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Epidemiology: Review of Final Study Report

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Subject:	PMR #3033-8 Final Study Report: "Cross-sectional Study to Define and Validate 'Doctor/Pharmacy Shopping' as Outcomes Suggestive of Abuse and/or Addiction"
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ACRONYMS

AIAA algorithmically indicated abuse and/or addiction

DPS doctor/pharmacy shopping

ER/LA Extended Release/Long Acting

IR Immediate Release

MEQ Morphine milligram equivalents

NDA New Drug Application

PMR Post-marketing Requirement

EXECUTIVE SUMMARY

This review evaluates the interim and final reports of the study conducted to fulfill extended release/long-acting (ER/LA) opioid analgesic PMR 3033-8, titled "Cross-sectional Study to Define and Validate 'Doctor/Pharmacy Shopping' as Outcomes Suggestive of Abuse and/or Addiction." PMR 3033-8 is one of three PMR studies that assess doctor/pharmacy shopping (DPS) measures in relation to different measures of misuse, addiction, and/or abuse.

The investigators developed several candidate definitions of DPS using prescription dispensing data in a cohort of U.S. adults who received either ≥2 opioid dispensings ("opioid cohort," 164,293 patients) or ≥2 diuretic dispensings ("diuretic cohort," 99,281 patients), during an 18-month period that began during the year 2012. Each candidate definition contained four ordinal categories which reflected increasing extent of DPS (*none*, *minimal*, *moderate*, and *extensive*) with either no overlap requirement (DPS-0), a 1-day (DPS-1), or a 10-day (DPS-10) overlap requirement for dispensings. Their method offered more granularity than prior research, which generally used a binary definition of doctor shopping (Parente et al. 2004, Katz et al. 2010, Cepeda et al. 2012, McDonald and Carlson 2014).The investigators selected the candidate definition with the greatest ability to discriminate between opioids and diuretics by modeling the probability of opioids vs. diuretics dispensings as a function of each candidate definition, in turn, with a logistic regression model, and comparing the models on their respective c-statistics, a measure of their ability to discriminate opioids vs. diuretics dispensings. The DPS-0 definition[a], which did not require any overlap of dispensings, had the greatest discrimination ability, but the c-statistic=0.563 still indicated poor discrimination.

Then, they (1) used the opioid cohort to assess the respective, multivariable-adjusted associations between DPS-0 and patient demographic, medical, and dispensing characteristics; and (2) evaluated DPS-0 as a predictor of algorithmically-indicated abuse and/or addiction (AIAA), by analyzing a dataset consisting of the prescription dispensing data linked to health care claims data. DPS-1 and DPS-10 were similarly evaluated, as sensitivity analyses. The outcome, AIAA, had been developed in a separate study to fulfill PMR 3033-7; however, validation using medical records had showed performance statistics of the claims-based algorithm that were below the pre-specified validity criteria, indicating poor performance of the algorithm in its ability to accurately identify abuse and addiction, as documented in the medical record.

The multivariable-adjusted associations between DPS-0 categories and patient characteristics were evaluated with a logistic regression model. Factors associated with

[a] The four ordinal categories of DPS-0 are:
None: ≤2 practices AND ≤2 outlets;
Minimal: EITHER (2 practices AND >2 outlets) OR (2 outlets AND >2 practices);
Moderate: EITHER (3 practices AND ≥3 outlets) OR (4 practices AND (3 or 4 outlets) OR (5 practices and 3 outlets);
Extensive: EITHER (4 practices AND ≥5 outlets) OR (5 practices AND ≥4 outlets) OR (≥6 practices AND ≥3 outlets).

increasing DPS were: receiving immediate-release opioids (alone or with ER/LA opioids), as opposed to ER/LA opioids only; male gender; total MEQ dispensed; number of dispensings that were self-paid; number of dispensings prescribed by non-specialists; and number of psychotropic medication fills.

Increasing DPS-0 category displayed a positive, significant association with AIAA in both bivariate (AIAA, *severe* vs. *none* DPS-0 OR=18.95, 95% CI: 15.47, 23.22) and multi-variable adjusted (OR=1.95, 95% CI: 1.51, 2.52) models. However, it displayed only modest ability at discriminating individuals with from those without AIAA. Adding DPS-0 to a model of pre-selected covariates made no improvement to predicting AIAA; however, FDA found that many of these covariates were also components of the AIAA definition itself. Upon FDA request, DPS-0 was added to a model of "core covariates" that had no shared components with the AIAA definition. When using this model, adding DPS-0 made a small improvement to the modest discrimination accuracy (increase in c-statistic from 0.741 to 0.797; increase in the proportion of variation in the outcome explained by the model from 0.08 to 0.118). Among those selected by the model as having AIAA, <2% were classified correctly (positive predictive value <2%); this was true for modeling any of the three DPS candidate definitions with the core covariates model.

In conclusion, the Sponsors' study fulfilled PMR 3033-8. The current results demonstrate that the definition of DPS evaluated in this study—using four categories with increasing numbers of practices and pharmacies over an 18-month period without regard to overlapping prescriptions—is significantly associated with AIAA prevalence, but it is a very weak marker of abuse and addiction as identified in claims data. The inferential value of these findings is severely limited by the fact that this claims-based outcome itself does not accurately identify people with abuse and addiction compared to medical record review. When we have reviewed the results of both the complementary PMR studies on DPS (3033-9 and 3033-10), which use different strategies to identify patients with misuse, abuse, and addiction, we may gain a fuller interpretation of this study's results and the utility of DPS measures for both clinical and research use.

1 INTRODUCTION

The purpose of this review is to determine whether the study has fulfilled PMR 3033-8, and to interpret the study findings with respect to the utility of doctor/pharmacy shopping (DPS) as an outcome indicating misuse, abuse, and/or addiction.

1.1 BACKGROUND

This review evaluates the final report from the study to fulfill ER/LA opioid analgesic PMR 3033-8 (formerly 2065-4A), titled "Cross-sectional Study to Define and Validate 'Doctor/Pharmacy Shopping' as Outcomes Suggestive of Abuse and/or Addiction," as well as the interim status report from this study. PMR 3033-8 is one of three PMR studies that assess DPS in relation to different measures of misuse, addiction, and/or abuse. These three studies were originally proposed to fulfill PMR 2065-4, which was issued to all holders of approved ER/LA opioid analgesic NDAs in September 2013. PMR 2065-4 required these sponsors to *conduct a study to define and validate*

'doctor/pharmacy shopping' as outcomes suggestive of misuse, abuse and/or addiction. With FDA's release and reissue of the ER/LA opioid analgesic PMRs in July 2015, these three studies became individual PMRs (3033-8, 3033-9, and 3033-10). PMR 3033-8, the subject of this review, states that the ER/LA opioid analgesic sponsors must conduct *an observational study using coded medical terminologies and other electronic healthcare data to define and validate doctor and/or pharmacy shopping outcomes by examining their association with abuse and/or addiction.* PMR 3033-9 uses a validated patient survey to assess the association between DPS and self-reported misuse and abuse, and PMR 3033-10 uses medical record review to assess the association between DPS and patient behaviors suggestive of misuse, abuse, and or addiction.

So-called "shopping behavior," i.e., seeking multiple prescriptions for opioids from multiple prescribers and pharmacies in an uncoordinated way (Cepeda et al. 2012), has been described in peer-reviewed analyses of prescription drug monitoring programs (Katz et al. 2010) and pharmacy claims databases (Cepeda et al. 2013, McDonald and Carlson 2014). As a potential proxy for misuse, addiction, and/or abuse, DPS has the advantage of ready availability in existing data sources; however, the DPS literature lacks a standard definition or validated measure of DPS. Part of FDA's motivation to require this study was to improve upon the methodological rigor of the DPS literature by measuring the extent to which certain opioid utilization patterns are associated with opioid misuse, abuse, or addiction. The current study builds upon the PMR 3033-7 study, which developed a measure, algorithmically indicated abuse and/or addiction (AIAA), by analyzing claims data, and evaluated its performance using review of medical record data.

1.2 REGULATORY HISTORY

The first ER/LA opioid analgesic was approved by the FDA in 1987, and numerous additional NDAs have been approved since. A complete list of ER/LA opioid analgesics and NDAs issued this PMR is included in **Appendix A**. In addition to the ER/LA opioid analgesic class-wide PMRs, FDA has taken multiple regulatory actions pertaining to the entire class of ER/LA opioid analgesics. A class-wide Risk Evaluation and Mitigation Strategy (REMS) took effect in 2012, and major labeling changes and a boxed warning were announced in 2013 and finalized in 2014.

1.3 PRODUCT LABELING

Appendix B contains labeling language from the ER/LA opioid analgesic MS Contin, (extended-release morphine sulfate), including *Indications and Usage, Abuse and Dependence,* and the Boxed Warning. This section briefly summarizes information relevant to this review; direct quotations are *italicized*.

- *Indications and Usage: indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.*
- *Drug Abuse and Addiction:*
    - A schedule II, controlled substance that is liable for abuse and criminal diversion

- *Drug-seeking* behaviors including *doctor shopping* are common among people who abuse or are addicted to opioids.

- *Boxed Warning:* [This drug] *exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing [this drug], and monitor all patients regularly for these behaviors and conditions.*

2 REVIEW METHODS AND MATERIALS

The following materials are the subject of this review:

- Final study report for PMR 3033-8 (formerly #2065-4A), titled "*Cross-sectional Study to Define and Validate 'Doctor/Pharmacy Shopping' as Outcomes Suggestive of Abuse and/or Addiction,*" submitted on June 21, 2017, amended on March 12, 2018.
- Interim status report for PMR 3033-8, submitted June 22, 2016. This report presented the results of analyses to derive the DPS categories and reported bivariate associations between DPS categories and various measures of health care utilization and patient characteristics.

The final study report was compared with the protocol and the interim status report. This review evaluated the final report's successful completion of the study objectives and planned analyses as described in the approved final protocol, as well as the validity and appropriate interpretation of the results, based on sound epidemiologic principles.

3 REVIEW RESULTS

3.1 STUDY OVERVIEW

The investigators developed several candidate definitions of DPS from prescription dispensing data in a cohort of U.S. adults who received either ≥2 opioid dispensings ("opioid cohort," 164,293 patients) or ≥2 diuretic dispensings ("diuretic cohort," 99,281 patients), during an 18-month period that began during the year 2012. The investigators selected the candidate definition with the greatest ability to discriminate between opioids and diuretics by modeling the probability of opioids *vs.* diuretics dispensings as a function of each candidate definition, in turn, with a logistic regression model, and comparing the models on their respective c-statistics, a measure of their ability to discriminate opioids vs. diuretics. Then, they used the opioid cohort to assess the association between DPS and patient demographic, medical, and dispensing characteristics, and evaluated DPS as a predictor of AIAA, by analyzing a dataset consisting of the prescription dispensing data linked to health care claims data.

3.2 STUDY OBJECTIVES

The primary study objectives for Study 3033-8 are to:

1. Formulate candidate definitions of doctor/pharmacy shopping by grouping patients in terms of characteristics of opioid dispensings (e.g., number of prescribing practices, number of pharmacies visited, type of payment [self-pay vs.

third-party payer]) for Immediate Release (IR) or Extended Release/Long Acting (ER/LA) opioids.
2. For each candidate definition of doctor/pharmacy shopping, evaluate its association with AIAA, as defined by PMR Study 3033-7 (formerly #2065-3B).

The secondary study objectives for Study 3033-8 are to:

1. Quantify how well patient characteristics correlate with AIAA among patients exhibiting DPS.
2. Evaluate the contribution of DPS to the prediction[b] of AIAA, after controlling for other patient characteristics.

3.3 STUDY METHODS

3.3.1 Design & Setting

This was a cross-sectional study of U.S. adults who received either ≥2 opioid dispensings ("opioid cohort," 164,293 patients) or ≥2 diuretic dispensings ("diuretic cohort," 99,281 patients), during an 18-month period that began during the year 2012. The selection, inclusion, and exclusion criteria were the same for both cohorts, except for the type of drug dispensed.

3.3.1.1 Selection, Inclusion and Exclusion Criteria

- Age 18-84 years at time of first dispensing in 2012
- Opioid analgesics could be either IR, ER/LA, or both.
- Patient data in PharMetrics Plus Database and in IMS Health (now IQVIA) Longitudinal Prescriptions (LRx) Database
- Had mental health coverage for the entire 18 months
- Had ≥1 dispensing recorded in LRx dated ≥365 days before their first opioid dispensing in 2012
- Had ≥18 months of observation after the dispensation, or PharMetrics Plus healthcare claims activity that suggested death[c] occurred in <18 months
- 100% of dispensings (all prescriptions, not only opioids) in PharMetrics Plus were also recorded in IMS LRx

[b] Here, the meaning of *prediction* was the measured relationship between independent and dependent variables in a regression model. The model was not used to predict a future event, as both the independent and dependent variables used information from all available timepoints in the study period.

[c] Death was identified from: hospital discharge status of "dead"; any non-hospital service with an ICD-9 code of Sudden Death (798x) not followed by later insurance claims; or by the occurrence of an ED visit associated with diagnoses consistent with fatal events and not followed by claims.

3.3.1.2 Data Sources

IMS investigators linked the IMS Health (IQVIA) LRx Database and IMS Health (IQVIA) PharMetrics Plus Database via a proprietary algorithm that uses 14 data fields.

IMS Health LRx Database

- 234 million patients, coverage throughout the US
- Data: prescription dispensing from outpatient retail pharmacies
- Each record includes: date, prescriber, prescriber practice group, prescriber specialty, medication, formulation, dose, days' supply dispensed payment method (including self-pay/cash)

IMS Health PharMetrics Plus Database

- 75 million patients (as of 2013), coverage throughout the US
- Data: claims from pharmacies, providers, and facilities
- Each record includes: date, patient demographic data, International Classification of Diseases-9 (ICD-9) diagnosis code for claim, type of health plan, date
- 97% of patients in database are commercially insured; 2% insured by Medicare; 1% insured by Medicaid

IMS Health Formulary Impact Analyzer (FIA)

- 58 million patients, coverage throughout the US
- Data: pharmacy claims that were rejected by the health plan
- This database was used for sensitivity analyses only

3.3.1.3 Protected Health Information Requirements

Institutional Review Board approval was not required for this study.

3.3.2 Exposure and Outcome

3.3.2.1 Exposure

The investigators used information from prescription dispensings in the IMS Health LRx Database to construct three candidate definitions of DPS. Their method offered more granularity than prior research, which generally used a binary definition of doctor shopping (Parente et al. 2004, Katz et al. 2010, Cepeda et al. 2012, McDonald and Carlson 2014). Here, each candidate definition contained four ordinal categories which reflected increasing extent of DPS: *none, minimal*, *moderate,* and *extensive*. Category cut-points were set so that people who exhibited any DPS above *none* were divided among the three upper categories roughly by 60%, 30%, and 10%. Although it was not explicitly stated, it appears that they chose this distribution to enhance precision of the results, as no other scientific rationale was given.

The Interim Status Report formally evaluated the three candidate definitions, and these candidate definitions' categories were defined by the number of:

- **Practices:** IMS LRx contains data on prescriber practice group. Unique prescribers who have no data on practice (55%) were treated as their own practice in the analysis. Additionally, a sensitivity analysis defined DPS by prescribers, not by practice.
- **Outlets:** These are outpatient pharmacies.
- **Days of overlap in prescriptions:** Defined as the number of days' supply left on a prescription – if any – when a subsequent prescription was filled. If there were two or more prior prescriptions with days' supply left, then the largest days' supply determined the number of days of overlap.

Table 1. Descriptions of three candidate definitions of Doctor/Pharmacy Shopping (DPS).

Category	*Definition*
DPS-0, defined with no requirement for overlapping dispensings.	
None	(No contributory dispensings) OR (2 practices AND 2 outlets)
Minimal	(2 practices AND >2 outlets) OR (2 outlets AND >2 practices)
Moderate	(3 practices AND ≥3 outlets) OR (4 practices AND (3 or 4 outlets) OR (5 practices and 3 outlets)
Extensive	(4 practices AND ≥5 outlets) OR (5 practices AND ≥4 outlets) OR (≥6 practices AND ≥3 outlets)
DPS-1, defined using dispensings that overlap by at least ONE day	
None	(No contributory dispensings)
Minimal	(2 practices AND 2 outlets AND <4 dispensings)
Moderate	(2 practices AND 2 outlets AND >3 dispensings) OR (2 practices AND >2 outlets AND 3 dispensings) OR (>2 practices AND 2 outlets)
Extensive	(2 practices AND >2 outlets AND >3 dispensings) OR (>2 practices AND >2 outlets)
DPS-10, defined using dispensings that overlap by at least TEN days	
None	(No contributory dispensings)
Minimal	(2 practices AND 2 outlets AND <4 dispensings)
Moderate	(2 practices AND 2 outlets AND >3 dispensings) OR (2 practices AND >2 outlets)
Extensive	(>2 practices AND 2 outlets AND >2 dispensings) OR (>2 practices AND >2 outlets)

Source: OPC Final Report, Appendix D, Table 4

DPS-1 Required ≥1 day's supply overlap between successive prescriptions to count the number of practices and number of outlets toward the DPS-1 index value. If there were multiple overlap events, the overlap event with the maximum number of dispensings was counted. **DPS-10** was similar, requiring ≥10 day's supply overlap.

For the rest of this review, we will use DPS-1, DPS-10, and DPS-0 when referring to a specific candidate definition. *DPS* without a suffix will refer either to all three models, or the underlying concept of doctor/pharmacy shopping.

3.3.2.2 Outcome

OPC investigators in PMR Study 3033-7 had previously developed the outcome **Algorithmically-Indicated Abuse and/or Addiction (AIAA)** by analyzing health care claims data; they evaluated the algorithm's performance against manual review of medical record data. This medical record review, performed by personnel trained on standard procedures, was used as the gold standard for AA. AIAA was coded as present or absent based on the investigator-selected cut-off value of the risk score, which itself was calculated by summing the components of AIAA (**Appendix D**) and transforming the risk score. The transformation (inverse logit) facilitated the application of the risk score to dichotomizing the population; it is a standard method for analyses that classify individuals by disease status. The 3033-7 primary study population was U.S. adult patients who received ≥60 days of ER/LA opioid products over a three-year period and who were enrolled in the Kaiser Permanente Washington (KPW) health plan. After developing the algorithm, the OPC investigators also evaluated the validity of AIAA for classifying similar patients from three, diverse study sites. Of note, at each study site, evaluation of AIAA relative to medical records showed that the validity performance measures, i.e., the positive predictive value[d] (PPV) and sensitivity[e], were below the authors' pre-specified validity criteria. Thus, DEPI agreed with the OPC that AIAA should not be applied to further studies. However, the PMR Study 3033-8 final report had already been submitted when DEPI completed its review of the Study 3033-7 final report.

Therefore, the current study's investigators selected a cut-point for AIAA based on evaluations in the Optum Research Database, the 3033-7 study site that was most like the current study, i.e., a commercial, fee-for-service health plan. In selecting a cut-point in the algorithm's risk score to indicate presence of AIAA, the authors sought to minimize the number of false-positives because they expected the AA prevalence to be lower in the current study than in the prior study conducted in Optum, which was selected based on greater quantity of ER/LA opioids. Thus, they selected a cut-point for the risk score, 0.368, that in the Optum data produced specificity[f]=0.90, sensitivity=0.42, PPV=0.62, and negative predictive value[g] (NPV)=0.88. Categories of AIAA were as follows:

- AIAA = 1 (present) if Risk Score >0.368
- AIAA = 0 (not present) if Risk score ≤0.368

3.3.3 Covariates

[d] The *positive predictive value* is the probability of truly having the condition (according to the gold-standard measure), conditional on a positive test result.

[e] The *sensitivity* is the probability of having a positive test result, conditional on truly having the condition (according to the gold-standard measure).

[f] The *specificity* is the probability of having a negative test result, conditional on truly not having the condition (according to the gold-standard measure).

[g] The *negative predictive value* is the probability of truly not having the condition (according to the gold-standard measure), conditional on a negative test result.

Appendix E contains the full list of covariates considered *a priori* for inclusion in the full model. Briefly, the categories of covariates were as follows (selected important variables in parentheses):

- Demographics (Sex; State of residence)
- Other drug groups dispensed (antidepressants; antipsychotics; hypnotics; anxiolytics; psycho-stimulants)
- Properties of the opioid dispensings during the study period (product type; number of opioid prescriptions written by non-specialists; number of times opioids were dispensed for self-payment; total MEQ dispensed)
- Pain diagnoses associated with insurance claims during the study period
- Non-pain diagnoses associated with insurance claims during the study period

Many of these variables measured factors that were components of the AIAA definition, e.g., insurance claim for opioid use disorder. Per FDA request (**Appendix I**), the Sponsor identified the covariates that had no overlap with components of the AIAA definition and evaluated these "core covariates" in an alternative model for Secondary Objective 2, which is "to evaluate the contribution of DPS to the prediction[h] of AIAA, after controlling for other patient characteristics." Core covariates were selected for the final Core Covariates Model by using an automated procedure, which is described in Section 3.3.5.2 below. The model included these core covariates:

Main independent variables:

U.S. Census Division

Number of dispensings by drug group:

Hypnotics

Psychostimulants

Non-pain diagnoses (ICD-9 code):

Benign neoplasms (210-219)

Blood/blood-forming organs (280-289)

Circulatory system (390-459)

Respiratory system (460-519)

Any self-paid opioid dispensings (Yes/No)

Interaction variables:

Respiratory system and Psychostimulants

Respiratory system and Benign neoplasms

[h] The meaning of *prediction* was the measured relationship between independent and dependent variables in a regression model. The model was not used to predict a future event, as both the independent and dependent variables used information from all available timepoints in the study period.

Of note, most of the covariates in **Appendix E** overlapped with components of the AIAA definition (**Appendix D**).

3.3.4 Sample Size and Statistical Precision

This claims-based study included 164,923 patients. The protocol did not address the desired precision of the results or assess the relationship between the study size and the results' precision (e.g., with power calculations). In the Discussion section (**Section 4**) FDA will provide interpretation of the results' precision.

3.3.5 Statistical Analyses

3.3.5.1 Primary Objective 1

Primary Objective 1 was to formulate candidate definitions of DPS by grouping patients in terms of characteristics of opioid dispensings. The prevalence of each category of DPS for patients receiving opioids was compared to its prevalence in a negative control population, patients receiving diuretics. The purpose of diuretic dispensing patterns was to approximate a baseline for variability in the numbers of prescribers and outlets. Like opioid analgesics, diuretics are used chronically; unlike opioids, they are not controlled substances subject to abuse and/or addiction.

There were three candidate definitions of DPS, and each had four levels, *none, minimal, moderate,* and *extensive,* as described above in **Section 3.3.2.1**. The investigators conducted the following analysis to select the candidate definition that best differentiated opioid dispensings from diuretic dispensings.

- For each candidate definition, the investigators
  - Calculated the number and percent of patients in each DPS category among patients receiving opioids and among patients receiving diuretics
  - Calculated the ratio in each DPS category of the percentage of patients dispensed opioids to percentage of patients dispensed diuretics
  - Fit a logistic regression model: the dependent variable was Opioid *vs.* Diuretic, and the independent variables were binary indicators for *minimal, moderate,* and *extensive* DPS. There were no covariates.
    - The model estimated odds ratios (OR) and 95% confidence intervals (CI) for opioid dispensing vs. diuretic dispensing, in each DPS category relative to *none*.
    - The model's c-statistic quantified how well the model discriminated between opioid dispensing patterns and diuretic dispensing patterns.

The investigators selected the candidate definition that yielded the largest c-statistic from the logistic regression model, indicating the greatest discrimination capability.

Additionally, the investigators considered total number of dispensings in each candidate definition and examined the distributions of patients in these categories (Interim Status Report, Tables 5-7) in an intermediate step, before proceeding to logistic regression

analysis. However, they collapsed categories over numbers of fills to achieve the 60-30-10 distribution among *minimal, moderate,* and *extensive* DPS.

Examine the degree to which DPS is associated with measures of patient characteristics and health care utilization:

First, the investigators conducted bivariate analyses in which they presented the distribution of DPS categories within levels of each covariate (list of covariates, **Appendix E**). Also, they presented the distribution of DPS categories by the presence vs. absence of a given attribute of the prescription drug monitoring program (PDMP) in the patient's state of residence. These six attributes of the PDMPs were:

- Mandatory registration of the prescriber in 2012,
- Mandatory registration of the pharmacy in 2012,
- Mandatory check with the PDMP before prescribing (no year stipulated),
- Mandatory check with the PDMP before dispensing (no year stipulated),
- Use of probabilistic or exact matches to link patients in 2014,
- The PDMP was online in 2011

Second, the investigators conducted a multivariable-adjusted, cumulative logistic regression model analysis in which DPS was a four-level dependent variable (i.e., *none, minimal, moderate, extensive*), and independent variables were selected for the model via an automated, stepwise selection procedure with a criterion for inclusion $P<0.1$.

3.3.5.2 Primary Objective 2

Primary Objective 2 is to evaluate the association of each DPS candidate definition with AIAA.

In the final report, the prevalence of AIAA was tabulated within category of DPS-0, cross-classified with category of each covariate (e.g., *minimal* DPS and 250-499 MEQ dispensed during study period).

To evaluate the association of <u>each candidate definition of DPS</u> (i.e., DPS-0, DPS-1, and DPS-10) with AIAA, the Sponsors compared the results of logistic regression models in which AIAA was the dependent variable:

- DPS and All Covariates model: Independent variables were DPS (binary variables indicated *minimal, moderate*, and *extensive)* and covariates that were selected from the list in **Appendix D** by fitting a series of regression models in an automated, stepwise selection procedure, with criterion for variable selection into the model $P<0.05$.
- All Covariates model: Retained the covariates from the previous model and dropped DPS.
- DPS-only model: Independent variables were *minimal, moderate,* and *extensive* DPS.

The models were compared based on the following statistics:

- C-statistic: discrimination between people with vs. without AIAA
- Pseudo-R^2: percent of variability in AIAA that is explained by the model

- Deviance statistic: statistical test for goodness-of-fit
- Hosmer-Lemeshow test: statistical test that the model has poor fit to the data

3.3.5.3 Secondary Objective 2

Note that Secondary Objective 1 is described below in **Section 3.3.5.4.**

Secondary Objective 2 is to evaluate the contribution of DPS to the model's ability to discriminate between people with vs. without AIAA, after controlling for other patient characteristics. As a note of clarification, the final report often referred to this as the *contribution of DPS to the prediction of AIAA;* however, the meaning of *prediction* was the measured relationship between independent and dependent variables in a regression model. The model was not used to predict a future event, as both the independent and dependent variables used information from all available timepoints in the study period.

There was an evaluation of the DPS-0 and All Covariates Model's ability to discriminate between patients with vs. without AIAA:

- The Full Model's receiver-operator characteristic (ROC) curve was plotted.
  - A brief explanation of using a multivariable model to generate a ROC curve follows. The Full Model estimates various probabilities of (AIAA=1) based on values of DPS and covariates. The ROC curve demonstrates the trade-off between sensitivity and specificity for every probability of (AIAA=1) estimated by the model, and the ROC curve identifies a predicted probability that accurately discriminates people who truly have AIAA from people who truly do not have AIAA. The hypothetical clinical application of this predicted probability would be to identify people with AIAA based on all the variables included in the model.
- The point on the ROC curve with the minimum distance from perfect sensitivity and perfect specificity is called the **point of maximum discrimination**, and it corresponds to a predicted probability of (AIAA=1), estimated by the model, that is the **most accurate cut-off value for discriminating between people with vs. without AIAA**.
- The investigators used this cut-off value to classify people as AIAA present or not, according to their model. Since people were also classified as to their AIAA status from the risk score developed to fulfill PMR 3033-7, that classification of AIAA was used as the gold standard for evaluating the accuracy of each model in the present study for discriminating people with vs. without AIAA. The measures of model validity were:
  - Sensitivity
  - Specificity
  - Positive predictive value (i.e., prevalence in those predicted positive)
  - Negative predictive value (i.e., prevalence in those predicted negative)

3.3.5.3.1 Secondary Objective 2 Sensitivity Analyses

In response to an Information Request from FDA (**Appendix I**), the Sponsors also performed several sensitivity analyses. One such analysis aimed to evaluate the contribution of DPS to discriminate between people with vs. without AIAA after adjusting for covariates that were not part of the definition of AIAA. For this, the logistic regression model used the Core Covariates from **Appendix D** instead of all covariates.

The other sensitivity analyses aimed to evaluate the influence of using multiple doctors/pharmacies in isolation from obtaining multiple prescriptions since increasing DPS categories incorporated increasing number of prescriptions in their definitions (Table 1). These sensitivity analyses were:

- Adding to the Core Covariates the following variables, in turn: *total MEQ dispensed, number of opioid dispensings*
- Restricting the population to patients with ≥5 prescriptions

3.3.5.4 Secondary Objective 1

Secondary Objective 1 was to quantify how well patient characteristics correlate with AIAA among patients exhibiting at least minimal DPS. The rationale for this sub-group analysis was that people with at least minimal DPS may represent a unique group who should be analyzed separately. The sponsor restricted the population to patients with minimal, moderate, or extensive DPS-0 (N=24,946), fit the DPS-0 Plus All Covariates model, and calculated the model fit statistics.

3.4 STUDY RESULTS

3.4.1 Primary Objective 1

Evaluate the ability of each candidate definition of DPS to discriminate between opioid dispensings and diuretic dispensings:

The interim status report presented the results of the analysis that evaluated candidate definitions for DPS (see **Appendix C**). The investigators selected the candidate definition with the highest c-statistic from a logistic regression model that modeled the probability of opioids *vs.* diuretics dispensings (**Table 2)**. DPS-0 had the greatest discrimination ability with a c-statistic=0.563, indicating poor discrimination. The authors explained why, for DPS-10, patients in the category for *extensive* DPS were less likely to be dispensed an opioid: "*The relationship may be the result of the typical values for days' supply associated with opioid and diuretic fills, which are much longer for diuretics and thereby allow for a greater possibility of 10-day overlaps."*

Table 2. Summary of Statistics from Three Candidate Definitions of DPS.

	Opioids		Diuretics					
	N	Percent	N	Percent	Ratio of percent	Opioid vs. Diuretic OR	95% CI	
DPS-1								
None	157,194	95.31%	97,265	97.97%	1.0	reference		
Minimal	6,576	3.99%	1,613	1.62%	2.5	2.5	2.4	2.7
Moderate	912	0.55%	337	0.34%	1.6	1.7	1.5	1.9
Extensive	241	0.15%	66	0.07%	2.2	2.3	1.7	3.0
Total	164,923		99,281					
c-statistic: 0.513								
DPS-10								
None	163,348	99.05%	97,803	98.51%	1.0	reference		
Minimal	1,390	0.84%	1,259	1.27%	0.7	0.66	0.61	0.71
Moderate	110	0.07%	105	0.11%	0.6	0.63	0.48	0.82
Extensive	75	0.05%	114	0.11%	0.4	0.39	0.29	0.53
Total	164,923		99,281					
c-statistic: 0.503								
DPS-0								
None	139,977	84.87%	96,776	97.48%	0.9	reference		
Minimal	16,431	9.96%	2,006	2.02%	4.9	5.7	5.4	5.9
Moderate	5,956	3.61%	450	0.45%	8.0	9.2	8.3	10.1
Extensive	2,559	1.55%	49	0.05%	31.4	36.1	27.2	47.8
Total	164,923		99,281					
c-statistic: 0.563								

Source: PMR 3033-8 Interim Status Report, Tables 10-12.

Examine the degree to which DPS-0 is associated with measures of patient characteristics and health care utilization:

The interim status report showed that the cumulative logistic regression model with a 4-level dependent variable for DPS-0 category showed a poor fit to the data, and so they fit an ordinary logistic regression model with a 2-level dependent variable, moderate/extensive DPS *vs.* none/minimal. They strengthened the stepwise-selection criterion for inclusion to $P<0.01$ because so many variables were included with $P<0.05$. **Appendix F** shows the cross-tabulation of each patient characteristic by DPS category and the *P*-value for each characteristic, calculated by the 2-level logistic regression model that was produced by the stepwise selection procedure. **Highlights of the results are below, adjusted for all other characteristics in the model:**

Opioid formulation was associated with *moderate/extensive* DPS: Compared to patients who received only ER/LA opioids, DPS was more common among patients who received only IR opioids (OR=2.67, 95% CI: 1.99, 3.57) and among patients who received both IR and ER/LA opioids (OR=5.19, 95% CI: 3.87, 6.95).

Variables positively associated with *moderate/extensive* DPS:

- Patient characteristics:
  - Male gender
  - Presence of certain ICD-9 Chapters for diagnoses (fracture, musculoskeletal, wounds & injuries)
- Health care utilization:
  - Number of dispensings prescribed by non-specialists
  - Number of dispensings that were self-paid
  - Total MEQ dispensed
  - Number of psychotropic medication fills during the study period (antipsychotics, anxiolytics, hypnotics, antidepressants)
  - Number of psychotropic medication fills during *365 days before* the study period (psychostimulants, antidepressants)

Variables negatively associated with *moderate/extensive* DPS:

- Patient characteristics:
  - Age
  - Presence of certain ICD-9 Chapters for diagnoses: neuropathic pain, endocrine, circulatory disorders
- No health care utilization variables were negatively associated with *moderate/extensive* DPS

Prevalence of *Extensive* Shopping Category by State and by PDMP characteristics:

As shown in **Table 3**, there was wide variation across states in the prevalence of *extensive* shopping behavior.

Table 3. States with highest and lowest prevalence of *Extensive* Doctor/Pharmacy Shopping (DPS-0).*

States with highest prevalence (>2.5%)				
NH	**DE**	**NJ**	**VA**	**AZ**
3.70%	3.20%	2.80%	2.70%	2.60%

States with lowest prevalence (<0.6%)					
KY	**OR**	**AR**	**IA**	**ME**	**ND**
0.50%	0.50%	0.50%	0.30%	0.00%	0.00%

Source: PMR 3033-8 Interim Status Report, Table 19.
*States with <100 patients were excluded: SD, MT, UT, VT, WY, AK, DC, HI.

For each PDMP characteristic, a modest reduction in the prevalence of *extensive* shopping behavior was observed among states where that PDMP characteristic was present, compared with states where that PDMP characteristic was absent (absolute differences ranged from 0.1% - 0.4%; **Table 4**). This reduction in the prevalence of

extensive DPS-0 category was typically offset by an increased prevalence of *minimal* DPS-0 category, rather than by the *none* category.

Table 4. Distribution of patients by category of the Doctor/Pharmacy Shopping (DPS-0) and by presence of state PDMP characteristics

			Doctor/Pharmacy Shopping Category							
		Total[a]	*None*		*Minimal*		*Moderate*		*Extensive*	
Pharmacy checks	No	161,015	136,658	84.9%	16,018	9.9%	5,828	3.6%	2,511	1.6%
	Yes	3,894	3,306	84.9%	412	10.6%	128	3.3%	48	1.2%
Prescriber checks	No	153,117	129,972	84.9%	15,212	9.9%	5,525	3.6%	2,408	1.6%
	Yes	11,792	9,992	84.7%	1,218	10.3%	431	3.7%	151	1.3%
PMP online	No	62,548	52,987	84.7%	6,260	10.0%	2,313	3.7%	988	1.6%
	Yes	102,361	86,977	85.0%	10,170	9.9%	3,643	3.6%	1,571	1.5%
Pharmacy registered	No	97,555	83,095	85.2%	9,509	9.7%	3,404	3.5%	1,547	1.6%
	Yes	67,354	56,869	84.4%	6,921	10.3%	2,552	3.8%	1,012	1.5%
Prescriber registered	No	134,103	113,920	84.9%	13,182	9.8%	4,814	3.6%	2,187	1.6%
	Yes	30,806	26,044	84.5%	3,248	10.5%	1,142	3.7%	372	1.2%
Probability match	No	139,305	117,952	84.7%	13,966	10.0%	5,128	3.7%	2,259	1.6%
	Yes	25,604	22,012	86.0%	2,464	9.6%	828	3.2%	300	1.2%

Source: PMR 3033-8 Interim Status Report, Table 20

PDMP, Prescription Drug Monitoring Program

[a] Totals sum to less than 164,923 because some state-specific values are not known.

3.4.2 Primary Objective 2

From this point in the review on, all results are from the final report.

When the association of DPS-0 with AIAA was evaluated by fitting an unadjusted logistic regression model, the odds of AIAA increased significantly with increasing category of DPS-0 **(Table 5)**. Despite its strong association with AIAA, DPS-0 explained 7% of the variation in odds of AIAA and displayed modest discrimination ability: c-statistic=0.689, pseudo-r^2= 0.070, and 49% of AIAA cases were in the *none* category **(Table 5)**. Each of the other candidate definitions of DPS had an even lower discrimination ability, as their categories for *minimal*, *moderate*, and *extensive* DPS had few people and large ORs with wide confidence intervals **(Table 5).** For these definitions, the *none* category also comprised 73% of AIAA cases for DPS-1 and 90% of AIAA cases for DPS-10.

Table 5. Candidate definitions of Doctor/Pharmacy Shopping (DPS): Unadjusted association with Algorithmically-identified Abuse/Addiction (AIAA), N=164,923 U.S. Adults, 2012-2014.

		AIAA	95% CI for Prevalence	Total (col %)	OR[a] (95% CI)
DPS-0 [b]					
None	**N**	391		139,977	Ref.
	Prev %	0.28	(0.25, 0.31)	84.9%	--
Minimal	**N**	183		16,431	4.02
	Prev %	1.11	(0.96, 1.29)	10.0%	(3.37, 4.80)
Moderate	**N**	90		5,956	5.48
	Prev %	1.51	(1.23, 1.85)	3.6%	(4.35, 6.90)
Extensive	**N**	129		2,559	18.95
	Prev %	5.04	(4.26, 5.96)	1.6%	(15.47, 23.22)
DPS-1[c]					
None	**N**	576		157,194	Ref
	Prev %	0.37	(0.34, 0.40)	95.3%	--
Minimal	**N**	123		6,576	5.18
	Prev %	1.87	(1.57, 2.23)	4.0%	(4.26, 6.31)
Moderate	**N**	70		912	22.61
	Prev %	7.68	(6.12, 9.59)	0.55%	(17.48,29.23)
Extensive	**N**	24		241	30.07
	Prev %	9.96	(6.78, 14.39)	0.15%	(19.57, 46.21)
DPS-10[d]					
None	**N**	713		163,348	Ref
--	**Prev %**	0.44	(0.41, 0.47)	99.0%	--
Minimal	**N**	62		1,390	10.65
	Prev %	4.46	(3.49, 5.68)	0.8%	(8.17, 13.88)
Moderate	**N**	12		110	27.93
	Prev %	10.91	(6.35, 18.10)	0.07%	(15.27, 51.09)
Extensive	**N**	6		75	19.83
	Prev %	8	(3.72, 16.37)	0.05%	(8.58, 45.83)
Population Total	**N**	793		164,923	
	Prev (%)	0.48	(0.45, 0.52)	100%	

Source: PMR 3033-8 Final Report: Table 3, Appendix D Table 2, Appendix D Table 3.
Prev, prevalence

[a] Calculated from an unadjusted logistic regression model of AIAA.

[b] Model c-statistic=0.689, pseudo-R^2 = 0.070

[c] Model c-statistic=0.616, pseudo-R^2 = 0.056

[d] Model c-statistic=0.546, pseudo-R^2 = 0.025

Association of AIAA and DPS within strata of covariates:

Within each strata of each covariate, generally, AIAA prevalence increased with increasing levels of DPS-0. Notably, this positive trend was observed within each level of the variables that measured the total quantity of opioid dispensed (prescriptions written by non-specialists, times opioids were dispensed for self-payment, and total MEQ dispensed; **Table 6**). An exception to this positive trend was that there were no AIAA cases among patients who received only ER/LA opioids and who were categorized as *moderate* or *extensive* DPS-0.

Within levels of DPS-0, AIAA prevalence was higher among patients age 18-34 years than patients age ≥35 years. Also, within level of DPS, AIAA prevalence increased with increasing number of dispensings for psychotropic drugs, and with increasing quantity of opioids prescribed, as reflected by three variables: prescriptions written by non-specialists, times opioids were dispensed for self-payment, and total MEQ dispensed (**Table 6**). However, AIAA prevalence exhibited little variation by gender or by medical diagnoses, after stratifying by DPS level.

Table 6. Count and Prevalence of Algorithmically-Identified Abuse/Addiction (AIAA) by cross-classified category consisting of level Doctor/Pharmacy Shopping (DPS-0) and level of opioid dispensing.

	DPS-0							
	None		Minimal		Moderate		Extensive	
	N[a]	%[a]	N[a]	%[a]	N[a]	%[a]	N[a]	%[a]
NUMBER OF OPIOID PRESCRIPTIONS WRITTEN BY NON-SPECIALISTS								
0	100	0.20%	15	0.80%	9	1.50%	1	1.90%
1	43	0.10%	17	0.60%	11	1.10%	4	2.80%
2	52	0.20%	15	0.50%	9	0.90%	5	2.50%
3	29	0.30%	17	0.80%	7	0.90%	5	2.80%
4-6	42	0.40%	17	0.60%	12	1.20%	23	4.00%
7-14	47	0.60%	36	1.90%	15	1.90%	33	4.60%
≥15	78	0.90%	66	3.50%	27	3.20%	58	8.30%
NUMBER OF TIMES OPIOIDS WERE DISPENSED FOR SELF-PAYMENT								
0	320	0.20%	122	0.90%	54	1.10%	59	3.50%
1	35	0.50%	31	2.00%	19	2.50%	28	6.30%
2	17	1.40%	16	4.10%	4	2.00%	17	9.20%
3	5	1.40%	5	3.80%	2	2.50%	7	7.80%
4+	14	2.60%	9	5.60%	11	9.10%	18	13.10%
TOTAL MEQ DISPENSED								
<250	189	0.20%	35	0.40%	25	0.90%	7	2.30%
250-499	45	0.30%	34	1.00%	9	0.70%	14	2.10%
500-999	41	0.50%	31	1.60%	17	2.00%	21	3.10%
1000-2499	44	1.40%	41	3.70%	16	2.90%	42	7.70%
2500-4999	34	3.00%	22	5.40%	15	6.90%	25	11.00%
5000-9999	24	4.30%	17	9.60%	5	5.30%	13	13.00%
10000+	14	16.50%	3	8.80%	3	12.00%	7	24.10%

Source: PMR 3033-8 Final Report, Appendix B.

[a] Each count and percentage is out of the total number of patients in that cross-tabulated category.

3.4.3 Secondary Objective 2

Note that the results for Secondary Objective 1 are in **Section 3.4.4**.

The study evaluated the contribution of DPS to predicting AIAA, after controlling for patient factors. The All Covariates Model, which included variables that were components of the AIAA definition (**Appendix G**), explained 35.8% of variation in AIAA odds and displayed excellent discrimination between people with vs. without AIAA at the model's point of maximum discrimination (pseudo-R^2=0.358, c-statistic=0.943). **Adding DPS-0 to the All Covariates Model made no improvement to discriminating AIAA** (pseudo-R^2=0.359, c-statistic=0.943), **and it made little change in the covariate ORs** (**Appendix G**). Still, **DPS-0 was significantly associated with**

increased odds of AIAA after adjusting for all covariates (relative to *none* category, *minimal* OR=1.56, 95% CI: 1.28, 1.89; *moderate* OR=1.56, 95% CI: 1.56, 95% CI: 1.20, 2.02; *extensive* OR=1.95, 95% CI: 1.51, 2.52). The largest OR in the model was for presence of any diagnosis from the ICD-9 Chapter for Mental Diagnoses, which includes opioid abuse and addiction (adjusted OR=15.64, 95% CI: 10.68, 22.92). The DPS-0 Plus All Covariates model could discriminate between people with vs. without AIAA with some accuracy at the point of maximum discrimination, but it still misclassified AIAA substantially (negative predictive value was 99.9%, positive predictive value was 3.4%).

3.4.3.1 Sensitivity Analyses

The Core Covariates Model, which included variables (**Appendix E**) that were not components of the AIAA definition, was also significantly associated with AIAA but had lower discrimination ability than the All Covariates Model (pseudo-R^2=0.080, c-statistic=0.741; **Appendix H**). Adding DPS-0 to the Core Covariates Model improved its discrimination ability, and a marginally significant statistic for the Hosmer-Lemeshow test suggested the model may have a poor fit to the data (pseudo-R^2=0.118, c-statistic=0.797, *P*=0.045 from Hosmer-Lemeshow test; **Appendix H**). The Sponsors explained one reason for the model's apparent poor fit was that the association of DPS-0 and AIAA may depend on the values of the core covariates. Similarly, the performance statistics for the DPS-0 Plus Core Covariates Model at the point of maximum discrimination showed that adding DPS-0 improved the sensitivity to just 73.6% and made essentially no difference in the specificity of 72.5% (**Table 7)**. When the other candidate definitions were substituted in turn for DPS-0 in the DPS Plus Core Covariates Model, they each improved the model's discrimination ability, but to a lesser extent than DPS-0 did (**Table 7; Appendix H, Tables H2-H3**).

Table 7. Performance statistics of models for discriminating between people with vs. without AIAA at each model's point of maximum discrimination.

	Core Covariates Model	Core Covariates Plus DPS Defined with		
		DPS-0	DPS-1	DPS-10
Sensitivity	64.19%	73.64%	68.73%	65.32%
Specificity	72.47%	72.54%	73.68%	73.06%
Positive predictive value (PPV; Prevalence in those predicted positive)	1.11%	1.28%	1.24%	1.16%
Negative predictive value (NPV)	99.76%	99.83%	99.80%	99.77%
Prevalence in those predicted negative (1 – NPV)	0.24%	0.17%	0.20%	0.23%

Source: PMR 3033-8 Final Report, Appendix D Table 8.

Next, the investigators augmented the core covariates with variables for number of opioid dispensings and total MEQ dispensed, in turn, and explored the extent to which adding DPS-0 to these models enhanced their discrimination ability (as measured by the c-statistic and pseudo-R^2). **In summary, augmenting the core covariates model with opioid dispensings, MEQ dispensed, or both, increased the model's discrimination ability, more than adding DPS-0 did** (**Table 8**). **Adding DPS-0 to the models with**

opioid dispensings and/or MEQ dispensed made almost no difference to the c-statistic and pseudo-R^2 (**Table 8**).

Table 8. Performance statistics of models for discriminating between people with vs. without AIAA at each model's point of maximum discrimination.

Model	C-Statistic	Pseudo-R^2	Hosmer-Lemeshow	
			Chi-square	P-value
Core Covariates	0.741	0.08	10.804	0.213
Core Covariates and Opioid Dispensings	0.816	0.147	28.305	<0.001
Core Covariates and MEQ Dispensed	0.813	0.151	13.2	0.105
Core Covariates, Opioid Dispensings, and MEQ Dispensed	0.819	0.158	13.658	0.091
DPS-0 Plus Core Covariates	0.797	0.118	15.851	0.045
DPS-0 Plus Core Covariates and Opioid Dispensings	0.829	0.164	27.487	0.001
DPS-0 Plus Core Covariates and MEQ Dispensed	0.829	0.167	19.122	0.014
DPS-0 Plus Core Covariates, Opioid Dispensings, and MEQ Dispensed	0.829	0.172	21.693	0.006
DPS-0 Only	0.689	0.07	.	.

Source: PMR 3033-8 Final Report Appendix D, Tables 5, 33-35.

The next sensitivity analysis restricted the study population to the 55,539 patients with ≥5 dispensings of opioids. AIAA prevalence, overall and in the DPS-0 *none* category, was higher in this sub-group compared to the whole population, (overall: 1.10% vs. 0.5%; *none* category: 0.62% vs. 0.28%). The AIAA ORs for the higher categories of DPS-0 in this sub-group were positive and significant, but they were closer to the null than the ORs estimated from the whole population (**Table 9**, compare to **Table 5** in whole study population).

Table 9. AIAA prevalence by category of DPS-0 among patients with ≥5 dispensings of opioids.

DPS-0		AIAA	95% CI for Prevalence	Total (column %)	DPS-0 OR[a] (95% CI)	DPS-0 Plus Core Covariates OR[b] (95% CI)
None	**N**	239		38,706	Ref.	Ref.
	Prevalence	0.62%	(0.54, 0.70)	69.69	--	--
Minimal	**N**	163		10,028	2.66	2.42
	Prevalence	1.63%	(1.40, 1.89)	18.06	(2.18, 3.25)	(1.98. 2.96)
Moderate	**N**	77		4,246	2.97	2.54
	Prevalence	1.81%	(1.45, 2.26)	7.65	(2.29, 3.85)	(1.95, 3.30)
Extensive	**N**	129		2,559	8.54	5.56
	Prevalence	5.04%	(4.26, 5.96)	4.61	(6.87,10.63)	(4.41, 7.01)
Total	**N**	608		55,539		
	Prevalence	1.10	(1.01, 1.18)	100.00		

Tabular statistics: Chi-square 3 df = 495.8; p <0.0001;
Test for trend z = 20.65; p <0.0001
[a] From logistic regression. c-statistic = 0.673; pseudo-R^2 = 0.050
[b] From logistic regression with adjustment for core covariates. c-statistic = 0.758; pseudo-R^2 = 0.092

Source: PMR 3033-8 Final Report, Appendix D Table 24.

3.4.4 Secondary Objective 1

Per protocol, the investigators also fit the models with All Covariates, Core Covariates, and Core Covariates and Opioid Dispensings after restricting the population to patients with *minimal*, *moderate*, or *extensive* DPS-0 (N=24,946). The model performance statistics suggest that the model comparing only the *moderate* and *extensive* DPS-0 categories to *minimal* DPS-0 provides weak discrimination ability of AIAA, and that it makes little improvement to discrimination of AIAA when added to All Covariates, Core Covariates, and Core Covariates and Opioid Dispensings (**Table 10)**. Repeating the analyses using the DPS-1 and DPS-10 definitions produced the same conclusions.

Table 10. Model Performance Statistics Calculated from Patients with *Minimal, Moderate,* or *Extensive* DPS-0.

	C-Statistic	Pseudo-R^2	Hosmer-Lemeshow	
			Chi-square	p
All Covariates[a]	0.916	0.307	6.59	0.58
DPS-0 Plus All Covariates[a]	0.916	0.308	7.76	0.46
Core Covariates	0.719	0.66	4.526	0.801
DPS-0 Plus Core Covariates	0.748	0.085	11.15	0.193
Core Covariates and opioid dispensings	0.794	0.13	10.637	0.223
DPS-0 Plus Core Covariates and opioid dispensings	0.801	0.135	14.575	0.068
DPS-0 only	0.631	0.037	0	1

Source: PMR 3033-8 Final Study Report, Appendix D, Tables 12-13.

[a] Note that within the reduced population, the automated selection procedure for a set of independent variables did not retain state of residence.

Apparent Deaths in the Study Population

Less than 1% of the study population had claims activity suggestive of death[i] over the 18 months of observation (0.72% overall, including 2.0% of patients with AIAA identified). Median time in days from first opioid dispensing until claims activity suggestive of death[i] increased with increasing DPS-0 (None: 230 days; Extensive: 320 days).

Planned Sensitivity Analyses of the DPS Definition

The investigators assessed the sensitivity of the results to using prescribing practices as the unit for measuring the extent of DPS. They recalculated DPS categories when each prescriber was counted separately from other prescribers in the same practice group. Overall, 0.8% of patients increased their DPS-0 category, and so the investigators concluded using prescribers instead of practice would not impact the analysis. However, basing categories on prescriber would increase the original *extensive* category by 9% (adding 236 to 2,559).

Since the DPS definition was based on completed dispensings, rejections of claims by the insurer may lower the number of practices and outlets as measured by pharmacy claims, thereby reducing the numbers of people classified in the higher categories of DPS. The investigators explored this as "suppressed shopping behavior," although the analysis could not ascertain whether the rejected claims truly represented shopping behavior. The investigators examined the potential impact of rejected pharmacy claims on the observed

[i] Death was identified from: hospital discharge status of "dead"; any non-hospital service with an ICD-9 code of Sudden Death (798x) not followed by later insurance claims; or by the occurrence of an ED visit associated with diagnoses consistent with fatal events and not followed by claims.

prevalence of apparent shopping behavior by tabulating the number of rejected claims by DPS category. The rejected claims rate increased markedly with increasing category of DPS, showing that people with higher numbers of completed dispensings from multiple prescribers and pharmacies also had a higher rate of rejected claims (**Table 11)**.

Table 11. Number of rejected claims and individuals by DPS-0 category.

	DPS-0 Categories				
	None	**Minimal**	**Moderate**	**Extensive**	**Total**
Individuals	137,634	16,320	5,905	2,553	162,412
Rejected claims	941	370	187	171	1669
Rejected claims per 1000 persons	6.8	22.7	31.7	67.0	10.3

Source: PMR 3033-8 Final Study Report, Table 10.

The investigators also assessed the sensitivity of the results to having available data on dispensings that were self-paid; this is a validity issue in studies that use claims databases, thereby missing data on self-paid dispensings. For this sensitivity analysis, all self-paid dispensing data were excluded. Therefore, N=2,511 patients (1.52%) were excluded from this sensitivity analysis because they only met the inclusion criterion of ≥2 dispensings in 18 months if their self-paid dispensings were counted. The investigators then recalculated the counts and frequencies by DPS category. Of eligible patients, 0.8% changed DPS category. The investigators concluded that there was no need for further analysis because the protocol specified a sensitivity analysis if >1% of patients were re-classified.

Finally, the investigators conducted a sensitivity analysis that assessed AIAA prevalence by DPS category among patients who had been excluded from the study population because these patients had 75-99% of their pharmacy claims from the PharMetrics database that were also found in IMS Health LRx data; the inclusion criterion was 100% of PharMetrics dispensings. Notably, there were 126,088 people (or 76% as many as the study population); both their overall AIAA prevalence (1.3%) and DPS prevalence (20.3%) were higher than what was found in the study population, and the bivariate association was weaker among these people than in it was among the study population. **In sum, the 100% criterion was excluding a relative large number of people differentially with respect to both AIAA and DPS.** The Discussion Section explains the implications for generalizability.

3.5 STUDY CONCLUSIONS

The investigators' primary conclusions were:

1. They had developed a definition for DPS, DPS-0, and found that it displayed a monotonic, positive association with AIAA.
2. Nevertheless, DPS-0 and the other DPS definitions had poor ability to discriminate people with vs. without AIAA. Most patients classified as positive for AIAA were in the *none* category of DPS, and most patients in the *extensive* category of DPS-0 were classified as negative for AIAA.
3. A model comprising pre-specified variables that described patient characteristics and health care utilization displayed substantially better discrimination of AIAA

than DPS-0, while DPS-0 made a very minor contribution to discriminating AIAA independent of these other variables. These results were explained in part by the redundancy between many of these pre-specified variables to components of the AIAA definition. Reducing the covariates to the core covariates that had no overlap with the AIAA definition explained less of the variation in AIAA, as expected, and this enabled an increase in the incremental contribution of DPS-0 to discriminating AIAA.

Furthermore, while acknowledging that a prior validation study had found poor performance of AIAA relative to medical records, the investigators defended the validity of AIAA in the present study population, based on their selected cut-point for AIAA with validated specificity =0.90, as well as some of their findings:

- AIAA prevalence of 0.5% was consistent with the 0.7% prevalence of pain reliever use disorder among U.S. adults age 26 years and older from the National Survey on Drug Use and Health 2015;
- In bivariate analysis, AIAA prevalence was nearly 16 times higher among patients with extensive DPS compared with none;
- At the point of maximum discrimination for the Full Model, prevalence of AIAA among those predicted positive was 30 times the prevalence of those predicted negative for AIAA (3.4% vs. 0.1%).

4 DISCUSSION

4.1 FULFILLMENT OF PMR

Having carefully reviewed the Interim Status Report and Final Report, we have determined that the Sponsors satisfactorily addressed all the concerns raised by FDA in its Information Request (Appendix I) and fulfilled all four objectives of PMR 3033-8.

4.2 INTERPRETATION OF RESULTS

The definition of DPS-0 successfully identified a pattern of filling opioid prescriptions from multiple prescribers and multiple pharmacies over an 18-month period, that exceeded the expectation for a chronic-use medication. The investigators evaluated three candidate definitions of DPS and selected the definition, DPS-0, that yielded the highest ratio of percent of patients who filled opioids prescriptions versus diuretics, the negative control, in each level of shopping behavior. The ratio was 31.4 in the *extensive* category, indicating this pattern was indeed far excessive of what would be expected for a chronic use medication. The respective ratios in the *minimal* and *moderate* categories were 4.9 and 8.0; it is uncertain whether these categories represent truly problematic behavior. **Also, the DPS-0 model overall had almost no ability to discriminate between patients dispensed opioids and patients dispensed diuretics (c-statistic=0.563), although it performed better than the DPS-1 and DPS-10 models.** A primary reason for the poor discrimination was, the large majority of both types of medicines were in the *"none"* category: 85% of opioids and 97% of diuretics. This is expected and acceptable because the DPS-0 definition sought to identify extreme,

unusual behavior. It is possible that other definitions of DPS exist that would perform better at discriminating patterns of opioid vs. diuretic dispensings.

AIAA is not a valid gold standard against which to evaluate DPS-0 because a previous validation study found that AIAA did not meet targeted validity criteria. This severely limits the inferential value of the results of analyses of DPS and AIAA. Specifically, the finding that DPS-0 did not discriminate well between people with vs. without AIAA cannot be interpreted to mean that DPS-0 is a poor marker of opioid abuse/addiction because AIAA did not demonstrate validity as a clinically meaningful measure. The present study defined AIAA by using a cut-point risk score which the validation study had identified as meeting its standard for high specificity, 0.90, among one of its study sites, 500 commercially-insured U.S. patients sampled from Optum's database. The performance characteristics of this cut-point for defining AIAA suggest that we should expect a substantial number of false-positive AIAA cases, as well as false-negatives (Specificity = 0.90, Sensitivity = 0.42, Positive Predictive Value=0.62). To explain what these metrics mean, the specificity = 0.90 means that people who truly do not have abuse/addiction, based on medical record review, have a 10% chance of being classified as positive AIAA (false positive). The sensitivity = 0.42 means that people who truly have abuse/addiction have a 42% of being classified as positive for AIAA (true positive). The validation study for PMR 3033-7 demonstrated a PPV of 0.62, meaning that only 62% of the people who were classified as AIAA positive truly had abuse/addiction, based on a review of the medical record. **The expected impact from this outcome misclassification would be to weaken the association of DPS-0 and opioid abuse/addiction, but the only way to know the impact with certainty is to repeat the DPS study with an abuse/addiction indicator that has demonstrated high validity.**

The Sponsors' assertion that AIAA was more accurate in the present study population than it was in the validation study population is not convincing. The explanation for the purported, greater accuracy in the present cohort was that it was made up of people with lower average opioid usage, i.e., patients received ≥2 opioid prescriptions over 18 months, and 94% received IR opioids only, compared to the validation study made up of patients who received ≥60 days' supply of ER/LA opioids over a three-year period. The evidence for greater accuracy of AIAA was indirect: the statistical results from the DPS study showed AIAA had low prevalence (0.5%) and a positive gradient across increasing categories of DPS-0. However, these two findings follow logically from the respective definitions of AIAA and DPS-0, since both count the number of opioid dispensings, and the present study population is defined by low opioid usage. In contrast, we are not reassured by the low AIAA prevalence for two reasons. First, this 0.5% prevalence of AIAA among U.S. adults with recent prescriptions for opioid analgesics is even lower than the 0.7% estimated prevalence of pain reliever use disorder in the general U.S. adult population, while we would expect that abuse/addiction prevalence would be higher among patients receiving multiple opioid analgesic prescriptions than among the general population. Second, the definition used for AIAA had low sensitivity, and so the algorithm's failure to identify people who truly have abuse/addiction is a likely explanation for the low prevalence of AIAA. Further complicating the assessment of the utility of AIAA in this study, some of the original algorithm's variables were modified because ICD-9 codes in the PharMetrics Plus data

were less detailed than the codes from the training data from Kaiser Permanente Washington. So, as with any claims-based algorithm, making a firm conclusion about the accuracy of AIAA requires its validation against medical records or diagnostic criteria.

Although increasing DPS category displayed a positive, significant association with AIAA in both bivariate and multi-variable adjusted models, DPS demonstrated weak performance in discriminating people with vs. without AIAA. The "DPS-0 Only" model demonstrated relatively weak discrimination (c-statistic=0.689) and explained a small percent of the AIAA variability (Pseudo-R^2 = 0.070). The protocol did not specify desired minimum values for performance metrics of the model to discriminate between people with vs. without AIAA at the model's point of maximum discrimination. Generally, minimum values for these performance metrics, sensitivity, specificity, PPV, and NPV, are set *a priori.*

The additional PMR studies that will respectively use data from patient self-report and medical records may provide more valuable information on DPS as a measure of abuse, misuse, and/or addiction. There are inherent challenges to using claims data to identify opioid abuse/addiction. One challenge is there is a continuum of severity for abuse and addiction. Also, in many situations, people do not divulge their opioid abuse to their healthcare provider voluntarily. Furthermore, the healthcare system is obviously not the only source for drugs of abuse, and many adverse outcomes such as overdose and infection may never generate a medical claim.

4.2.1 Limitations

One major limitation in this study is the assumption that the abuse potential of opioids is the only source of difference between dispensing patterns for opioids and dispensing patterns for diuretics, when the patient's demographic characteristics, health status, and the indicated course of treatment could be other sources of difference between dispensing patterns for these two drug classes. The protocol did specify that the comparison for developing the DPS definition was diuretics, and it has strengths for that purpose: low abuse potential, chronic use, and high prevalence. Future studies may improve upon this study's rigor by evaluating candidate definitions for DPS against multiple negative controls, e.g., oral hypoglycemic agents, long-acting beta agonists.

Another important limitation of the study design is generalizability. Factors that are significant for generalizability are:

- **Private health plan:** Members of commercial health insurance plans constituted 97% of the study population, and so the findings may not generalize to patients covered by Medicaid or Medicare.
- **Complete capture of all prescription claims in LRx and PharMetrics Plus.** Patients who were excluded based on having 75-99% of their PharMetrics claims captured in IMS LRx records had higher DPS prevalence, higher AIAA prevalence, and weaker association between DPS and AIAA. These statistics suggest their exclusion affected generalizability, although the reasons for the imperfect capture of prescription claims were beyond the scope of the study.
- **Type of opioid product:** The study population was fairly representative of the broader US population in terms of the proportion of opioid recipients who

received IR products only (94% in this study). The conclusions of shopping behavior therefore would apply more to IR opioids. This is significant because DPS appears to be far less common in patients receiving ER/LA prescriptions, consistent with the results of a previous study of US claims data (cite Cepeda et al. 2013).

- **Data from 2012-2014 may not reflect the contemporary prescribing environment**. Since that time, widespread implementation of PDMP and utilization review programs has occurred with the goal of preventing DPS. Also, the annual number of opioid prescriptions has declined, and so if the study were to be replicated in 2017-2018, the included patient profile might differ from the present study population with respect to prevalent comorbidities and overall opioid usage.

The sensitivity analysis of the impact of death (as measured in healthcare claims) on DPS is substantially limited by the under-ascertainment of deaths in healthcare claims data. The Sponsor cross-tabulated the mortality rate by DPS-0 category and concluded, *"[n]one of these figures were of a magnitude that might affect the interpretation of the study results."* (Source: Final report submitted by the Sponsor, page 24.) Without linkage to death records data, deaths were under-ascertained in this study. Therefore, it is unclear what the impact on the results may have been if mortality differed by DPS-0 category. As an aside, the finding that mortality was lower among people who fulfilled the criteria for DPS is likely an artifact; patients would need to live long enough to fill the larger number of prescriptions that define a higher category of DPS. This is similar to immortal time bias.

4.2.2 Strengths

The analysis included data on self-paid dispensings and rejected insurance claims in the analysis, which adds confidence to our prior conclusions that DPS-0 showed poor discrimination of AIAA, despite its significant association with AIAA. Including self-paid dispensings and rejected insurance claims also is potentially useful for future analyses of DPS using dispensing data. Including self-paid dispensings and rejected insurance claims in the analysis is informative because many payers have set reimbursement limits on opioid quantity, e.g., number of pills dispensed, total daily MEQ.

In the present study, sensitivity analyses examined the impact on the results from relying solely on insurance claims data. For example, two planned sensitivity analyses quantified the extent to which the DPS prevalence by category changes due to excluding data on (1) rejected claims and (2) self-paid dispensings. These sensitivity analyses must be interpreted with caution since it was impossible to verify that the rejected claims or self-paid dispensings truly reflected shopping behavior. The per-protocol analyses tabulated these data and showed that these two mechanisms lead to data missing-not-at-random. To inform prescription drug abuse prevention research, it is more valuable to quantify the degree of misclassification by category and how this misclassification changes the prevalence of each DPS category. We can quantify this by calculating the following under each sensitivity analysis scenario:

- The percent of the population in each DPS-0 category. For example, the extensive shopping category was 1.6% of the original population and 1.45% after excluding self-pay,
- The percent out of the *original number* in each DPS category that would be misclassified due to excluding these data. For example, excluding self-payment classified 7% of the original number in the *extensive* DPS-0 category: (182 misclassified plus 6 excluded out of 2,559 people).

The rate of rejected claims per 1000 patients increased with increasing categories of DPS-0 (which was defined by completed claims); this relation has not been evaluated in the literature. Some proportion of these rejected claims may reflect shopping behavior, although the extent is uncertain. Another possible explanation is that people with more dispensings also have more opportunity for a rejected claim. Considering that DPS-0 category also reflects increasing number of opioid dispensings, it would have been helpful to see the proportion of all claims that were rejected by DPS category.

The sensitivity analysis that excluded data on self-paid dispensings suggested that conducting the study using only insurance claims data would likely produce a somewhat weaker association between DPS-0 and abuse/addiction. Exclusion of self-paid dispensings caused 0.8% of patients to be re-classified into a lower DPS-0 category, including 7% of the original *extensive* category. The expected result is to "enrich" the lower categories with people who have more opioid dispensings, and who are thus at higher risk for abuse/addiction. Also, excluding self-paid dispensings made 1.5% of the main study population ineligible for the sensitivity analysis, and they were predominantly in the *none* category of DPS-0. This is because these people did not have at least one insurance-paid dispensing in 2012 and at least one in the subsequent 18 months.

An evaluation of defining DPS-0 using prescriber instead of practice showed it would misclassify a few patients as *extensive* DPS-0. Using individual prescribers to define DPS-0 would increase the size of the *extensive* category by 9% with misclassified patients. While this is a small amount of misclassification, even a small amount of misclassifying lower categories as *extensive* could affect the results since *extensive* is the smallest category. The results of this evaluation are useful for interpreting the study results to fulfill PMR 3033-10, as they define DPS with number of individual prescribers.

The sample size was sufficiently large so that precision of the results was not an obstacle to drawing conclusions. Having interpreted these results, it is also worthwhile to mention that most of the analyses produced results that were statistically significant.

5 CONCLUSION

The Sponsors' study fulfilled PMR 3033-8. The current results demonstrate that DPS—defined here using four categories of increasing numbers of practices and pharmacies over an 18-month period without regard to overlapping prescriptions—was significantly associated with AIAA prevalence, in bivariate analysis and controlling for other characteristics through multivariable-adjusted analysis. However, DPS was ineffective at discriminating people with vs. without AIAA. Among those selected by the model as having AIAA, <2% were classified correctly (PPV<2%); this was true for modeling any of the three DPS candidate definitions with the core covariates model. The interpretation

of this ineffective discrimination and poor ability to identify patients with AIAA is unclear, since AIAA itself did not meet targets for validity compared to medical record review. When we have reviewed the results of both the complementary PMR studies on DPS (3033-9 and 3033-10), which use different strategies to identify patients with misuse, abuse, and addiction, we may gain a fuller interpretation of this study's results and the utility of DPS measures for both clinical and research use.

6 RECOMMENDATIONS

Comment to be conveyed to the Sponsor:

We have determined that you have satisfactorily addressed all the concerns we raised in our Information Request and fulfilled all four objectives of PMR 3033-8.

7 REFERENCES

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8. APPENDICES

8.1 APPENDIX A: ER/LA OPIOID ANALGESICS AND NDAS ISSUED PMR 3033-8

DRUG NAME	Application Type / Number	Sponsor
Arymo ER (Morphine Sulfate)	NDA 208603	Egalet Corp
Belbuca (Buprenorphine Buccal)	NDA 207932	Endo
Butrans (Buprenorphine Transdermal)	NDA 21306	Purdue
Duragesic (Fentanyl Transdermal)	NDA 19813	Janssen
Dolophine (Methadone HCl)	NDA 6134	Roxane
Embeda (Morphine Sulfate and Naltrexone HCl)	NDA 22321	Alpharma
Exalgo (Hydromorphone HCl)	NDA 21217	Mallinckrodt
Hysingla (Hydrocodone Bitartrate)	NDA 206627	Purdue
Kadian (Morphine Sulfate)	NDA 20616	Allergan Sales LLC
Morphabond (Morphine Sulfate)	NDA 206544	Inspirion
MS Contin (Morphine Sulfate)	NDA 19516	Purdue
Nucynta ER (Tapentadol)	NDA 200533	Janssen
Opana ER (Oxymorphone HCl) - old	NDA 21610	Endo
Opana ER (Oxymorphone HCl) - new	NDA 201655	Endo
Oxycontin (Oxycodone HCl)	NDA 22272	Purdue
Targeniq ER (Oxycodone HCl and Naloxone HCl)	NDA 205777	Purdue
Troxyca ER (Oxycodone and Naltrexone)	NDA 207621	Pfizer
Vantrela ER (Hydrocodone Bitartrate)	NDA 207975	Teva
Xtampza ER (Oxycodone)	NDA 208090	Collegium
Zohydro ER (Hydrocodone Bitartrate)	NDA 202880	Pernix

8.2 APPENDIX B: RELEVANT INFORMATION FROM THE MS CONTIN LABEL

Boxed WARNING: ADDICTION, ABUSE, AND MISUSE; LIFE-THREATENING RESPIRATORY DEPRESSION; ACCIDENTAL INGESTION; NEONATAL OPIOID WITHDRAWAL SYNDROME; and RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Addiction, Abuse, and Misuse
MS CONTIN® exposes patients and other users to the risks of opioid addiction, abuse, and misuse, which can lead to overdose and death. Assess each patient's risk prior to prescribing MS CONTIN, and monitor all patients regularly for the development of these behaviors and conditions *[see Warnings and Precautions (5.1)]*.

Life-Threatening Respiratory Depression
Serious, life-threatening, or fatal respiratory depression may occur with use of MS CONTIN. Monitor for respiratory depression, especially during initiation of MS CONTIN or following a dose increase. Instruct patients to swallow MS CONTIN tablets whole; crushing, chewing, or dissolving MS CONTIN tablets can cause rapid release and absorption of a potentially fatal dose of morphine *[see Warnings and Precautions (5.2)]*.

Accidental Ingestion
Accidental ingestion of even one dose of MS CONTIN, especially by children, can result in a fatal overdose of morphine *[see Warnings and Precautions (5.2)]*.

Neonatal Opioid Withdrawal Syndrome
Prolonged use of MS CONTIN during pregnancy can result in neonatal opioid withdrawal syndrome, which may be life-threatening if not recognized and treated, and requires management according to protocols developed by neonatology experts. If opioid use is required for a prolonged period in a pregnant woman, advise the patient of the risk of neonatal opioid withdrawal syndrome and ensure that appropriate treatment will be available *[see Warnings and Precautions (5.3)]*.

Risks From Concomitant Use With Benzodiazepines Or Other CNS Depressants
Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death *[see Warnings and Precautions (5.4), Drug Interactions (7)]*.

- Reserve concomitant prescribing of MS CONTIN and benzodiazepines or other CNS depressants for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

INDICATIONS AND USAGE

MS CONTIN is indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Limitations of Use

- Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with

extended-release opioid formulations *[see Warnings and Precautions (5.1)]*, reserve MS CONTIN for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.

- MS CONTIN is not indicated as an as-needed (prn) analgesic.

DRUG ABUSE AND DEPENDENCE

Controlled Substance

MS CONTIN contains morphine, a Schedule II controlled substance.

Abuse

MS CONTIN contains morphine, a substance with a high potential for abuse similar to other opioids including fentanyl, hydrocodone, hydromorphone, methadone, oxycodone, oxymorphone, and tapentadol. MS CONTIN can be abused and is subject to misuse, addiction, and criminal diversion *[see Warnings and Precautions (5.1)]*.

The high drug content in extended-release formulations adds to the risk of adverse outcomes from abuse and misuse.

All patients treated with opioids require careful monitoring for signs of abuse and addiction, because use of opioid analgesic products carries the risk of addiction even under appropriate medical use.

Prescription drug abuse is the intentional non-therapeutic use of an over-the-counter or prescription drug, even once, for its rewarding psychological or physiological effects. Drug addiction is a cluster of behavioral, cognitive, and physiological phenomena that develop after repeated substance use and includes: a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal.

"Drug-seeking" behavior is very common in persons with substance use disorders. Drug-seeking tactics include emergency calls or visits near the end of office hours, refusal to undergo appropriate examination, testing, or referral, repeated “loss” of prescriptions, tampering with prescriptions and reluctance to provide prior medical records or contact information for other healthcare provider(s). “Doctor shopping” (visiting multiple prescribers to obtain additional prescriptions) is common among drug abusers and people suffering from untreated addiction. Preoccupation with achieving adequate pain relief can be appropriate behavior in a patient with poor pain control.

Abuse and addiction are separate and distinct from physical dependence and tolerance. Healthcare providers should be aware that addiction may not be accompanied by concurrent tolerance and symptoms of physical dependence in all addicts. In addition, abuse of opioids can occur in the absence of true addiction.

MS CONTIN, like other opioids, can be diverted for non-medical use into illicit channels of distribution. Careful record-keeping of prescribing information, including quantity, frequency, and renewal requests, as required by state and federal law, is strongly advised.

Proper assessment of the patient, proper prescribing practices, periodic re-evaluation of therapy, and proper dispensing and storage are appropriate measures that help to limit abuse of opioid drugs.

Risks Specific to Abuse of MS CONTIN

MS CONTIN is for oral use only. Abuse of MS CONTIN poses a risk of overdose and death. This risk is increased with concurrent abuse of MS CONTIN with alcohol and other central nervous system depressants. Taking cut, broken, chewed, crushed, or dissolved MS CONTIN enhances drug release and increases the risk of overdose and death.

Due to the presence of talc as one of the excipients in MS CONTIN, parenteral abuse can be expected to result in local tissue necrosis, infection, pulmonary granulomas, embolism and death, and increased risk of endocarditis and valvular heart injury. Parenteral drug abuse is commonly associated with transmission of infectious diseases such as hepatitis and HIV.

8.3 APPENDIX C: CANDIDATE DEFINITIONS OF DOCTOR/PHARMACY SHOPPING BEHAVIOR

	Opioids		Diuretics					
	N	Percent	N	Percent	Ratio of percent	Opioid vs. Diuretic OR 95% CI		
DPS-1								
None	157,194	95.31%	97,265	97.97%	1.0			
Minimal	6,576	3.99%	1,613	1.62%	2.5	2.5	2.4	2.7
Moderate	912	0.55%	337	0.34%	1.6	1.7	1.5	1.9
Extensive	241	0.15%	66	0.07%	2.2	2.3	1.7	3.0
Total	164,923		99,281					
c-statistic: 0.513								
DPS-10								
None	163,348	99.05%	97,803	98.51%	1.0	reference		
Minimal	1,390	0.84%	1,259	1.27%	0.7	0.66	0.61	0.71
Moderate	110	0.07%	105	0.11%	0.6	0.63	0.48	0.82
Extensive	75	0.05%	114	0.11%	0.4	0.39	0.29	0.53
Total	164,923		99,281					
c-statistic: 0.503								
DPS-0								
None	139,977	84.87%	96,776	97.48%	0.9	reference		
Minimal	16,431	9.96%	2,006	2.02%	4.9	5.7	5.4	5.9
Moderate	5,956	3.61%	450	0.45%	8.0	9.2	8.3	10.1
Extensive	2,559	1.55%	49	0.05%	31.4	36.1	27.2	47.8
Total	164,923		99,281					
c-statistic: 0.563								

Source: PMR 3033-8 Interim Status Report, Tables 10-12

8.4 APPENDIX D: MODEL FOR ALGORITHMICALLY-INDICATED ABUSE AND/OR ADDICTION

Source: PMR 3033-8 Final Report, Appendix A.

(b) (4)

14 PAGES WITHHELD IN FULL AS B(4)/CONFIDENTIAL COMMERCIAL INFORMATION

8.5 APPENDIX E: FULL COVARIATE LIST

Note: Covariates are **bold font** if the Sponsors identified them as core covariates, i.e., not part of the definition of algorithmically-identified abuse/addiction

Characteristic	Categories
Age	*18-24, 25-34, 35-44, 45-54, 55-64, 65-74, 75-84
Sex	*Female, Male
State of residence	US states; *PA
Drug groups used (1) during the 18-month observation period and (2) in the 12 months preceding the observation period. Number of dispensings for:	
Antidepressants	*0, 1, 2-4, 5-9, 10-19, 20+
Antipsychotics	*0, 1, 2-4, 5-9, 10-19, 20+
Hypnotics	***0, 1, 2-4, 5-9, 10-19, 20+**
Anxiolytics	*0, 1, 2-4, 5-9, 10-19, 20+
Psycho-stimulants	***0, 1, 2-4, 5-9, 10+**
Type of opioid used during the observation period	IR only, *ER/LA only, both IR and ER/LA
Pain diagnoses associated with insurance claims during the observation period	
Arthritis	*No, Yes
Back pain	*No, Yes
Fractures	*No, Yes
Headaches	*No, Yes
Malignancy	*No, Yes
Musculoskeletal pain	*No, Yes
Neuropathies	*No, Yes
Wounds/injuries	*No, Yes
Diagnoses (by ICD9 Chapter) associated with insurance claims during the observation period	
Infectious and parasitic diseases (001-139)	*No, Yes
Benign neoplasms (210-229)	***No, Yes**
Endocrine nutritional, metabolic, immune disorders (240-279)	*No, Yes
Disease of blood and blood-forming organs (280-289)	***No, Yes**
Mental disorders (290-319)	*No, Yes
Nervous system and sense organs (320-389)	*No, Yes
Circulatory system (390-459)	***No, Yes**
Respiratory system (460-519)	***No, Yes**
Digestive system (520-579)	*No, Yes
Genitourinary system (580-629)	*No, Yes
Complications of pregnancy, childbirth, puerperium (630-679)	*No, Yes
Skin and subcutaneous tissue (680-709)	*No, Yes
Congenital anomalies (740-759)	*No, Yes
Symptoms, signs and ill-defined conditions (780-799)	*No, Yes
Injury and poisoning (800-999)	*No, Yes
Non-DPS characteristics of opioid dispensings during the observation period	
Number from prescriptions written by non-specialists.	*0-1, 2, 3, 4-6, 7-14, 15+
Number dispensed for self-payment without insurance	***0, 1, 2, 3, 4+**
Total MEQ dispensed in 18 months	*<250, 250-499, 500-999, 1000-2499, 2500-4999, 5000-9999, 10,000+

Source: PMR 3033-8 Final Report, Sections 4 - 5

8.6 APPENDIX F: INDIVIDUAL CHARACTERISTICS AND HEALTH CARE UTILIZATION IN ASSOCIATION WITH DPS CATEGORY

Source: PMR 3033-8 Interim Status Report, Appendix B.

Appendix B. Individual characteristics tabulated by Shopping Behavior Category

	Shopping Category					Stepwise regression	
	None	Minimal	Moderate	Extensive	Total	p-value (Pr>ChiSq) and OR for 2-level	
Total	139,977	16,431	5,956	2,559	164,923	Cum Logistic [a]	2-level Logistic
%	84.87	9.96	3.61	1.55	100.00		
State of residence (categorical, 50 levels, see Table 18)						$<10^{-10}$	$<10^{-10}$
Age						$<10^{-10}$	$<10^{-10}$
18-24	11,292	1,399	609	193	13,493		1.00
	83.69	10.37	4.51	1.43	100.00		(ref)
25-34	19,397	2,838	1,139	476	23,850		0.77
	81.33	11.90	4.78	2.00	100.00		(0.70-0.85)
35-44	30,232	3,911	1,432	651	36,226		0.50
	83.45	10.80	3.95	1.80	100.00		(0.46-0.55)
45-54	40,138	4,599	1,602	699	47,038		0.35
	85.33	9.78	3.41	1.49	100.00		(0.32-0.39)
55-64	33,029	3,175	1,024	489	37,717		0.27
	87.57	8.42	2.71	1.30	100.00		(0.24-0.30)
65-74	4,882	431	137	48	5,498		0.20
	88.80	7.84	2.49	0.87	100.00		(0.17-0.24)
75-84	1,007	78	13	3	1,101		0.07
	91.46	7.08	1.18	0.27	100.00		(0.04-0.12)
Sex						$1x\ 10^{-10}$	.0001
Female	71,652	8,511	3,077	1,368	84,608		1.00
	84.69	10.06	3.64	1.62	100.00		(ref)
Male	68,325	7,920	2,879	1,191	80,315		1.11
	85.07	9.86	3.58	1.48	100.00		(1.05-1.16)
Type of Opioid Dispensed						$<10^{-10}$	$<10^{-10}$
ER/LA only	1,132	151	40	10	1,333		1.00
	84.92	11.33	3.00	0.75	100.00		(ref)
IR and ER/LA	5,560	1,948	942	879	9,329		5.19
	59.60	20.88	10.10	9.42	100.00		(3.87-6.95)
IR only	133,285	14,332	4,974	1,670	154,261		2.67
	86.40	9.29	3.22	1.08	100.00		(1.99-3.57)

Appendix F continued on next page…

Appendix F, continued…

	Shopping Category					Stepwise regression	
	None	Minimal	Moderate	Extensive	Total	p-value (Pr>ChiSq) and OR for 2-level	
Total	139,977	16,431	5,956	2,559	164,923	Cum	2-level
%	84.87	9.96	3.61	1.55	100.00	Logistic [a]	Logistic
Antidepressant fills during the observation period [b]						3×10^{-8}	5×10^{-6}
0 : 0 [c]	94,216	9,155	2,983	804	107,158		
	87.92	8.54	2.78	0.75	100.00		
1 : 1, 2	9,691	1,453	607	294	12.045		
	80.46	12.06	5.04	2.44	100.00		
2 : 3 - 7	9,681	1,598	619	311	12,209	OR per unit increase	
	79.29	13.09	5.07	2.55	100.00	1.05 (1.03-1.07)	
3 : 8 - 14	9,282	1,426	544	290	11,542		
	80.42	12.35	4.71	2.51	100.00		
4 : 15 - 24	9,038	1,393	517	306	11,254		
	80.31	12.38	4.59	2.72	100.00		
5 : 25+	8,069	1,406	686	554	10,715		
	75.31	13.12	6.40	5.17	100.00		
Antidepressant fills in the 365 days before the observation period [b]						.05	5×10^{-5}
0 : 0 [c]	104,285	11,038	3,694	1,202	120,219		
	86.75	9.18	3.07	1.00	100.00		
1 : 1, 2	8,573	1,313	548	284	10,718		
	79.99	12.25	5.11	2.65	100.00		
2 : 3 - 5	6,826	1,105	418	222	8,571	OR per unit increase	
	79.64	12.89	4.88	2.59	100.00	1.04 (1.02-1.06)	
3 : 6 - 9	6,405	932	399	227	7,963		
	80.43	11.70	5.01	2.85	100.00		
4 : 10 - 14	7,318	1,034	405	231	8,988		
	81.42	11.50	4.51	2.57	100.00		
5 : 15+	6,570	1,009	492	393	8,464		
	77.62	11.92	5.81	4.64	100.00		

Appendix F continued on next page…

Appendix F continued…

	Shopping Category					Stepwise regression	
	None	Minimal	Moderate	Extensive	Total	p-value (Pr>ChiSq) and OR for 2-level	
Total	139,977	16,431	5,956	2,559	164,923	Cum	2-level
%	84.87	9.96	3.61	1.55	100.00	Logistic [a]	Logistic
Antipsychotic fills during the observation period [b]						1×10^{-6}	$<10^{-10}$
0 : 0 [c]	136,189	15,557	5,494	2,156	159,396		
	85.44	9.76	3.45	1.35	100.00		
1 : 1	806	208	109	94	1,217		
	66.23	17.09	8.96	7.72	100.00		
2 : 2, 3	717	180	96	74	1,067	OR per unit increase	
	67.20	16.87	9.00	6.94	100.00	1.10 (1.07-1.13)	
3 : 4 - 8	805	191	90	78	1,164		
	69.16	16.41	7.73	6.70	100.00		
4 : 9 - 19	781	150	68	97	1,096		
	71.26	13.69	6.20	8.85	100.00		
5 : 20+	679	145	99	60	983		
	69.07	14.75	10.07	6.10	100.00		
Antipsychotic fills in 365 days before the observation period [b]						0.008	NR [c]
0 : 0 [c]	137,374	15,901	5,656	2,301	161,232		
	85.20	9.86	3.51	1.43	100.00		
1 : 1	630	98	63	62	853		
	73.86	11.49	7.39	7.27	100.00		
2 : 2, 3	481	117	72	54	724		
	66.44	16.16	9.94	7.46	100.00		
3 : 3 - 7	543	123	60	58	784		
	69.26	15.69	7.65	7.40	100.00		
4 : 8 - 12	436	96	53	42	627		
	69.54	15.31	8.45	6.70	100.00		
5 : 13+	513	96	52	42	703		
	72.97	13.66	7.40	5.97	100.00		
Anxiolytic fills during the observation period [b]						$<10^{-10}$	$<10^{-10}$
0 : 0 [c]	98,605	9,526	3,146	861	112,138		
	87.93	8.49	2.81	0.77	100.00		
1 : 1	14,792	2,090	715	311	17,908		
	82.60	11.67	3.99	1.74	100.00		
2 : 2, 3	9,273	1,548	610	296	11,727	OR per unit increase	
	79.07	13.20	5.20	2.52	100.00	1.10 (1.09-1.12)	
3 : 4 - 8	6,748	1,257	553	361	8,919		
	75.66	14.09	6.20	4.05	100.00		
4 : 9 - 19	5,656	1,073	495	338	7,562		
	74.80	14.19	6.55	4.47	100.00		
5 : 20+	4,903	937	437	392	6,669		
	73.52	14.05	6.55	5.88	100.00		

Appendix F continued on next page…

Appendix F, continued…

	Shopping Category					Stepwise regression	
	None	Minimal	Moderate	Extensive	Total	p-value (Pr>ChiSq) and OR for 2-level	
Total	139,977	16,431	5,956	2,559	164,923	Cum	2-level
%	84.87	9.96	3.61	1.55	100.00	Logistic [a]	Logistic
Anxiolytic fills in the 365 days before the observation period [b]						0.06	NR [c]
0 : 0 [c]	112,209	12,032	4,086	1,349	129,676		
	86.53	9.28	3.15	1.04	100.00		
1 : 1	10,525	1,460	552	326	12,863		
	81.82	11.35	4.29	2.53	100.00		
2 : 2	3,988	651	257	128	5,024		
	79.38	12.96	5.12	2.55	100.00		
3 : 3 - 5	4,986	840	337	208	6,371		
	78.26	13.18	5.29	3.26	100.00		
4 : 6 - 11	4,521	749	409	266	5,945		
	76.05	12.60	6.88	4.47	100.00		
5 : 12+	3,748	699	315	282	5,044		
	74.31	13.86	6.25	5.59	100.00		
Hypnotic fills during the observation period [b]						$<10^{-10}$	$<10^{-10}$
0 : 0 [c]	122,070	13,389	4,628	1,708	141,795		
	86.09	9.44	3.26	1.20	100.00		
1 : 1	5,091	855	324	178	6,448		
	78.95	13.26	5.02	2.76	100.00		
2 : 2 - 4	3,946	658	298	195	5,097	OR per unit increase	
	77.42	12.91	5.85	3.83	100.00	1.06 (1.05-1.08)	
3 : 5 – 10	2,940	495	239	158	3,832		
	76.72	12.92	6.24	4.12	100.00		
4 : 11 - 21	2,928	524	220	142	3,814		
	76.77	13.74	5.77	3.72	100.00		
5 : 22+	3,002	510	247	178	3,937		
	76.25	12.95	6.27	4.52	100.00		
Hypnotic fills in the 365 days before the observation period [b]						NR	NR
0 : 0 [c]	126,478	14,310	4,992	1,932	147,712		
	85.62	9.69	3.38	1.31	100.00		
1 : 1	3,726	542	239	134	4,641		
	80.28	11.68	5.15	2.89	100.00		
2 : 2, 3	2,544	395	173	122	3,234		
	78.66	12.21	5.35	3.77	100.00		
3 : 4 - 7	2,529	387	174	121	3,211		
	78.76	12.05	5.42	3.77	100.00		
4 : 8 - 12	2,288	407	198	123	3,016		
	75.86	13.49	6.56	4.08	100.00		

Appendix F Continued on next page…

Appendix F, continued…

	Shopping Category					Stepwise regression	
	None	Minimal	Moderate	Extensive	Total	p-value (Pr>ChiSq) and OR for 2-level	
Total	139,977	16,431	5,956	2,559	164,923	Cum	2-level
%	84.87	9.96	3.61	1.55	100.00	Logistic [a]	Logistic
5 : 13+	2,412	390	180	127	3,109		
	77.58	12.54	5.79	4.08	100.00		
Psychostimulant fills during the observation period [b]						.0002	NR
0 : 0 [c]	128,440	14,496	5,060	2,057	150,053		
	85.60	9.66	3.37	1.37	100.00		
1 : 1	2,018	286	132	70	2,506		
	80.53	11.41	5.27	2.79	100.00		
2 : 2,3	2,321	352	155	74	2,902		
	79.98	12.13	5.34	2.55	100.00		
3 : 4 - 7	2,348	382	179	91	3,000		
	78.27	12.73	5.97	3.03	100.00		
4 : 8 - 16	2,579	422	195	112	3,308		
	77.96	12.76	5.89	3.39	100.00		
5 : 17+	2,271	493	235	155	3,154		
	72.00	15.63	7.45	4.91	100.00		
Psychostimulant fills in the 365 days before the observation period [b]						6×10^{-5}	$<10^{-10}$
0 : 0 [c]	131,690	15,068	5,318	2,195	154,271		
	85.36	9.77	3.45	1.42	100.00		
1 : 1	1,723	276	123	60	2,182		
	78.96	12.65	5.64	2.75	100.00		
2 : 2, 3	1,939	291	124	61	2,415	OR per unit increase	
	80.29	12.05	5.13	2.53	100.00	1.10 (1.07-1.12)	
3 : 4 - 6	1,750	253	124	66	2,193		
	79.80	11.54	5.65	3.01	100.00		
4 : 7 - 11	1,526	275	130	83	2,014		
	75.77	13.65	6.45	4.12	100.00		
5 : 12+	1,349	268	137	94	1,848		
	73.00	14.50	7.41	5.09	100.00		

Appendix F continued on next page…

Appendix F, continued…

	Shopping Category					Stepwise regression	
	None	Minimal	Moderate	Extensive	Total	p-value (Pr>ChiSq) and OR for 2-level	
Total	139,977	16,431	5,956	2,559	164,923	Cum	2-level
%	84.87	9.96	3.61	1.55	100.00	Logistic [a]	Logistic
Diagnoses during the observation period [b]							
Arthritis	57,157 82.52	7,899 11.40	2,837 4.10	1,375 1.99	69,268 100.00	.06	NR
Back pain	60,798 81.33	9,032 12.08	3,323 4.45	1,604 2.15	74,757 100.00	NR	NR
Fracture	16,853 80.02	2,736 12.99	1,001 4.75	471 2.24	21,061 100.00	$<10^{-10}$	2×10^{-8} 1.20 (1.13-1.28)
Headache	8,954 79.69	1,453 12.93	523 4.65	306 2.72	11,236 100.00	NR	NR
Malignancy	17,068 84.54	2,115 10.48	661 3.27	346 1.71	20,190 100.00	NR	NR
Musculo-skeletal	70,622 82.20	9,915 11.54	3,661 4.26	1,721 2.00	85,919 100.00	$<10^{-10}$	$<10^{-10}$ 1.19 (1.13-1.25)
Neuropathic pain	11,976 81.25	1,797 12.19	626 4.25	341 2.31	14,740 100.00	.02	.009 0.90 (0.84-0.97)
Wounds & Injuries	11,398 77.05	2,108 14.25	830 5.61	457 3.09	14,793 100.00	$<10^{-10}$	$<10^{-10}$ 1.38 (1.28-1.48)
Infection	25,968 82.49	3,578 11.37	1,335 4.24	598 1.90	31,479 100.00	.0007	NR
Benign neoplasm	22,708 85.08	2,662 9.97	931 3.49	390 1.46	26,691 100.00	NR	NR
Endocrine	64,006 84.46	7,823 10.32	2,697 3.56	1,255 1.66	75,781 100.00	2×10^{-10}	1×10^{-6} 0.88 (0.84-0.93)
Blood disorders	11,636 80.70	1,822 12.64	606 4.20	355 2.46	14,419 100.00	.008	NR
Mental disorders	49,306 80.27	7,758 12.63	2,849 4.64	1,514 2.46	61,427 100.00	.008	NR
Nervous disorders	59,132 82.83	7,909 11.08	2,896 4.06	1,454 2.04	71,391 100.00	.0001	NR
Circulatory disorders	55,745 84.40	6,831 10.34	2,336 3.54	1,133 1.72	66,045 100.00	.0003	.005 0.93 (0.88-0.98)
Respiratory disorders	71,900 83.81	9,129 10.64	3,275 3.82	1,482 1.73	85,786 100.00	.03	NR

Appendix F continued on next page…

Appendix F continued…

	Shopping Category					Stepwise regression	
	None	Minimal	Moderate	Extensive	Total	p-value (Pr>ChiSq) and OR for 2-level	
Total	139,977	16,431	5,956	2,559	164,923	Cum Logistic [a]	2-level Logistic
%	84.87	9.96	3.61	1.55	100.00		
Digestive disorders	48,608 82.46	6,801 11.54	2,409 4.09	1,128 1.91	58,946 100.00	$<10^{-10}$	9×10^{-9} 1.16 (1.10-1.22)
Genitourinary disorders	50,502 83.11	6,813 11.21	2,407 3.96	1,040 1.71	60,762 100.00	$<10^{-10}$	9×10^{-8} 1.15 (1.09-1.21)
Pregnancy & complications	3,406 81.52	518 12.40	179 4.28	75 1.80	4,178 100.00	9×10^{-5}	NR
Skin disorders	45,712 83.79	5,814 10.66	2,097 3.84	932 1.71	54,555 100.00	2×10^{-5}	.002 1.08 (1.03-1.14)
Congenital disorders	4,000 83.66	535 11.19	160 3.35	86 1.80	4,781 100.00	.02	.004 0.81 (0.71-0.94)
Signs and symptoms	96,297 83.28	12,759 11.03	4,527 3.91	2,051 1.77	115,634 100.00	$<10^{-10}$	.002 1.10 (1.03-1.16)
Injury and poisoning	26,711 79.52	4,397 13.09	1,674 4.98	807 2.40	33,589 100.00	$<10^{-10}$	$<10^{-10}$ 1.29 (1.22-1.36)
Number of non-specialist fills [b]						$<10^{-10}$	$<10^{-10}$
1 : 1 [c]	73,287 91.58	4,951 6.19	1,596 1.99	195 0.24	80,029 100.00		1.00 (ref)
2 : 2	28,357 87.08	3,009 9.24	996 3.06	202 0.62	32.564 100.00		1.73 (1.60-1.87)
3 : 3	10,488 77.71	2,049 15.18	783 5.80	177 1.31	13,497 100.00		2.28 (2.09-2.48)
4 : 4-6	10,486 71.61	2,620 17.89	961 6.56	576 3.93	14,643 100.00		2.48 (2.29-2.68)
5 : 7-14	8,374 70.98	1,930 16.36	781 6.62	712 6.04	11,797 100.00		2.12 (1.95-2.30)
6 : 15+	8,985 72.50	1,872 15.11	839 6.77	697 5.62	12,393 100.00		1.41 (1.28-1.54)
Number of self-paid fills [b]						$<10^{-10}$	$<10^{-10}$
0 : 0 [c]	131,454 86.41	14,173 9.32	4,796 3.15	1,704 1.12	152,127 100.00		1.00 (ref)
1 : 1	6,413 69.78	1,578 17.17	756 8.23	443 4.82	9,190 100.00		2.14 (1.99-2.30)
2 : 2	1,214 61.04	388 19.51	202 10.16	185 9.30	1,989 100.00		2.75 (2.43-3.12)

Appendix F continued on next page…

Appendix F continued…

	Shopping Category					Stepwise regression	
	None	Minimal	Moderate	Extensive	Total	p-value (Pr>ChiSq) and OR for 2-level	
Total	139,977	16,431	5,956	2,559	164,923	Cum	2-level
%	84.87	9.96	3.61	1.55	100.00	Logistic [a]	Logistic
3 : 3	361	131	81	90	663		3.43
	54.45	19.76	12.22	13.57	100.00		(2.83-4.16)
4 : 4+	535	161	121	137	954		3.23
	56.08	16.88	12.68	14.36	100.00		(2.75-3.79)
Total MEq dispensed [b]						$<10^{-10}$	$<10^{-10}$
1 : <250 [c]	28,318	366	96	0	28,780		1.00
	98.39	1.27	0.33	0.00	100.00		(ref)
2 : 250-499	42,958	3,105	869	28	46,960		5.28
	91.48	6.61	1.85	0.06	100.00		(4.27-6.52)
3 : 500-999	26,230	3,973	1,307	202	31,712		11.36
	82.71	12.53	4.12	0.64	100.00		(9.22-14.01)
4 : 1000-2499	17,393	3,275	1,171	510	22,349		15.63
	77.82	14.65	5.24	2.28	100.00		(12.65-19.32)
5 : 2500-4999	7,758	1,656	598	369	10,381		18.26
	74.73	15.95	5.76	3.55	100.00		(14.67-22.73)
6 : 5000-9999	6,219	1,262	520	347	8,348		21.46
	74.50	15.12	6.23	4.16	100.00		(17.18-26.80)
7 : 10,000+	11,101	2,794	1,395	1,103	16,393		29.59
	67.72	17.04	8.51	6.73	100.00		(23.75-36.86)
					c-statistic	0.775	0.822

[a] Cumulative logistic regression over four levels of shopping behavior. Note that the score test for the proportional odds assumption of shopping level over covariates rejected this model ($\chi^2 = 1955$ on 204 d.f. $p<10^{-11}$).

[b] See Appendix C for definitions.

[c] Entered into the regression equation as a single ordinal variable.

[c] NR – Not retained in stepwise regression. For the cumulative logistic the p-value for retention was 0.1. In the two-level logistic, the p-value for retention was 0.01.

8.7 APPENDIX G: AIAA ODDS RATIOS ESTIMATED BY THE ALL COVARIATES MODEL AND BY DPS-0 PLUS ALL COVARIATES MODEL

Characteristic		Covariates Only	Shopping and Covariates		
				95% Confidence Bounds	
		OR	OR	Lower	Upper
Shopping Behavior	None	-	Ref	-	-
	Minimal	-	1.56	1.28	1.89
	Moderate	-	1.56	1.20	2.02
	Extensive	-	1.95	1.51	2.52
Age Group	18-24	Ref	Ref	-	-
	25-34	0.46	0.46	0.35	0.60
	35-44	0.26	0.27	0.20	0.35
	45-54	0.26	0.27	0.21	0.36
	55-64	0.16	0.18	0.13	0.24
	65-74	0.04	0.04	0.02	0.10
	75-84	0.00	0.00	[a]	[a]
Gender	Female	Ref	Ref	-	-
	Male	2.21	2.21	1.89	2.59
State of Residence (51 levels)					
Number of dispensings of					
Antidepressants	None	Ref	Ref	-	-
	1	1.88	1.85	1.34	2.54
	2-4	2.34	2.29	1.78	2.96
	5-9	2.31	2.27	1.77	2.91
	10-19	1.81	1.80	1.43	2.27
	20+	2.14	2.07	1.57	2.73
Antipsychotics	None	Ref	Ref	-	-
	1	2.21	2.11	1.42	3.13
	2-4	3.82	3.76	2.79	5.06
	5-9	2.82	2.73	1.85	4.01
	10-19	3.44	3.41	2.45	4.73
	20+	1.29	1.30	0.56	3.00
Anxiolytics	None	Ref	Ref	-	-
	1	1.62	1.57	1.20	2.05
	2-4	1.91	1.84	1.44	2.33
	5-9	2.51	2.40	1.86	3.10
	10-19	3.34	3.36	2.68	4.21
	20+	3.98	3.93	2.92	5.30

Source: PMR 3033-8 Final Report, Appendix C.

Appendix G continued on next page…

Appendix G, continued…

Characteristic		Covariates Only OR	Shopping and Covariates OR	95% Confidence Bounds Lower	Upper
Opioid Type	ER/LA only	Ref	Ref	-	-
	IR only	0.59	0.52	0.32	0.84
	IR and ER/LA	1.24	1.04	0.66	1.64
Pain diagnoses (present versus absent)					
Back pain		1.40	1.40	1.18	1.67
Malignancy		0.63	0.62	0.48	0.81
Wounds/injuries		1.89	1.81	1.51	2.17
Nonpain diagnoses by ICD-9 chapter (present versus absent)					
Infectious/parasitic		1.31	1.31	1.10	1.55
Blood / blood-forming organs		1.36	1.36	1.10	1.67
Mental		15.35	15.64	10.68	22.92
Nervous / sensory		1.40	1.39	1.18	1.64
Circulatory		1.43	1.43	1.21	1.70
Respiratory		0.79	0.79	0.68	0.93
Digestive		1.26	1.25	1.07	1.47
Congenital anomalies		0.60	0.60	0.37	0.97
Symptoms, signs, ill-defined conditions		1.27	1.25	0.99	1.58
Injury and poisoning		1.91	1.86	1.58	2.18
Number of self-paid dispensings of opioids	0	Ref	Ref	-	-
	1	2.01	1.87	1.49	2.35
	2	3.18	2.86	2.05	3.99
	3	2.52	2.19	1.27	3.78
	4+	4.24	3.94	2.74	5.67
Total MEq dispensed	<250	Ref	Ref	-	-
	250-499	1.39	1.23	0.96	1.58
	500-999	1.92	1.65	1.27	2.14
	1000-2499	3.39	2.82	2.13	3.73
	2500-4999	4.71	3.96	2.82	5.56
	5000-9999	5.70	4.84	3.25	7.21
	10000+	12.16	10.39	5.82	18.57

[a] Asymptotic limits not available (zero events at this level)

Source: PMR 3033-8 Final Report, Appendix C.

8.8 APPENDIX H: CONTRIBUTION OF DPS TO DISCRIMINATION OF AIAA, AFTER ADJUSTING FOR CORE COVARIATES

Table H1. Summary statistics for models to predict Algorithmically-identified Abuse/Addiction (AIAA) with All Covariates and/or Doctor/Pharmacy Shopping (DPS-0) with no requirement of overlapping days' supply.

		All Covariates Model	DPS-0 Plus All Covariates	DPS-0
C-Statistic		0.943	0.943	0.689
Pseudo-R^2		0.358	0.359	0.070
Hosmer-Lemeshow	**Chi-square**	11.05	14.27	0.00
	df	8	8	1
	p	0.20	0.07	1.0
Deviance (-2 log L)		6451.6	6439.7	9344.9
	Drop in deviance vs. preceding model		11.921	-2905.2
	Change in df		3	97
	p		0.008	<0.001

Source: PMR 3033-8 Final Report, Table 4.

Table H2. Summary statistics for models to predict Algorithmically-identified Abuse/Addiction (AIAA) with Core Covariates and/or Doctor/Pharmacy Shopping (DPS-0) with no requirement of overlapping days' supply.

		Core Covariates Model	DPS-0 Plus Core Covariates	DPS-0
C-Statistic		0.741	0.797	0.689
Pseudo-R^2		0.080	0.118	0.070
Hosmer-Lemeshow	**Chi-square**	10.804	15.851	.
	df	8	8	.
	p	0.213	0.045	.
Versus Intercept-only model	**Log likelihood ratio (LLR)**	799.887	1187.611	702.389
	df	27	30	3
	p	<0.001	<0.001	<0.001
Versus preceding model	**Change in LLR**		387.724	-485.222
	Change in df		3	-27
	p		<0.001	<0.001
p-values are the upper tails obtained on referring each LLR to a chi-square distribution on the degrees of freedom indicated.				

Source: PMR 3033-8 Final Report, Appendix D, Table 5.

Table H3. Summary statistics for models to predict Algorithmically-identified Abuse/Addiction (AIAA) with Core Covariates and/or Doctor/Pharmacy Shopping (DPS-1) with requirement of ≥1 days' supply overlap.

		Core Covariates Model	DPS-1 Plus Core Covariates	DPS-1
C-Statistic		0.741	0.771	0.616
Pseudo-R^2		0.080	0.107	0.056
Hosmer-Lemeshow	**Chi-square**	10.804	16.412	.
	df	8	8	.
	p	0.213	0.037	.
Versus Intercept-only model	**Log likelihood ratio (LLR)**	799.887	1073.877	563.059
	df	27	30	3
	p	<0.001	<0.001	<0.001
Versus preceding model	**Change in LLR**		273.99	-510.818
	Change in df		3	-27
	p		<0.001	<0.001
p-values are the upper tails obtained on referring each LLR to a chi-square distribution on the degrees of freedom indicated.				

Source: PMR 3033-8 Final Report, Appendix D, Table 6.

Table H3. Summary statistics for models to predict Algorithmically-identified Abuse/Addiction (AIAA) with Core Covariates and/or Doctor/Pharmacy Shopping (DPS-10) with requirement of ≥10 days' supply overlap.

		Core Covariates Model	DPS-10 Plus Core Covariates	DPS-10
C-Statistic		0.741	0.753	0.546
Pseudo-R^2		0.080	0.090	0.025
Hosmer-Lemeshow	**Chi-square**	10.804	15.294	.
	df	8	8	.
	p	0.213	0.054	.
Versus Intercept-only model	**Log likelihood ratio (LLR)**	799.887	903.631	250.871
	df	27	30	3
	p	<0.001	<0.001	<0.001
Versus preceding model	**Change in LLR**		103.744	-652.76
	Change in df		3	-27
	p		<0.001	<0.001
p-values are the upper tails obtained on referring each LLR to a chi-square distribution on the degrees of freedom indicated.				

Source: PMR 3033-8 Final Report, Appendix D, Table 7.

8.9 APPENDIX I: FDA INFORMATION REQUEST

Information Request from Division of Epidemiology II and Division of Biometrics VII:

Having carefully reviewed the Interim Status Report and Final Report, we have found that, in its current form, this study has not met three of the four study objectives (Primary Objective #2 and Secondary Objectives #1 and #2). In addition, we are requesting some clarification related to Primary Objective #1. Below we outline additional analyses that the OPC should conduct in order to meet the objectives of the study and allow FDA reviewers to determine whether this PMR has been fulfilled. We can arrange a teleconference to clarify our requests if needed. The OPC should submit answers to our clarifying questions and the final results of the requested analyses no later than December 15, 2017 and submit an amended final study report addressing the FDA's requests, in both clean and tracked changes formats, no later than January 31, 2018.

Primary Objective #1
Formulate candidate definitions of doctor/pharmacy shopping by grouping patients in terms of
characteristics of opioid dispensings.

Definitions of levels of doctor/pharmacy shopping (DPS) in Table 1 of the Final Report are not consistent with those used in the PMR Study 3033-10 and those presented in a poster at ICPE in August 2017 (Esposito DB, Cepeda MS, Lyons J, Yin R, Lanes S. Comparison of a Doctor and Pharmacy Shopping Measure for Opioid Analgesics Using Claims Data with Medical Chart Review to Identify Misuse, Diversion, Abuse and/or Addiction).

The table below shows the three definitions presented in Table 1 of the PMR Study 3033-8 Final Report, Section 5.5 in the PMR Study 3033-10 Final Report, and the Methods Section of the ICPE poster:

	Definition		
Shopping categories	**Study 3033-8 Final Report**	**Study 3033-10 Final Report**	**ICPE poster**
None	1 practice OR 1 outlet OR (2 practices and 2 outlets)	1 or 2 prescribers AND 1 or 2 pharmacies	≤2 prescribers and ≤2 pharmacies
Minimal	(2 practices AND >2 outlets) OR (2 outlets AND >2 practices)	2 prescribers AND >2 pharmacies OR 3 or 4 prescribers AND 2 pharmacies	2 prescribers and >2 pharmacies or 3-4 prescribers and 2 pharmacies
Moderate	(3 practices AND ≥3 outlets) OR (4 practices AND (3 or 4 outlets) OR (5 practices and 3 outlets)	3 or 4 prescribers AND >2 pharmacies OR >4 prescribers AND 2 pharmacies	3-4 prescribers and >2 pharmacies or >4 prescribers and 2 pharmacies
Severe	(4 practices AND ≥5 outlets) OR (5 practices AND ≥4 outlets) OR (≥6 practices AND ≥3 outlets)	>4 prescribers AND >2 pharmacies	>4 prescribers AND >2 pharmacies

Query 1

We request that the OPC confirm that the following scenarios would be classified into the "None" category according to the PMR study 3033-8 definition, and we request how the same scenarios would be categorized according to the PMR Study 3033-10 and ICPE poster definitions:

A. A patient with 1 practice (prescribers) and > 2 outlets (pharmacies)
B. A patient with 1 outlet and > 2 practices.

Further examples of apparent discrepancies in the definitions include the following scenarios. A patient with 2 outlets and 5 practices will be classified as minimal shopping according to the study 3033-8 definition, whereas the same patient will be classified as

moderate shopping according to PMR Study 3033-10 and the ICPE poster definitions. Also, a patient with 4 practices and 5 outlets will be classified as severe based on the PMR Study 3033-8 definition whereas the same patient will be classified as moderate shopping based on the PMR Study 3033-10 and ICPE poster definitions.

Query 2

Clarify the definition the PMR Study 3033-8 used with respect to numbers of practices and outlets. In particular, please provide the doctor/pharmacy shopping category for each cell in the following table.

		Practice					
		1	2	3	4	5	≥6
Outlets	1						
	2						
	3						
	4						
	5						
	≥6						

Query 3

Explain the discrepancies in the three definitions presented, i.e., in the PMR Study 3033-8 Final Report, PMR Study 3033-10 Final Report, and the ICPE Poster.

Primary Objective #2

For each candidate definition of doctor/pharmacy shopping, evaluate its association with algorithmically-identified abuse and/or addiction (AIAA), as defined by PMR Study 3033-7 (Formerly #2065-3B).

The Final Report evaluated only one of the three candidate definitions of DPS in association with AIAA. Also, the Interim Status Report presented two alternative definitions of DPS and stated they would be evaluated in association with AIAA as sensitivity analyses. These sensitivity analyses were not included in the Final Report. For each definition, present the AIAA OR for each DPS category from the crude and adjusted models and the statistics calculated for Tables 4 and 5.

1. Candidate Definition #1: requires ≥1 day of overlap to qualify as shopping behavior
2. Candidate Definition #2: requires ≥10 days of overlap to qualify as shopping behavior

Alternative definitions of DPS from the Interim Status Report:

Alternative 1) *A plausible ad hoc reclassification that would reduce the off-diagonal counts would be to (1) reduce the Shopping Behavior level by one step for individuals with three or fewer fills from non-specialists who are not already in the "minimal" group and (2) increase the Shopping Behavior classification by one step for persons with 15 or more fills from non-specialists with at least minimal Shopping Behavior.* (Interim Status Report, Page 18).

Alternative 2) *Analogously to the situation with non-specialist prescribers, a plausible reclassification would be to (1) decrease the Shopping Behavior classification by one step for persons with less than 2500 MEq over 18 months and (2) increase the classification by one step for those with at least 10,000.* (Interim Status Report, Page 19).

Secondary Objective #1

Quantify how well patient characteristics correlate with AIAA among patients exhibiting doctor/pharmacy shopping behaviors.

It appears that patient characteristics used in the Full Model, i.e., the model that examines AIAA as a function of DPS and patient characteristics, contains multiple covariates that were also used to construct the AIAA algorithm itself. (We will refer to the model used to develop AIAA as the *Algorithm Development Model*). Therefore, these covariates would be expected to be highly associated with AIAA, and thus decrease explanatory ability of DPS when used in the Full Model together**.**

In order for us to better understand the associations between DPS, covariates, and the AIAA outcome, we ask that the OPC re-analyze the data after identifying and removing such covariates from the Covariates-only Model and Full Model. We also recognize that removing every covariate that was also included in the Algorithm Development Model will limit the Full Model's ability to determine the independent explanatory ability of the number of prescribers/pharmacies after accounting for the number of dispensings. In other words, both approaches introduce some bias to estimating the independent association of DPS with AIAA. The most appropriate response would be to present a range of estimates that DPS categories may have on the probability of AIAA, depending on the covariates that are included in the model.

To start, please identify all covariates that were also used to derive the variables used in the Algorithm Development Model.

Once these covariates have been identified, we request that the OPC fit multiple versions of the models as a sensitivity analysis and formally compare them based on the statistics presented in Table 4 of the Final Report.

First, remove from the Covariates-only and Full Models the following covariates:

- age,
- gender,
- number of anxiolytics dispensings,
- number antidepressants dispensings,

- number of antipsychotics dispensings
- variables related to pain diagnoses,
- *mental disorders* diagnoses
- total MEq dispensed
- any other covariates that the OPC identifies as present in the Algorithm Development Model

The OPC should then fit the following models

Model	Covariates that should be removed from the covariates-only and full models	Covariates that should be added back to the list of covariates
Sensitivity Analysis A	All from the bullet list above	none
Sensitivity Analysis B	All from the bullet list above	Number of dispensings
Sensitivity Analysis C	All from the bullet list above	Total MEq dispensed
Sensitivity Analysis D	All from the bullet list above	Number of dispensings, Total MEq dispensed

Furthermore, we request to see the odds ratios by DPS category and the model fit statistics from Table 4 when the analytic sample is restricted to patients with ≥5 dispensings. In this sub-group, please perform Sensitivity Analysis E: run the shopping-only, covariates-only, and full models with the variables from Sensitivity Analysis A.

Please note, we request that Sensitivity Analyses A-E be performed on each candidate definition and alternate definition identified in Primary Objective #2.

Secondary Objective #2

Evaluate the contribution of identified doctor/pharmacy shopping behavior to the prediction of AIAA, after controlling for other patient characteristics.

The problem with Secondary Objective #1 also applies to this objective. It is not unexpected that DPS would make a relatively minor contribution to the prediction of AIAA in a model containing covariates that are part of the outcome algorithm. We ask that the OPC re-analyze the data by running Sensitivity Analyses A-E on each candidate definition and alternate definition identified in Primary Objective #2.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

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