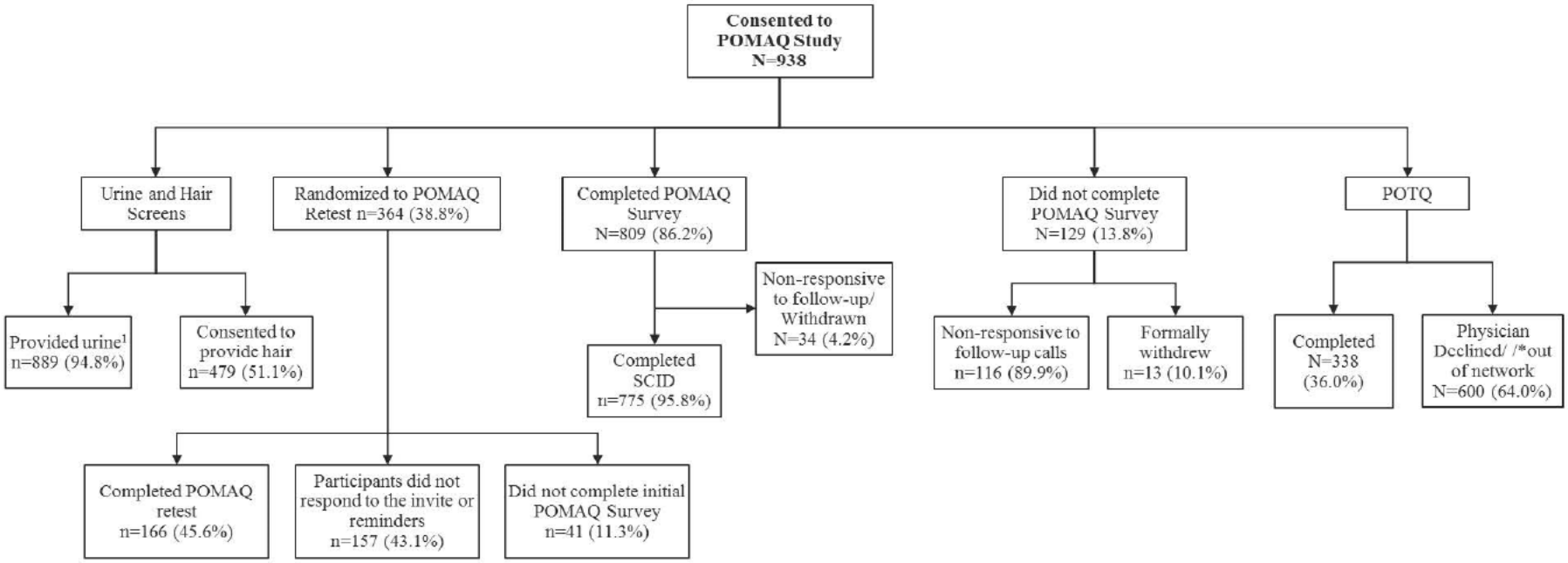
When patients who completed the POMAQ were compared to those who did not, there were some differences in behavior. On average, completers had been with the clinical practice for significantly less time (6.2 years) compared to non-completers (8.8 years). Completers were also significantly more likely to have had a broken bone/fracture or post-operative pain or be taking oxycodone or tramadol. The differences in opioid analgesic medication duration were not statistically significant. There were also no differences in abuse behaviors – approximately 5% of both the completer and non-completer populations had a history of abuse of opioids or other substances. When the urine and hair testing results were examined, a greater proportion of non-completers were positive for substances that they did not indicate they had taken on the POMAQ compared to completers.

The low response rate for the initial study and the low retest-completion rate were concerning to FDA, as was the discrepancy in hair and urine testing results. While the lack of differences in abuse behaviors was somewhat reassuring, the actual number of participants was still quite low (30 completers were known to misuse or abuse opioids, compared to 2 non-completers). This raised the possibility that there still could be some type of selection bias in the validation population.

In addition to the population issues, FDA was also concerned that the recall period of a year was possibly too long, particularly considering that most surveys ask about a 3-month period. In conjunction with this, it was not clear which version of the POMAQ was used for the retest, since surveys that use both a 1-year and a 3-month recall period were described in the report.

While the Agency made these concerns known to the sponsor group, no additional analyses were requested at this point, since each party agreed that these issues could be addressed in a final report that would also include the other items needed for a content validation analysis (i.e., concurrent/concordance analysis, latent class analysis, predictive validity analysis, theoretical framework).

Figure 2. POMAQ validation population



[1] N=49 participants did not provide urine sample: n=22 participants were unable to void, but provided hair samples; n=25 participants were unable to void due to medical reasons (e.g. just provided sample to their physician, BPH, incontinence); and n=2 participants (Pt IDs (b) (6) provided urine samples, but spilled their samples in clinic and were unable to provide a second sample.

Final Report, part 2

The second part of the final report contained most of the additional information requested by FDA as part of the content validation assessment. This included several additional surveys, sociodemographic and medical information, including medical records for the prior year, and urine and hair drug test results for patients who provided samples. Additional survey instruments[3] measured pain, general health, opioid abuse or misuse, and the tendency for a patient to provide socially desirable responses rather than true answers. Measures included descriptive statistics for each questionnaire, percent agreement/concordance, prevalence- and bias-adjusted kappa statistics, and an LCA. Each of the supporting questionnaires was assessed individually and compared to the POMAQ results where relevant.

Table 5 summarizes the results for the supporting surveys. In general, few patients had responses indicating current or past prescription opioid misuse or abuse. Of note, the physician survey (POTQ-V2) that explored patient opioid abuse was only returned for 338 patients. A minority of the 600 physicians who did not respond were out of network, but most were either not comfortable completing the form (N=220), or either were not the patient's opioid prescriber, felt it assessed the physician's practice, or saw no value in completing the survey (N=331). Even so, the responses did not statistically significantly differ between respondents who did and did not complete the POMAQ, with approximately 7% of respondents having scores that may indicate misuse. Patients generally self-reported fair to poor health, with some physical impairment. There was evidence of some social desirability bias, particularly among female patients.

Table 5. Summary of Additional Questionnaire Responses

Questionnaire	Summary
PDUQp	Approximately 3% of men and 2% of women scored positive for substance use disorder (SUD). Approximately 20% of patients did not meet the threshold for SUD, but had violated their medication agreement, or should have their medication discontinued due to opioid-specific behaviors.
POTQ – V2	Completed by 338 physicians: 600 were out of network, not comfortable completing the form, or did not return for other (unspecified) reason. Approximately 3% of patients had results that may indicate opioid misuse.
SCID-I	1.2% of total patient population had either current or past abuse, while 2.3% had current or past dependence
MOS SF-36	On a scale of 0-100, with higher scores indicating better health, the mean (SD) general health score was 44.7 (22.2). The score for physical function was 41.0 (24.9), while pain was 31.4 (16.9). The general health and physical function score were in the poor to fair range. Men scored slight higher than women.
BPI-SF	The average pain score was 4.9 (SD 1.8) on a scale of (0 to 10, with 10 being the worst), with the current overall pain score being 4.6(SD 2.4).

[3] See Appendix A for a description of the additional survey instruments.

	The average pain interference score was 5.3 (SD 2.5), indicating moderate interference. Women tended to rate both pain and interference higher than men.
SDRS	The mean (SD)score was 40.0 (30.7), indicating responses with moderate social desirability among the total sample. Women had a higher average score, 44.5 (30.0) compared to 35.3 (30.8) for men.

Construct validity of the POMAQ responses were supported by corroborating responses on the PDUQp and POTQ V2. Similar evidence was found among the SCID-I interviews with most patients with current substance use, abuse or dependence also reporting the use of the substance on the POMAQ. The LCA yielded a 4-class solution with the following groups: "high risk" (n=30), "at risk" (n=154), "chronic pain, low risk" (n=473), and "chronic pain, comorbid conditions" (n=152). Compared to the other groups, the "high risk" group was generally: younger, majority male, a shorter mean duration of pain, greater alcohol use, a greater proportion of participants with two or more opioid analgesics prescribed, and a greater frequency of endorsement of POMAQ items which may indicate misuse/abuse behaviors.

When comparing EMR prescription data for opioid analgesics to what participants reported they had been taking over the past 3 months, the percent agreement was high. However, as with the urine screens and POMAQ responses, mismatches occurred between what participants reported they were taking in and what was actually prescribed over the past 3 months as documented in their EMR. This could have been due to participants not always knowing the correct name of the medications they took but could also reflect that participants often have multiple prescriptions for opioid analgesic medications and that their prescribed treatments changed over the course of 3 months.

When urine test results were compared to POMAQ results, the agreement was generally in the moderate to good range, both for accepted laboratory cut-off threshold values (used as the legal standard for drug testing) and for the lowest levels of detection threshold (used for research purposes, as it is a lower threshold than the legal standard). The false negative percentage (POMAQ: no, present in urine) was below 1% for most of the drugs tested – among opioid analgesics, only hydromorphone had a higher percentage at 5.5%. The false positive percentage (POMAQ: yes, absent in urine) was generally higher, from 1% to 20%. Interestingly, oxycodone, hydrocodone, and their major metabolites had false positive percentages between 40 and 45%, although the false negatives were less than 5%. Due to the structure of the analysis, however, it is not clear if the percentages were the same among individuals who were taking the drug as prescribed and individuals who may have been misusing or abusing the drug.

The hair sample analysis showed the same pattern, except for oxymorphone. Specifically, the false negative percentages were much higher compared to other opioid analgesic products, and the lab cut-off and lowest level of detection levels were different (lab cut-off false negative = 10.9%, lowest level of detection = 16.7%). The false-positive levels were 24.5% and 19.8% for the lab-cutoff and lowest level of detection thresholds, respectively. Further analyses by the investigators indicated that patients may not have known the name of the drug they were taking (i.e., oxycodone vs oxymorphone). In addition, since the samples were collected an average of 22 hours after the patient's last dose, metabolites with shorter half-lives may have already been at undetectable levels.

FDA analysts concurred with the sponsor group that the POMAQ compared favorably with the other surveys and information, demonstrating adequate validity. However, the following observations were also made:

- The POMAQ measures prevalence of misuse- and abuse-related behaviors, but this is a single survey applied to outcomes that develop over time. Repeated POMAQ testing should be considered, as this may serve to refine the prevalence estimates.
- In addition, patient recall over 3-month and 1-year periods may not be accurate enough for reliable estimates of the prevalence of misuse and/or abuse. Consider repeat POMAQ testing at shorter intervals, e.g., 1 month.
- Misuse and abuse behaviors were relatively rare in the patient population, so wider testing of the POMAQ in more diverse settings is encouraged.
- The scoring algorithm is fairly complex, and some of the questions are repetitive. Future versions should consider shortening the survey, simplifying the scoring process, and providing clear, step-by-step instructions scoring.

Additional Validation Sub-studies

FDA requested two additional validation studies to further assess content validation. For each study, two pain or addiction experts would individually categorize 50 POMAQ questionnaires to determine if the respondent was abusing or misusing opioid analgesics. The selected cases did not overlap, so a total of 100 POMAQ responses were analyzed. Each case was categorized into no misuse or abuse, misuse (not of clinical concern), misuse (of clinical concern), abuse, diversion, or other. The two categories of misuse were intended to differentiate between non-systematic or isolated instances of abuse and systematic misuse that may warrant further attention from the patient's physician. In the event of a disagreement, the case would be adjudicated by a third specialist that had not been involved in the development or testing for the POMAQ. In the first study, the ratings would be done using only the POMAQ responses, with no additional information. In the second study, the experts would have access to all patient information as well as the POMAQ responses. The raters would not have access to the final POMAQ categorization prior to making their decision.

A total of 60 records were reviewed for the first validation study. The raters agreed on the classification in 32 cases (53.3%), with disagreements for 28 cases (46.7%). During the adjudication process, it was revealed that most of the mismatches involved differences in classifying no misuse, misuse, or abuse based either on the reason for or frequency of an activity (e.g.1 -5 times/month vs. 6-10 times/month). Of note, six rater mismatches were between non-clinical and clinical abuse. Since the POMAQ does not distinguish between these two concepts, these categories were eliminated. When compared to the POMAQ results, the categories agreed for 47 (78.3%) cases. Most mismatches (N=7 of 13, 53%), were rated as misuse by the raters but no misuse by POMAQ.

Fifty records were reviewed in the second validation study. Based on the results of the first validation sub-study, patients were categorized into no misuse, misuse, or abuse. Raters agreed on the classification for 34 (68%) of cases and disagreed for the remaining 13. After adjudication, the patient classification was changed for 4 of the 13 cases. When the 34 cases that raters agreed on were compared to the POMAQ results, the rater classification differed in four cases (11.8%).

Based on these analyses, several wording and scoring changes were made to the POMAQ. Additional questions were also suggested, primarily to include medical marijuana and to accommodate individuals who were attempting to take less opioid analgesic, but these were not implemented in this version. The nature of these changes led to FDA's recommendation that the POMAQ scoring algorithm be simplified, since much of the disagreement was due to how the expert clinicians interpreted patient responses. An additional limitation, possibly contributing the low rater agreement, was that misuse and abuse are

diagnosed over time, and also rely on patient familiarity to determine. Attempting to diagnose misuse or abuse without being able to observe patients over time and with mainly cross-sectional information (except for the EMR data) was difficult; due to these issues, the FDA analysts interpreted the POMAQ results as estimated prevalence or likelihood of misuse or abuse. With repeated applications, the POMAQ estimates should improve.

4.3 ER/LA STUDY PMR 3033-5

Table 6. Protocol Summary

Rationale	The recent (2013) reformulation of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) Substance Use Disorder (SUD) diagnosis, aligned across substances, was supported by extensive evidence. At the severe end, DSM-5 SUD diagnoses represent addiction. While evidence for DSM-5 SUD/addiction to prescription opioid analgesics was consistent with other substances, evidence on opioid use disorder/addiction was not available from patients with chronic pain. In such patients, accurately diagnosing addiction may require assessing extra information about positively endorsed criteria (e.g., whether the behavior had therapeutic or non-therapeutic intent) and adjusting the diagnostic computer algorithms accordingly. The Psychiatric Research Interview for Substance and Mental Disorders (PRISM) is a diagnostic interview with strong reliability and validity that has been used as a gold standard in other studies. PRISM-5 is the only computer-assisted diagnostic interview available for DSM-5. A specifically-tailored version of the PRISM-5, the PRISM-5-Op, has been prepared for use in PMR Study #2065-1 that includes a specific substance disorders module focused on prescription opioid analgesics, including assessment of the extra information that may be necessary for accurate diagnoses of addiction in the specific case of patients with chronic pain. The purpose of Study #2065-2b is to validate the PRISM-5-Op.
Objectives	The primary objective for Study 2b is to validate PRISM-5-Op measures of DSM-5 prescription opioid SUD/addiction in patients who have, or have had, a prescription for opioid analgesics for at least 30 days to treat chronic pain. The objectives will include addressing the validity of diagnoses made without and with adjustments for patients with chronic pain, i.e., incorporating patterns of opioid analgesic use (as prescribed vs. other than as prescribed) in evaluating withdrawal and tolerance, and incorporating the intent of behaviors in evaluating the DSM-5 SUD/addiction behavioral criteria and craving (therapeutic, i.e., to treat pain vs. non- therapeutic, e.g., to get high). The study will also determine the most valid diagnostic threshold for considering addiction to be present and determine any evidence of differential item functioning (DIF) for any of the eleven DSM-5 SUD/addiction criteria when applied to prescription opioid analgesics.
Data source	Data collected from two groups of patients who have or have had a prescription for opioid analgesics to treat chronic pain: 300 low-risk patients, and 300 high-risk patients. Data sources will include PRISM-5-Op interview data, self-administered questionnaires, medical record data, and expert clinician review of all materials.

Design	Cross-sectional evaluation to validate the construct validity (convergent, discriminant) of the PRISM-5-Op diagnoses with a set of variables using the Multitrait-Multimethod Matrix (MTMM) paradigm (e.g., treatment for addiction, personal and family history of substance use disorders); and latent trait modeling to determine the relationship of the PRISM-5-Op DSM-5 prescription opioid SUD/addiction criteria to each other. Additionally, materials from a subset of 100 of the Study 2b participants will undergo extensive review by two clinical experts in the LEAD validation procedure. Reliability will be determined by conducting blind PRISM-5-Op re-interviews 1-14 days after the first interview with 100 low-risk and 100 high-risk patients.
Population	The study population will consist of adult patients who have or have had a prescription for opioid analgesics to treat chronic pain, recruited from two types of treatment settings, "low-risk" and "high-risk". The first type is the "low-risk" type: university-affiliated, medically well-managed pain or rehabilitation medicine clinics. The second is the "high-risk" type. These are university- affiliated addiction treatment settings, largely detoxification units. We aim to recruit patients from four low-risk clinics, and four high-risk settings. Patients will all be age 18 or older, English-speaking, and lacking cognitive, hearing or vision impairments that would preclude participation in interviews or completion of self-administered questionnaires.
Primary Outcomes	PRISM-5-Op diagnoses of DSM-5 SUD/addiction to prescription opioid analgesics. These diagnoses will be in two forms: unadjusted, meaning that the criteria will be rated positive if present without regard to the intent of the behavior, and adjusted, i.e., that criteria will be rated positive only if structured evaluation indicates that they represent therapeutic intent) rather than treatment of pain (therapeutic intent). The set of seven variables to be included in the MTMM matrix of convergent and discriminant validators of the unadjusted and adjusted diagnoses will include: 1. Treatment for addiction, primarily determined by recruitment site but also by patient self-report and medical record data. 2. Personal history of DSM-5 SUD for other substances, ascertained by the PRISM-5-Op and medical records. 3. Family history of SUDs, as ascertained with measures from the AUDADIS-IV. 4. Psychiatric comorbidity, as measured by the PRISM-5-Op and the medical record. 5. Route of administration other than pills swallowed whole, ascertained with a self-report measure1 6. Pain level – ascertained with the Brief Pain Inventory (short form) 7. Medical conditions associated with chronic pain, ascertained by patient self-report and from the medical record.
Study period	First patient entered June 2015 Last patient entered July 2016
Final Report Date	November, 2016

4.3.1 FDA Protocol Comments

The final protocol was submitted after extensive comments by FDA on a prior version. At FDA's request, the protocol was updated to include references to prior validity testing, a process to compare the PRISM-5-OP results to those of two independent experts (LEAD procedure), an item response analysis, and reliability/concordance testing.

The PRISM-5-OP will be primarily used to assess addiction in ER/LA PMR 3033-1, however, the overall instrument has a wider focus. The protocol includes measures related to several "external validators", which were chosen because they had a positive association with substance use disorder. Despite extensive discussions with the OPC investigators, FDA could not ascertain why these specific factors (addiction treatment, history of other substance use disorders, family history of substance use disorders, history of childhood maltreatment, history of psychiatric comorbidity) were selected. In addition, while there is a positive correlation between these "validators" and substance abuse disorder, the relationship is not clear cut or absolute, and they could not provide a clear explanation of how mismatches (e.g., substance use disorder diagnosis without the presence of a "validator" or vice versa) would be interpreted within the "external validator" framework. However, since these factors were of secondary interest to the ER/LA PMR investigation and independent of the information on addiction that would be obtained, FDA let the protocol proceed.

4.3.2 Results Summary

The study population consisted of 258 high-risk and 348 low-risk patients. High risk patients were selected from individuals at two sites in treatment for any type of addiction, and who currently or at some time in the past had received a 30-day prescription of opioid analgesics to treat chronic pain. Low risk patients were those with a current, 30-day opioid analgesic prescription who were being treated at a pain or rehabilitation clinic. Appendix B present schematics of how the final study population was achieved.

Among the total population, 50.5% (N=306) patients were 50 years old or older. However, this represented 18.2% (N=47) of high-risk participants vs. 74.4% (N=266) of low-risk participants. There was a similar imbalance in the other sociodemographic factors. Overall, the study population had a 50-50 gender split, but men accounted for 65.5% (N=169) of high-risk patients and only 38.2% (N=137) of low-risk patients. Finally, while 69.3% (N=420) of the total sample had completed some college, that included 53.5% (N=138) of high-risk patients compared to 81% (N=282) of low-risk patients. Table 7 presents demographic information for the final study sample.

Table 7. Descriptive sociodemographic information

Characteristic	Whole Sample (N=606)	High risk sites (N=258)	Low risk sites (N=348)
Age			
20-29	13.7	26.4	4.3
30-39	20.8	39.5	6.9
40-49	15.0	15.9	14.4
≥50	50.5	18.2	74.4
Male	49.8	65.5	38.2
Race			
White	77.9	74.8	80.2
Black	7.4	6.6	8.0
Hispanic	11.2	15.1	8.3

Other	3.5	3.5	3.4
Some College	69.3	53.5	81.0
Any Employment	23.9	22.1	25.3
Public Health Insurance	76.9	90.7	66.7
Private Health Insurance	35.8	13.2	52.6
ER Opioid Prescription*	40.6	33.7	45.7

*Participants were asked if they had ever been prescribed an ER/LA opioid analgesic medication

Outcomes were presented in three ways: Unadjusted, DSM-5 adjusted, and fully adjusted. (The DSM-5 criteria are listed in Table 8.) "Adjustment" was defined as follows:

- Unadjusted - meaning that the criteria were rated positive if present without regard to any extenuating circumstances. (Note that DSM-5 defines the presence of substance use disorder/addiction of two of the criteria are present.)
- DSM-5-adjusted - withdrawal and tolerance were not rated positive (i.e., adjusted) if they occurred among participants who used opioid analgesics as prescribed;
- Fully-adjusted - in addition to the DSM-5 adjustment, 8 of the DSM-5 criteria were rated positive only if patient information from structured assessment indicated that the criteria represented addiction indicators (non-therapeutic intent) rather than treatment of pain (therapeutic intent). Withdrawal and tolerance were not further assessed beyond the DSM-5 adjustment, and persistent desire or repeated attempts to quit/cut down was only rated positive if the patient had made repeated attempts to quit/cut down (i.e., persistent desire was excluded from the adjustment).

Table 8. DSM-5 Substance Use Disorder/Addiction Criteria[4]

DSM-5 Substance Use Disorder Criteria (≥2 criteria required for minimal diagnosis)
1. Hazardous use (i.e., use in unsafe surroundings or circumstances)
2. Social/interpersonal problems due to use
3. Neglected major roles to use
4. Used larger amounts/longer
5. Persistent desire or repeated attempts to quit/cut down
6. Much time spent using
7. Continued use despite physical *OR* psychological problems
8. Activities given up to use
9. Craving
10. Withdrawal *OR* use to avoid withdrawal
11. Tolerance

Table 9 shows the overall results for the PRISM-5-Op testing. The prevalence of SUD/addiction ranged from 51% (unadjusted) to 31% (fully adjusted) overall. However, when the results were examined by

[4] Available at "https://www.asam.org/docs/default-source/education-docs/dsm-5-dx-oud-8-28-2017.pdf?sfvrsn=70540c2_2"

high- or low- risk groups, the prevalence in the high-risk groups was between 62% and 60%, while prevalence in the low-risk group decreased from 43% (unadjusted) to 10% (fully-adjusted). The study also assessed severity by examining the number of DSM factors that were positive in the study population. The high-risk respondents consistently had the most individuals in the "severe: ≥ 6 criteria" category, while the majority of low-risk respondents were in the "none: 0 or 1 criterion" category.

Table 9. Overall PRISM-5-Op results

SUD/Addiction Diagnosis	Overall Study Population	High-Risk Respondents	Low-Risk Respondents
Unadjusted	51%	62%	43%
DSM-5 Adjusted	44%	62%	32%
Fully Adjusted	31%	60%	10%

The supporting statistical analyses showed moderate reliability in the population that was retested, measured by the kappa statistic. Values were consistently between 0.4 and 0.6 but tended to be lower in the high-risk group. Internal consistency (measured by Cronbach's alpha) was also high. When the PRISM-5-Op results were compared to the expert assessment, the sensitivity of the instrument 0.95 for the DSM-5 adjusted diagnosis of SUD/addiction and 0.93 for the fully-adjusted diagnosis, with a specific of 0.88 for the DSM-5 adjusted diagnosis and 0.95 for the fully-adjusted diagnosis. PPV and NPV values were all above 0.9, and the kappa statistic was above 0.80.

As a side note, during the validation study, the interviewers reported instances of respondent's experiencing extreme distress during questions on to the external validators, so that part of the official PRISM instrument was dropped and replaced with shorter, less intrusive validated surveys. The external validator of childhood maltreatment was not replaced, but one for tampering was added. The prevalence of these validators ranged from 30% (tampering) to 71% (history of psychiatric issues) in the overall sample. The range was from 60% (family history of substance use disorder) to 100% (prior addiction treatment) in the high-risk sample, and from 10% (prior addiction treatment) to 55% (history of psychiatric issues, tampering) in the low-risk sample.

FDA reviewers concluded that the PRISM-5-Op demonstrated adequate validity and reliability in a population of patients on chronic opioid analgesic therapy. FDA did not request any further modifications to the survey instrument itself, although some additional sensitivity analyses were added. FDA also believed that the scoring algorithm could be simplified, but, again, this was not necessary for use in ER/LA PMR 3033-1.

5 DISCUSSION

The OPC was required to conduct a series of studies to better characterize the safety of long-term opioid analgesic use. As a part of that endeavor, they performed a series of investigations to validate two questionnaires, the POMAQ (ER/LA PMRs 3033-3 and 3033-4) and the PRISM-5-Op (ER/LA PMR 3033-5) that measured misuse, abuse, and addiction related to prescription opioid analgesics for chronic pain. **While FDA recommends that the validation process continue for each of these instruments, the investigations summarized in this document fulfill their respective PMRs.**

ER/LA PMR 3033-3 was a qualitative investigation to evaluate the face validity of the POMAQ. This survey was recently developed by one of the ER/LA PMR sponsors, and reworked and formatted for the ER/LA PMR studies. Because it was new, both the survey questions and process needed to be tested in a group of patients on opioid analgesic therapy to ensure that it was understandable, appeared to measure

the concepts of interest, and not unduly burdensome for either patients or survey personnel (i.e., face validity).

ER/LA PMR 3033-4 continued the validity assessment of the POMAQ, but from a quantitative perspective. Using several other questionnaires, urine and hair samples, and recent EMR and prescription data, the POMAQ was benchmarked against the other surveys and presence or absence of opioids and other drugs in patient urine and hair samples. In addition, a subset of patients had their POMAQ responses and additional information reviewed by independent experts, and their assessments were compared to the POMAQ results.

These investigations served to validate the POMAQ, and further refine both the questions and the scoring and interpretation of the survey. At the end of this process, FDA concluded that the instrument was a valid and reliable indicator of misuse and abuse in a population of patients treated long-term with opioid analgesics for chronic pain. The main strengths of these studies included that the instruments had been specifically developed for this PMR series, and that the sponsor group had followed the framework of FDA's PRO guidance in the validation process. The biggest limitation was that the POMAQ is a cross-sectional measure of outcomes that happen over time. In addition, the scoring algorithm was quite complex. Because of this, the instrument is assessing the prevalence of misuse and abuse behaviors in respondents. FDA recommends repeated administration of the POMAQ during a study to obtain the most precise estimates.

To measure the outcome of addiction, the sponsor group chose to customize a pre-existing survey, the PRISM, in ER/LA PMR 3033-5. For the ER/LA PMR studies, the sponsor group updated the survey to include DSM-5 SUD criteria and added questions to make it specific to a population of patients on long-term opioid analgesic therapy for chronic pain. The instrument also evaluated a series of "external validators", but that was of secondary interest to FDA.

The PRISM-5-Op was evaluated using a similar quantitative approach as the POMAQ, including a comparison with expert opinion. Both the sponsor group and the FDA found it to be a valid instrument for measuring SUD and/or addiction. Although the "external validator" analysis results were not as clear cut, the PRISM-5-Op can also provide some insight into misuse and abuse behaviors. The strengths of this analysis were the use of a previously validated instrument and the use of the PRO framework in the study. The biggest limitation was the complex scoring algorithm, which FDA believed lowered the agreement between the PRISM-5-Op results and the independent expert assessment.

In summary, the goal of these three studies was to provide validated, consistent, operationalized outcome definitions of misuse, abuse, and addiction for the ER/LA PMR study series. This was important because the overarching goal of the ER/LA PMR studies is to determine the risks of misuse, abuse, and addiction associated with the use of opioid analgesics for chronic pain and having a clear and common definition of the outcomes is essential. The POMAQ and PRISM-5-Op both demonstrated the ability to ascertain misuse, abuse, and SUD/addiction at an acceptable level for the ER/LA PMR studies. As a result, these instruments will be used in ER/LA PMR 3033-1, a prospective cohort study investigating the risks of misuse, abuse, and addiction in a cohort of patients prescribed opioid analgesics for chronic pain. FDA also expects that these instruments can form the basis of future studies in the arena of misuse and abuse research and hopes that the validation work started by the OPC can be extended to other appropriate populations of patients with pain conditions.

6 APPENDIX A – QUESTIONNAIRE DESCRIPTIONS

Brief Pain Inventory – Short Form (BPI-SF)
The patient completed BPI-SF has 5 items; 4 items on pain intensity, and 1 item with seven sub-questions to assess the degree that pain interferes with activities. All items use an 11-point numerical rating scale. The BPI-SF provided benchmark data regarding the level of pain the participants are experiencing.

Medical Outcomes Study: 36-Item Short Form Health Survey Instrument (MOS SF-36)
The MOF SF-36 is a self-administered, validated questionnaire that measures the following eight health aspects (physical functioning, role limitations due to physical problems, social functioning, bodily pain, mental health, role limitations due to emotional problems, vitality, and general health perception). These domains also combine to form two component summary scores evaluating mental health (Mental Component score) and physical health (Physical Component score). Higher scores indicate a better HRQL. This measure was used to benchmark generic health status data on the patient sample.

Physician Opioid Therapy Questionnaire – Version 2 (POTQ V2)
The POTQ V2 is an 11-item scale completed by the treating physician to assess misuse of opioids. With the help of the patient's chart, the treating clinician answers questions which reflect the behaviors of multiple unsanctioned dose escalations; episodes of lost or stolen prescriptions; frequent unscheduled visits to the pain center or emergency room; excessive phone calls; and inflexibility around treatment options. Patients who are rated positively on three or more of the items meet criteria for prescription opioid abuse.

Prescription Drug Use Questionnaire – Patient Version (PDUQp)
The PDUQ includes 42 questions assessing abuse and misuse by pain patients administered in an interview. The Patient Version of the PDUQ (PDUQp) is a 31-item questionnaire derived from the items of the original tool designed for self-administration. The PDUQp was used as one of the criterion outcome measures to compare responses for the POMAQ.

Socially Desirable Response Set Five-Item Survey (SDRS-5)
To evaluate bias towards socially desirable responses, the SDRS-5, a set of 5 items was administered. The extent to which socially desirable responses are given within the SDRS-5 provides an indication of the extent to these responses may have been provided for other self-report measures.

Structured Clinical Interview for DSM-IV-TR Axis I Disorders (SCID-I) Substance Use Disorders Module
The SCID-I is a widely used diagnostic instrument to reliably determine Axis I disorders in non-patient and patient populations. Patients will be assessed for substance dependence and abuse at the screening visit. The Non-Alcohol Substance Use Disorders questions from the SCID I Substance Abuse/Dependence Module will be used to evaluate and document substance use patterns and DSM-IV symptoms of substance abuse and dependence for several classes of illicit drugs, including opiates.

7 APPENDIX B – ER/LA PMR 3033-5 STUDY POPULATION SELECTION

Figure 3 – Low-Risk Population

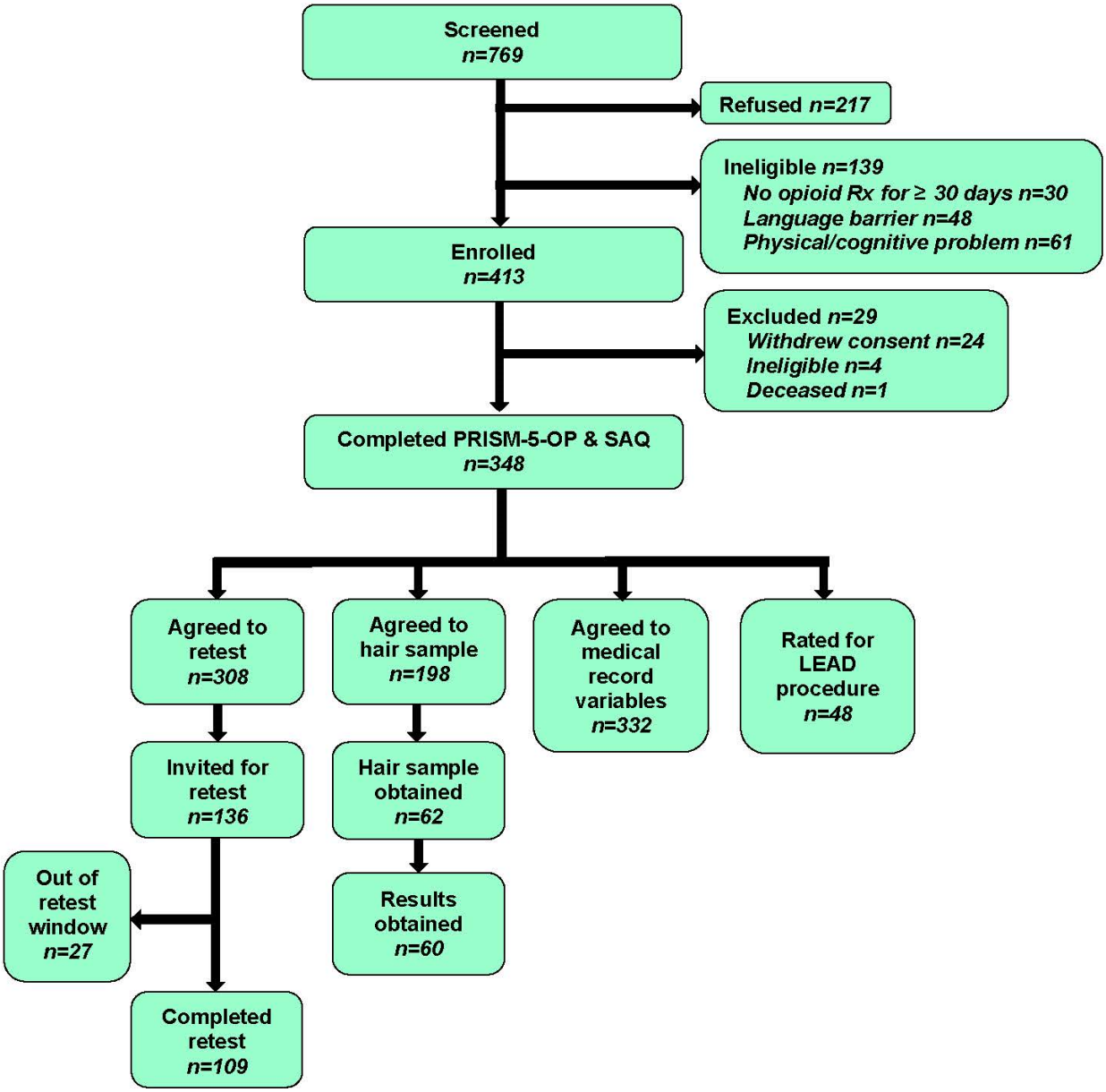
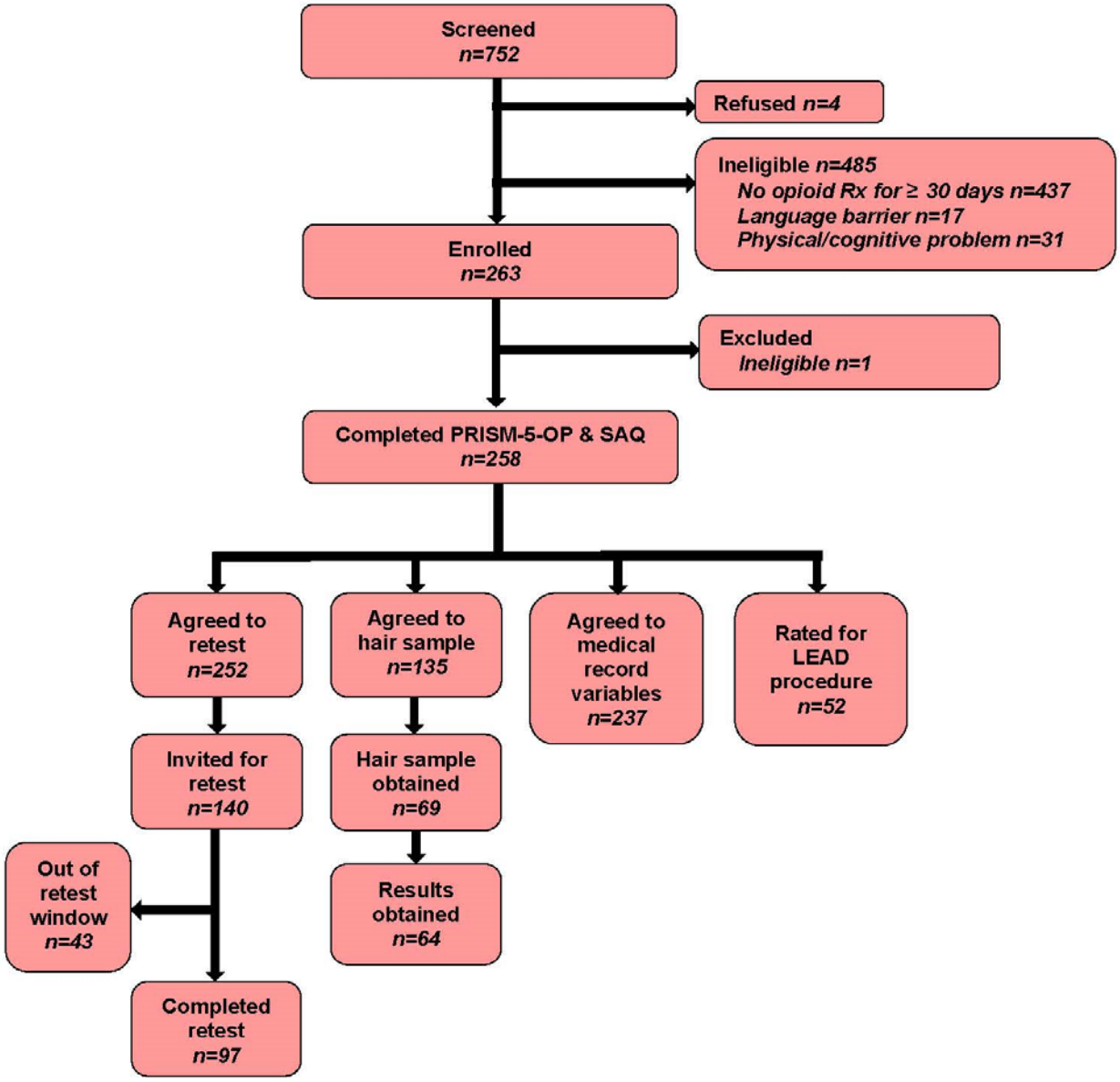


Figure 4 – High-Risk Population



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/s/

CYNTHIA J KORNEGAY
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JUDY A STAFFA
11/20/2019 04:24:15 PM