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Epidemiology: Review of Final Study Report

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Subject:	Review of Final Study Report for Extended-Release/Long-Acting Opioid Analgesic (ER/LA OA) PMR 3033-10
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EXECUTIVE SUMMARY

Background: In September 2013, the FDA issued a letter to sponsors of approved ER/LA opioid analgesic NDAs, requiring postmarketing studies to assess the risks of misuse, abuse, addiction, overdose, and death.[a] It was ultimately determined that ten observational studies would be necessary to answer these questions (Studies #3033-1 through #3033-10, previously # 2065-1 through # 2065-4).

The subject of this review, PMR #3033-10, specifically, requires "a*n observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.*" When applied to drugs with potential for abuse, the term "doctor/pharmacy shopping" refers to a patient's practice of seeking prescriptions from multiple prescribers without their coordination or knowledge. At present, there is no standard definition of doctor/pharmacy shopping, and its relation to misuse, abuse, and/or addiction has not been well characterized. However, there is no ideal "gold" standard against which to measure the performance of doctor/pharmacy shopping metrics. Therefore, the Opioid PMR Consortium (OPC) is conducting three complementary studies, PMR #3033-8, #3033-9, and #3033-10, that evaluate these metrics in different settings and compare against different measures of misuse, abuse, and addiction—respectively, an administrative claims-based algorithm, patient self-report, and potentially aberrant behaviors documented in the medical record.

The amended Final Study Report for PMR #3033-10, submitted March 14, 2018 is the subject of this review. **The purpose of this review is twofold: (1) to determine whether this study fulfills PMR #3033-10, and (2) to interpret the findings of the study as they relate to doctor/pharmacy shopping outcomes metrics as a measure of possible misuse, abuse, and/or addiction.**

Methods: This study was a retrospective analysis of prescription opioid dispensing history and review of linked medical records, using the HealthCore Integrated Research Database (HIRD). The study population included adult patients with at least two opioid dispensings; at least one opioid must have been dispensed in 2012 with an additional one within the following 18 months. Patients were excluded if their charts could not be obtained, or if they had a known history of substance abuse identified through the administrative claims data. A four-category doctor/pharmacy shopping classification scheme based on that developed in PMR #3033-8 was evaluated in relation to behaviors suggestive of misuse, diversion, abuse, and/or addiction documented in the medical record. Behavior outcomes were defined as having at least one, two, and three behaviors documented, or having at least one behavior in either of two behavior clusters derived using cluster analysis. One cluster included behaviors that explicitly referenced abuse, misuse, and addiction; the other cluster included behaviors that suggested excessive healthcare utilization. The doctor-shopping models, both with and without covariates, were also evaluated for their ability to predict the behavior outcomes and to discriminate between those with and without potentially aberrant behavior outcomes.

Results: Overall, 78% of eligible opioid users in the HIRD showed no shopping, 11% minimal shopping, 8% moderate shopping, and 4% severe shopping. Compared to those in the no shopping group, those with higher levels of possible shopping behavior were younger and female, had higher levels of healthcare utilization, general pain complaints, and psychiatric comorbidity,

[a] https://www fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf

and a higher total number of opioid dispensings.

Compared to the no shopping category, only the severe doctor/pharmacy shopping category (>4 opioid prescribers and >2 pharmacies during an 18-month period) was significantly associated with having at least one, two, or three behaviors (AORs 2.4, 3.3, 6.3, respectively) or having a behavior in either cluster (AORs 4.1 and 2.1) identified in the medical record. Although a gradient was observed for mild and moderate shopping categories, being in these categories was not significantly associated with any of the potentially aberrant behavior outcomes.

Across all outcomes, the adjusted model consisting of the doctor/pharmacy shopping category and covariates performed modestly better than the covariate-only model in predicting the outcome, suggesting that the inclusion of doctor/pharmacy shopping category does contribute significant explanatory information to modeling the probability of identifying a potentially aberrant behavior in the medical record, after accounting for the number of opioid dispensings, other healthcare utilization measures, and sociodemographic information.

For the shopping-only and shopping-and-covariates models to predict each of the five outcomes, a cut-off value was selected to maximize the sum of sensitivity and specificity of classifying the outcome. Sensitivity ranged from 0.41 to 0.73, specificity ranged from 0.61 to 0.77, positive predictive value (PPV) ranged from 0.19 to 0.64, and negative predictive value (NPV) ranged from 0.59 to 0.96.

Interpretation and Conclusions: This study met its stated objectives and fulfills PMR #3033-10. Although the study was not able to validate a doctor-pharmacy shopping classification scheme against a gold-standard measure of clinically-confirmed misuse, abuse, and/or addiction, it provided some valuable insights on the value of doctor-pharmacy shopping metrics. Being in the most extreme shopping category (>4 opioid prescribers and >2 pharmacies during an 18-month period) was significantly associated with having behaviors in the medical record potentially related to misuse, abuse, and/or addiction. However, neither alone nor in combination with other patient and prescription characteristics, did shopping category discriminate well between patients with and without these behaviors. In particular, the positive predictive value was low, indicating that a high proportion of patients who would be identified as "severe doctor shoppers" using this definition do not have any evidence of aberrant behaviors in their medical record. Therefore, although claims-based evidence of use of multiple prescribers and pharmacies may be one factor possibly indicating an elevated risk of misuse, abuse, and/or addiction, it should not be used as a proxy outcome for abuse, misuse, diversion, and/or addiction, as it is likely to misclassify a high proportion of patients. As expected, the study had multiple limitations—including, importantly, the exclusion of individuals with claims for substance use disorders and the limited ability to detect misuse, abuse, and addiction in the medical record— and it will be most useful when findings are interpreted together with those of its complementary doctor/pharmacy-shopping studies, PMR 3033-8 and 3033-9.

1 INTRODUCTION

1.1 BACKGROUND AND REGULATORY HISTORY

The first extended-release/long-acting (ER/LA) opioid analgesic was approved by the FDA in 1987. Since this time, multiple additional NDAs have been approved. Based on a review of the literature, the Food and Drug Administration (FDA) concluded that more data are needed regarding the serious risks of misuse, abuse, addiction, overdose, and death associated with the long-term use of extended release/long acting (ER/LA) opioid analgesics. Thus, in September 2013, the FDA issued a letter to sponsors of approved ER/LA opioid analgesic NDAs, requiring

five postmarketing studies to assess these risks—four observational studies and one randomized trial.[b] It was ultimately determined that ten observational studies and one trial would be necessary to answer the questions posed in the original five post-marketing requirements (PMRs), and in February 2016, the original four PMRs were released and a new letter sent re-issuing the PMRs as ten observational studies and one trial.[c] The ten observational studies are labeled Study #3033-1 through #3033-10 (Previously # 2065-1 through # 2065-4).

PMR #3033-10, specifically, requires "a*n observational study using medical record review to evaluate the association between doctor/pharmacy shopping outcomes and patient behaviors suggestive of misuse, abuse and/or addiction.*" When the applied to drugs with potential for abuse, the term "doctor/pharmacy shopping" refers to a patient's practice of seeking prescriptions from multiple prescribers without their coordination or knowledge. At present, there is no single standard definition of doctor/pharmacy shopping, or a model that adequately describes doctor/pharmacy shopping and its relation to misuse, abuse, and/or addiction. Furthermore, there is not an ideal "gold" standard against which to measure the performance of doctor/pharmacy shopping metrics. Therefore, the Opioid PMR Consortium (OPC) is conducting three complementary studies, PMR #3033-8, #3033-9, and #3033-10, that evaluate these metrics in different settings and comparing against different measures of misuse, abuse, and addiction—respectively, an administrative claims-based algorithm, patient self-report, and potentially aberrant behaviors documented in the medical record. The overarching objective of these three studies is to define and validate possible doctor/pharmacy shopping metrics as measures indicative of misuse, diversion,[d] abuse, and/or addiction.

On June 22, 2017 the OPC submitted the Final Study Report of Observational Study #3033-10, conducted to fulfill PMR #3033-10. In response to a November 6, 2017 FDA Information Request, the OPC submitted an amended Final Study Report for this study on March 14, 2018. This amended report is the subject of this review. **The purpose of this review is twofold: (1) to determine whether this study fulfills PMR #3033-10, and (2) to interpret the findings of the study as they relate to doctor/pharmacy shopping outcomes metrics as a measure of possible misuse, abuse, and/or addiction.**

1.2 REVIEW METHODS AND MATERIALS

The subject of this review is the amended Final Study Report for "Observational Study #3033-10 (formerly #2065-4C): Retrospective cohort study to evaluate the relation between doctor/pharmacy shopping and outcomes suggestive of misuse, diversion, abuse and/or addiction by medical record review," submitted to FDA on March 14, 2018.

We will determine whether the objectives outlined in the final, approved study protocol have been met and the planned analyses have been conducted, thereby fulfilling the PMR. We will also summarize and interpret the findings of the study using fundamental principles of epidemiology.

2 REVIEW RESULTS

[b] https://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM367697.pdf

[c] https://www fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM484415.pdf

[d] The OPC included diversion as an outcome of interest in this study. Although FDA agreed to its inclusion as an exploratory outcome, the focus of this review will be the safety outcomes explicitly required as part of the PMR: misuse, abuse, and addiction.

2.1 STUDY OVERVIEW

	Study
1.1 Objectives/Aims/Scope	To assess whether the percentage of patients with behaviors suggestive of misuse, diversion, abuse and/or addiction described in the medical record increased across increasing categories of possible doctor/pharmacy shopping behavior.
1.2.1 Design	
1.2.1.1 Type/setting	Retrospective analysis of prescription opioid dispensing history and review of linked medical records
1.2.1.2 Data Source	HealthCore Integrated Research Database^{SM} [HIRD]
1.2.1.3 Time Period	2012-2014
1.2.1.4 Criterion (Selection) Standards	Adult patients with at least two opioid dispensings; at least one opioid must have been dispensed in 2012 with an additional one within the following 18 months. Patients must have had continuous enrollment in a health plan included in the HIRD for at least six months prior to and for at least 18 months following the date of the first IR or ER/LA opioid dispensing. Patients were excluded if their charts could not be obtained, or if they had a known history of substance abuse identified through the administrative claims data.
1.2.3 Exposure/Intervention	Category of possible doctor/pharmacy shopping: 1. No shopping behavior • 1 prescriber OR • 1 pharmacy OR • 2 prescribers AND 2 pharmacies 2. Minimal shopping behavior • 2 prescribers AND >2 pharmacies OR • 3 or 4 prescribers AND 2 pharmacies 3. Moderate shopping behavior • 3 or 4 prescribers AND >2 pharmacies OR • >4 prescribers AND 2 pharmacies 4. Severe shopping behavior • >4 prescribers AND >2 pharmacies
1.2.4 Outcome(s)	Five primary outcomes: • Two are clusters of behaviors that represent two latent underlying factors among the behaviors suggestive of

	misuse, diversion, abuse, and/or addition. Clusters are derived using factor analysis, or cluster analysis. One cluster included behaviors that explicitly referenced abuse, misuse, and addiction; the other cluster included behaviors that suggested excessive healthcare utilization. • The other three primary outcomes include having documented in the medical record at least one, at least two, and at least three of the behaviors suggestive of misuse, diversion, abuse, and/or addition.

1.2.5 Covariates	• Age in years
	• Gender
	• Geographic region of residence
	• Type of opioids used
	  ○ Immediate release (IR) only
	  ○ ER/LA only
	  ○ Both IR and ER/LA
	• Number of total opioid dispensings
	• Number of distinct prescribers identified
	• Number of distinct pharmacies identified
	• Duration of opioid use
	• Opioid dose
	• Individual psychiatric comorbidities and number
	• Individual pain diagnoses and number
	• Use of other medications with abuse potential
	• Types of healthcare facilities where the patient sought care
	• Number of office visits

1.2.6 Sample Size	A stratified random sample of patients was selected for medical record review; the number of patients in each of the four categories of doctor/pharmacy shopping, based on pre-specified power calculations, was as follows: • No shopping behavior: 115 patients • Minimal shopping behavior: 139 patients • Moderate shopping behavior: 147 patients • Severe shopping behavior: 189 patients
1.2.7 Statistical Analyses	Descriptive statistics: the number and percentage of patients in each category having any of the five outcomes. For each of the outcomes, the association with possible doctor/pharmacy shopping category status was examined using

	logistic regression, computing crude and adjusted odds ratios (ORs) and their 95% confidence intervals (CIs) to compare the following possible doctor/pharmacy shopping categories: • Minimal versus no shopping • Moderate versus no shopping • Severe versus no shopping In addition to crude and adjusted models, a covariates-only model was constructed for each outcome and compared to the full model to evaluate the additional contribution of doctor/pharmacy shopping to the model. The receiver operating characteristic (ROC) curve of the unadjusted model (i.e., logistic model including doctor/pharmacy shopping only) and full model were calculated, identifying the point on the ROC curve that maximized the sum of sensitivity and specificity. Performance metrics of the unadjusted and the full models (sensitivity, specificity, positive predictive value, and negative predictive value to discriminate patients with each outcome) were calculated based on this cut-off point.
1.2.8 Study Results	Overall, 78% of eligible opioid users in the HIRD showed no shopping, 11% minimal shopping, 8% moderate shopping, and 4% severe shopping. Only the severe doctor/pharmacy shopping category was significantly associated with having at least one, two, or three behaviors (Adjusted ORs 2.4, 3.3, 6.3, respectively) or having a behavior in either cluster (Adjusted ORs 4.1 and 2.1). A gradient was observed for mild and moderate shopping categories, but being in these categories was not significantly associated with any of the potentially aberrant behavior outcomes. Across all outcomes, the adjusted model consisting of the doctor/pharmacy shopping category and covariates performed modestly better than the covariate only model in predicting the outcome, suggesting that the inclusion of doctor/pharmacy shopping category does contribute significant explanatory information to modeling the probability of detecting a potentially aberrant behavior, after accounting for the number of opioid dispensings, other healthcare utilization measures, and sociodemographic information. Using a cut-off point that maximized the sum of sensitivity and specificity and the performance of the shopping-only (unadjusted) and shopping-and-covariates (adjusted) models in predicting each of the five outcomes, sensitivity ranged from 0.41 to 0.73, specificity ranged from 0.61 to 0.77, positive predictive value (PPV) ranged from 0.19 to 0.64, and negative predictive value (NPV) ranged from 0.59 to 0.96.

	Within the severe shopping category, 56% had evidence in the medical record that the prescriber was aware of at least one other prescriber.
1.2.9. Conclusions	Being in the most extreme doctor/pharmacy shopping category (>4 opioid prescribers and >2 pharmacies during an 18-month period) was significantly associated with having behaviors in the medical record potentially related to misuse, abuse, and/or addiction. However, neither alone or in combination with other patient and prescription characteristics, did shopping category discriminate well between patients with and without these behaviors.

2.2 STUDY OBJECTIVES/SPECIFIC AIMS/SCOPE

The overarching objective of PMR studies #3033-8, #3033-9, and #3033-10 was to define and validate possible doctor/pharmacy shopping as outcomes suggestive of misuse, diversion, abuse, and/or addiction.

The objective of Study #3033-10 was to assess whether the percentage of patients with behaviors suggestive of misuse, diversion, abuse, and/or addiction described in the medical record increased across pre-specified increasing categories of possible doctor/pharmacy shopping behavior.

2.3 STUDY METHODS

2.3.1 Design & Setting

2.3.1.1 Study Type

This was a retrospective analysis of prescription opioid dispensing history linked to review of medical records.

2.3.1.2 Data Source, Setting & Time Period

The study was conducted in the HealthCore Integrated Research Database (HIRD), a large administrative insurance and health plan database with longitudinal medical and pharmacy claims. For the subset of patients who are "fully insured," meaning that risk for patient insurance costs is held by the health plan contributing data to the HIRD rather than by an employer group for which only administrative services are offered by the contributing health plan, the HIRD can be linked to inpatient and outpatient medical records from healthcare providers who submit claims captured in the data source. As of July 2014, the database contained approximately 36.1 million lives with medical and pharmacy eligibility, of which 8.5 million were currently active.

The first recorded dispensing of an IR or ER/LA opioid in 2012 defined the index date. The baseline period included all data prior to the index date, and had a minimum duration of six months per the study inclusion criteria. The follow-up period during which the investigators assessed possible doctor/pharmacy shopping behavior included the first 18 months following the index date. For patients with a presumed death event prior to 18 months after the index date, the follow-up period consisted of the time between the index date and the claims-identified presumed

death.[e]

2.3.1.3 Study Population: Inclusion and Exclusion Criteria

Patients meeting the following criteria were eligible to be selected for medical record review.

Inclusion:

- Patients 18 years or older on the date of first IR or ER/LA opioid dispensing that occurred in 2012.
- Patients with at least two dispensed opioids (IR or ER/LA). One must have occurred in 2012 with an additional one within the following 18 months.
- Continuous, fully insured enrollment with medical and pharmacy eligibility in a health plan included in the HIRD for at least six months prior to the start of the follow-up period.
- Continuous enrollment in a health plan contributing data to the HIRD during the follow-up period of 18 months unless claims-identified, presumed death ended the follow-up period.

Exclusion:

The following criteria excluded patients from the stratified random sample for medical record review:

- Patients who could not be classified into one of the four defined possible doctor/pharmacy shopping categories (e.g., patients with missing prescriber ID and pharmacy ID for all opioid dispensings recorded during the patient's observation period).
- Patients for whom no medical records could be accessed (e.g., patients seeking care from out of network providers only, patients whose health care providers refuse to release medical records).
- **Patients with substance abuse identified through the administrative claims data at any time were excluded because it is not permissible to access their medical records identified in the HIRD.** Patients were excluded if they had any ICD-9-CM diagnosis or Healthcare Common Procedure Coding System (HCPCS) codes for substance abuse identified in administrative claims data (codes provided in **Appendix A**).

A stratified random sample of patients included in the sampling frame (i.e., individuals who met all inclusion and exclusion criteria) was selected based on their respective possible doctor/pharmacy shopping category, and medical records were requested from all providers who prescribed an opioid that was subsequently dispensed for each selected patient.

[e] "Presumed deaths" were defined based on the definition applied in Study #3033-8. This approach includes a combination of discharge status codes for hospitalizations and ER encounters with selected diagnosis codes, followed by an absence of future medical claims more than seven days after the ER episode.

2.3.2 Outcome & Exposure

Possible Doctor/Pharmacy Shopping:

Four categories of possible doctor/pharmacy shopping were specified using the total number of prescribers (i.e., healthcare providers with a prescriber ID listed on an opioid dispensing) and number of pharmacies where patients obtained opioids over an 18 month period. The doctor/pharmacy shopping categories were based on the definitions developed in PMR Study #3033-8[f] and adapted slightly for use in Studies 3033-9 and 3033-10 because the data source used in these studies does not contain the information that would be required to define practices or outlets. These modifications and definitions were described in detail in the August 10, 2015 report titled "OPC OSW: Study 4A - Cross-sectional Study to Define and Validate "Doctor/pharmacy Shopping" as outcomes suggestive of abuse and/or addiction: Definitions of Shopping Behavior in Health Insurance Data for Use in Studies 4B and 4C."

Medical records were obtained for a pre-specified number of individuals from each possible doctor/pharmacy shopping category and abstracted to identify behaviors consistent with misuse, abuse, addiction, and/or diversion of opioid analgesics. Shopping categories were as follows:

1. No shopping behavior
    - 1 prescriber, OR
    - 1 pharmacy, OR
    - 2 prescribers and 2 pharmacies
2. Minimal shopping behavior
    - 2 prescribers AND >2 pharmacies OR
    - 3 or 4 prescribers AND 2 pharmacies
3. Moderate shopping behavior
    - 3 or 4 prescribers AND >2 pharmacies OR
    - >4 prescribers AND 2 pharmacies
4. Severe shopping behavior
    - >4 prescribers AND >2 pharmacies

Outcomes:

The following behaviors were identified through abstraction of all available medical records from an opioid prescriber during the 18 month follow-up period. These items were selected on the basis of literature review, consultation with clinical experts, and discussion with the FDA. Literature references and scientific rationale for each of these items, as well as additional detail regarding the medical record review process were described in the Medical Record Plan (**Appendix B**), which was requested and reviewed by FDA previously in conjunction with the study protocol.

- Laboratory findings
    - Abnormal urine/blood screen
- Observed clinical consequences of opioid abuse
    - Opioid overdose
    - Death related to opioid use
    - Over-sedated with opioids/intoxicated from opioids
- Suspicious health care utilization
    - Cancels pain clinic visits, no show or no follow-up
    - Excessive phone calls requesting opioids

    - Excessive visits requesting opioids
    - Requested refills instead of clinic visit
    - Reported lost or stolen prescriptions
        - Loses medications more than once
    - Requested early refills more than once from same provider
    - Was discharged from practice because of egregious aberrant behavior or placed on a watch list
    - Resisted therapy changes/alternative therapy
    - Patient has persistent/non-modifiable pain
    - Multiple causes of pain are reported
    - Third party required to manage patient's medications
    - Sold prescription
- Inappropriate dose, source, or route used
    - Obtained opioids from a non-medical source
    - Forged prescription
    - Injected drug
    - Used additional opioids than those prescribed
    - Unauthorized dose escalation
    - ER visit to get opioids
    - Saved/hoarded unused medication
    - Solicited opioids from other providers
- Explicit reference to misuse, diversion, abuse, and/or addiction
    - Abused prescribed drug
    - Physician believes patient is addicted
    - Patient believes patient is addicted
    - Family believes patient is addicted
    - Used opioids for purpose other than pain
- Risk factors
    - Spouse/significant other has a drug abuse problem
    - Concurrent or history of substance abuse
    - Concurrent or history of abuse of alcohol
    - Use of alcohol for pain management

To better understand the relationship between possible doctor/pharmacy shopping behavior and communication across providers, the investigators also collected data from each medical record showing markers of communication and triage. For each medical record, they identified whether there was notation describing:

(1) whether the physician referred or received a consultation report from another office setting concerning pain management,
(2) whether the physician authorized or provided follow-up care after an ER visit for pain,
(3) whether the medical record indicated any knowledge of another opioid prescriber, and
(4) whether the medical record indicated that a Prescription Drug Monitoring Program was consulted.

Outcomes for sensitivity analyses

In addition, outcomes were specified for two sensitivity analyses. These outcomes were defined and analyses performed in individuals who did not qualify to have medical record data obtained.

(1) To assess the impact of the exclusion of patients for whom 18 months of follow-up were unavailable, the investigators used claims-identified addiction/substance abuse treatment as an outcome. The outcome of claims-identified addiction/substance abuse treatment was defined using the same criteria that were used to specify this exclusion from the main analysis.
(2) To better understand the impact of the requirement that patients have 18 months of follow-up on potentially undiagnosed behaviors suggestive of misuse, abuse, or addiction that could lead to termination of employment and therefore commercial insurance, the investigators also used health plan discontinuation as an outcome variable.

2.3.3 Covariates

The following characteristics were also ascertained during the baseline and follow-up periods from administrative claims data in the HIRD.

- Age in years
- Gender
- Geographic region of residence
- Type of opioids used
    - IR only
    - ER/LA only
    - Both IR and ER/LA
- Number of total opioid dispensings
- Number of distinct prescribers identified
- Number of distinct pharmacies identified
- Duration of opioid use
- Opioid dose
- Individual psychiatric comorbidities (i.e., alcoholism, anxiety disorder, bipolar disorder, history of suicide attempt, post-traumatic stress disorder, sleep disorder, and somatoform disorder) and number
- Individual pain diagnoses (i.e., abdominal pain, amputation, arthritis, arthropathies, osteoarthritis, and musculoskeletal pain, back pain, chronic pain, fibromyalgia, headache, malignancy, multiple sclerosis, neuropathic pain, peripheral vascular disease with claudication, ischemic extremity pain and/or skin ulcers, and stroke) and number
- Use of other medications with abuse potential
- Types of healthcare facilities where the patient sought care
- Number of office visits

2.3.4 Sample Size/Power

A stratified random sample of patients was selected for medical record review; the target number of patients in each of the four categories defined in Study 3033-8 was as follows:

- No shopping behavior: 115 patients
- Minimal shopping behavior: 139 patients
- Moderate shopping behavior: 147 patients
- Severe shopping behavior: 189 patients

Details of the reasoning behind the specified targets by category and relevant assumptions were

included in the study protocol and were based on expected prevalence of shopping behavior and a target precision of ±5% for the percent of patients in each category with behaviors suggestive of misuse, abuse, and/or addiction.

2.3.5 Statistical Analyses

The investigators conducted descriptive analyses of demographic characteristics, clinical characteristics, healthcare utilization, and medication use as captured in the HIRD administrative data during the baseline and follow-up periods for the following groups of individuals meeting study criteria:

1. Patients for whom medical records were reviewed
2. Patients for whom medical records could not be obtained
3. Patients eligible for medical record review
4. Patients with at least two opioids dispensed who were not eligible for medical record review (e.g., insufficient health plan enrollment, long-term care or abuse exclusions were met)

For those individuals for whom medical records were obtained, they then assessed the number and percentage of patients in each possible doctor/pharmacy shopping category with each specific behavior, no behaviors, at least one and up to 34 (all) of the defined behaviors suggestive of misuse, diversion, abuse, and/or addiction in the medical record.

How these behaviors correlate with each other was then assessed using hierarchical cluster analysis with the centroid linkage clustering method without variable standardization in SAS 9.4 (SAS Institute, Cary, North Carolina). To allow for different groupings of behaviors, the investigators evaluated several clustering strategies, including allowing the algorithm to produce an unrestricted number of clusters and limiting to five or fewer clusters. They ultimately limited to a three-cluster solution given the low prevalence of the behaviors suggestive of misuse, diversion, abuse, and/or addiction. They then assigned patients to each cluster based on whether they exhibited at least one of the behaviors assigned to that cluster group. As such, clusters were not mutually exclusive. Also, one of these clusters was excluded from the analysis due to sparse numbers.

For each of the resulting clusters and for patients with at least one, at least two, and at least three behaviors identified (five outcomes), the association with doctor/pharmacy shopping category status was examined by computing odds ratios (ORs) and their 95% confidence intervals (CIs) to compare the following possible doctor/pharmacy shopping categories:

- Minimal versus no shopping
- Moderate versus no shopping
- Severe versus no shopping

Adjusted models were created, with the number of covariates included in the adjusted models for each of the five outcomes limited to nine, allowing for six events per covariate. Variables were selected for inclusion in the final models using the threshold of p-value <0.30 or if there were *a priori* assumptions (e.g., reasons based on clinical knowledge) for including them in the model, or if they changed the association by 10% or more. The follow variables were retained in the final model regardless of their p-values: age, gender, number of opioid dispensings, and number of pain diagnoses.

In addition to adjusted models that included doctor/pharmacy shopping categories and covariates, for each outcome a covariate-only model was constructed which included all the covariates identified in the adjusted model without the doctor/pharmacy shopping category. The performance

of the three sets of models (doctor/pharmacy shopping categories only, doctor/pharmacy shopping categories and covariates, and covariates only) for each outcome were compared with regard to C-statistics and pseudo R-squared. In addition, for the doctor/pharmacy shopping category only models and the doctor/pharmacy shopping categories and covariate models, predicted probabilities of the outcomes were calculated and cut-offs were selected that maximized the sum of sensitivity and specificity. Based on the selected cut-offs, sensitivity, specificity, positive predictive value, and negative predictive value were calculated. To formally evaluate the contribution of doctor/pharmacy shopping category in the presence of all the covariates, likelihood ratio tests were performed to compare the doctor/pharmacy shopping and covariate model to the covariate-only model.

In addition, three pre-specified sensitivity analyses were conducted:

(1) OR and 95% CI for claims-identified addiction/substance abuse treatment comparing each possible doctor/pharmacy shopping category versus "no shopping." This was performed separately for patients with and without at least 18 months of continuous health plan eligibility,

(2) OR and 95% CI for health plan discontinuation comparing each possible doctor/pharmacy shopping category versus "no shopping,"

(3) logistic regression model for the outcome of cluster 2 in which the covariate "count of individual pain diagnoses" is excluded from the model, given overlap with the medical record identified behavior "multiple pain diagnoses," which was included in this cluster.

Finally, markers of communication and triage were described by showing the number and proportion of patients for whom cross-provider communication is documented as determined through comparison of medical record and claims-based findings.

2.4 STUDY RESULTS

Description of the Study Population:

Of 8,689,706 individuals who were enrolled in the HIRD in 2012, 12% had an opioid dispensed that year. Of these patients, 55% had a second opioid dispensed within 18 months after the first pharmacy fill was identified. After applying study inclusion and exclusion criteria, 243,554 (78%) individuals were classified as no shopping, 35,073 (11%) minimal shopping, 23,543 (8%) moderate shopping, and 10,302 (3%) severe shopping. This distribution was similar to that observed in PMR #3033-8.

Overall, patients with medical records reviewed were very similar to the sampling frame of eligible opioid users from which they were drawn. For individuals included in medical record review, the median number of records identified and sought for chart review was two for those with no shopping, three for those with minimal shopping, four for those with moderate shopping and six for those with severe shopping. A higher proportion of requested records could not be obtained in the higher shopping categories (21% for those with no shopping, 24% for those with minimal shopping, 28% for those with moderate shopping, and 31% for those with severe shopping. Additionally, patients in higher shopping categories were more likely to be excluded due to claims-identified abuse or addiction. Only 2% of those in the no shopping category, versus 16% of those in the severe shopping category, were excluded for this reason. Patients in higher shopping categories were also more likely to leave their health plan prior to 18 months from the start of follow-up.

Among patients included in the medical record review, compared to those in the no shopping group, those with higher levels of possible shopping behavior:

- were younger (e.g., median age 47 years for severe shopping versus 55 for no shopping

category)

- were more likely to be female (62% for severe shopping versus 54% for no shopping category)
- had higher levels of healthcare utilization in terms of office visits, ER visits, hospitalizations, and use of specific medication classes
- had a higher occurrence of general pain complaints such as back pain (73% versus 55% during follow-up), headache (42% versus 16%), and abdominal pain (47% versus 30%)
- had higher prevalence of psychiatric comorbidity, and higher use of non-opioid medications of abuse potential such as benzodiazepines (48.1% for severe shopping vs. 32.2% for no shopping category at baseline; 68.3% vs 44.3% at follow-up)
- had a higher total number of opioid dispensings (median 15 for severe shopping versus four for no shopping category),
- were more likely to have a history of opioid use prior to the first dispensing in 2012 that triggered the start of the follow-up period (83% for severe versus 70% for no shopping category).
- were more likely to use both ER/LA and IR opioids during follow-up (32.3% for severe shopping category versus 4.3% for no shopping category). Less than 2% of patients used ER/LA opioids exclusively.

Behaviors identified in medical record:

Overall, individual patients had between zero and eight of the 34 behaviors suggestive of abuse, misuse, addiction, and/or diversion identified in the medical records reviewed (**Table 1**). Zero behaviors were identified for 64% of individuals in the no shopping category, 58% in the minimal shopping category, 56% in the moderate shopping category, and 39% in the severe shopping category (**Table 1**).

The most frequently observed behavior in the medical record was report of multiple causes of pain (19% in the no shopping, 22% in the minimal shopping, 16% in the moderate shopping, and 29% in the severe shopping categories). Individual behaviors that were substantially more common in patients in the severe shopping versus no shopping category—although no testing for statistical significance was done— included resisting therapy changes (19% versus 8%), ER visits to obtain opioids (15% versus 3%), unauthorized dose escalation (11% versus 2%), and alcohol abuse (8% versus 1%). The proportions of patients who cancelled pain clinic visits, saved or hoarded medication, or were documented as using opioids for a non-pain purpose were low and similar across shopping categories. Explicit references to misuse, diversion, abuse, and/or addiction were uncommon in all shopping categories; however, it is important to note that patients with recognized substance abuse identified in the claims data could not be included in the medical record review. No medical records included mention of opioid overdose, death related to opioid use, excessive phone calls for opioids, patient selling a prescription, obtaining opioids from a non-medical source, forged prescription, or injection of opioids.

Table 1: Potential misuse, abuse, diversion and/or addiction-related patient behaviors identified in medical records

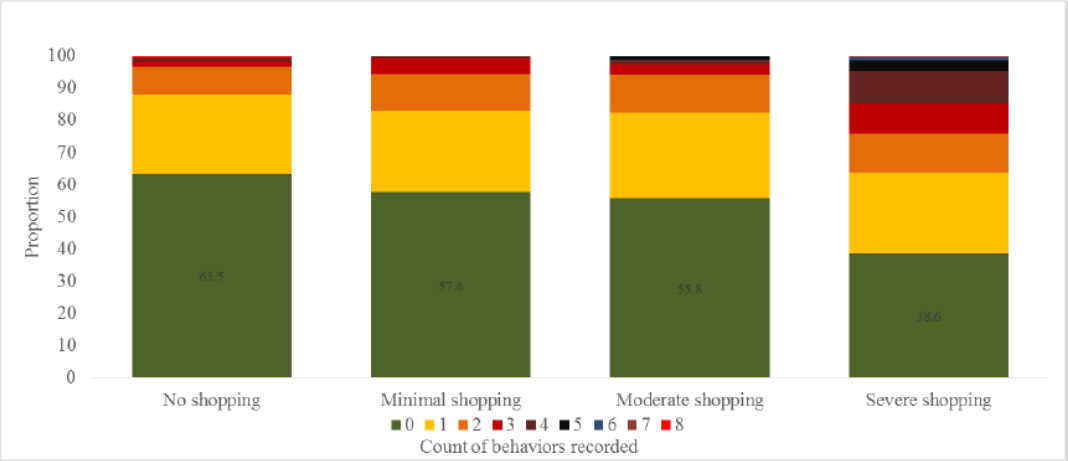
TABLE 5: MISUSE, DIVERSION, ABUSE AND/OR ADDICTION RELATED FINDINGS FROM MEDICAL RECORDS								
	No shopping		Minimal shopping		Moderate shopping		Severe shopping	
	N = 115		N = 139		N = 147		N = 189	
	N	%	N	%	N	%	N	%
Number of behaviors identified in the medical record								
Mean, SD	0.57, 1.06		0.66, 0.92		0.72, 1.04		1.44, 1.61	
Median	0		0		0		1	
Range (min, max)	0, 8		0, 4		0, 5		0, 7	
Count								
0	73	63.5	80	57.6	82	55.8	73	38.6
1	28	24.3	35	25.2	39	26.5	47	24.9
2	10	8.7	16	11.5	17	11.6	23	12.2
3	2	1.7	7	5.0	5	3.4	18	9.5
4	1	0.9	1	0.7	2	1.4	19	10.1
5	0	0.0	0	0.0	2	1.4	6	3.2
6	0	0.0	0	0.0	0	0.0	2	1.1
7	0	0.0	0	0.0	0	0.0	1	0.5
8	1	0.9	0	0.0	0	0.0	0	0.0
Specific behaviors identified in the medical record								
Laboratory findings								
Abnormal urine/blood screen	1	0.9	0	0.0	3	2.0	2	1.1
Observed clinical consequences of opioid abuse								
Oversedated with opioids/intoxicated from opioids	1	0.9	0	0.0	2	1.4	4	2.1
Opioid overdose	0	0.0	0	0.0	0	0.0	0	0.0
Death related to opioid use	0	0.0	0	0.0	0	0.0	0	0.0
Suspicious health care utilization								
Multiple causes of pain are reported	22	19.1	30	21.6	23	15.6	54	28.6
Resisted therapy changes/alternative therapy	9	7.8	10	7.2	17	11.6	36	19.0
Cancels pain clinic visits/No show or no follow-up	8	7.0	6	4.3	6	4.1	17	9.0
Patient has persistent/non-modifiable pain	3	2.6	5	3.6	7	4.8	22	11.6
Requested refills instead of clinic visit	5	4.3	5	3.6	4	2.7	21	11.1
Requested early refills more than once from same provider	0	0.0	1	0.7	1	0.7	5	2.6
Was discharged from practice or placed on a watch list	0	0.0	0	0.0	2	1.4	4	2.1
Reported lost or stolen prescriptions	0	0.0	3	2.2	1	0.7	1	0.5
Excessive visits requesting opioids	0	0.0	0	0.0	0	0.0	2	1.1
Third party required to manage patient's medications	0	0.0	1	0.7	0	0.0	1	0.5
Loses medications more than once	0	0.0	1	0.7	0	0.0	0	0.0
Excessive phone calls requesting opioids	0	0.0	0	0.0	0	0.0	0	0.0
Sold prescription	0	0.0	0	0.0	0	0.0	0	0.0
Inappropriate dose, source or route used								
ER visits to get opioids	3	2.6	13	9.4	12	8.2	28	14.8
Unauthorized dose escalation	2	1.7	2	1.4	4	2.7	20	10.6
Solicited opioids from other providers	0	0.0	2	1.4	5	3.4	12	6.3
Save/hoard unused medication	2	1.7	1	0.7	3	2.0	3	1.6
Used additional opioids than those prescribed	1	0.9	0	0.0	3	2.0	2	1.1
Obtains opioids from a non-medical source	0	0.0	0	0.0	0	0.0	0	0.0
Forged prescription	0	0.0	0	0.0	0	0.0	0	0.0
Injected drug	0	0.0	0	0.0	0	0.0	0	0.0
Explicit reference to misuse, diversion, abuse and/or addiction								
Physician believes patient is addicted	1	0.9	1	0.7	2	1.4	6	3.2
Use opioids for purpose other than pain	2	1.7	3	2.2	2	1.4	3	1.6
Patient believes patient is addicted	1	0.9	0	0.0	1	0.7	2	1.1
Family believes patient is addicted	0	0.0	0	0.0	1	0.7	2	1.1
Abused prescribed drug	0	0.0	0	0.0	0	0.0	1	0.5
Risk factors								
Concurrent or history of abuse of alcohol	1	0.9	4	2.9	5	3.4	15	7.9
Concurrent or history of substance abuse	4	3.5	3	2.2	2	1.4	7	3.7
Spouse/significant other has a drug abuse problem	0	0.0	1	0.7	0	0.0	1	0.5
Use of alcohol for pain management	0	0.0	0	0.0	0	0.0	1	0.5

Abbreviations: SD: standard deviation, and US: United States.

Source: PMR 3033-10 Amended Final Study Report Appendix D Study Tables, Table 5

There was a gradient in which more behaviors were observed in higher shopping categories, with a change being particularly notable between the moderate and severe categories (**Figure 1**).

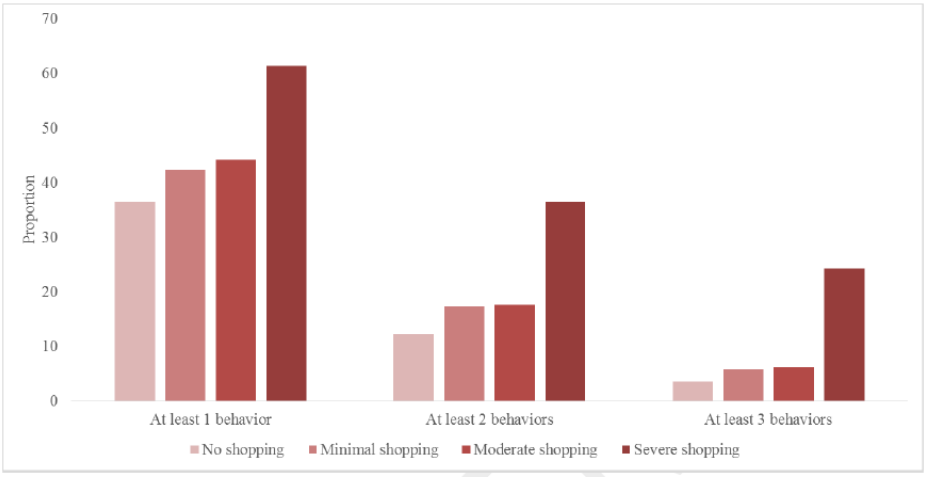
Figure 1. Proportion of individuals by count of behaviors suggestive of misuse, diversion, abuse, and/or addiction in medical records and doctor/pharmacy shopping categories



Source: PMR 3033-10 Amended Final Study Report Appendix D Study Tables, Figure 2

The proportion of patients with at least one, two, and three identified behaviors increased across shopping categories, as shown in **Figure 2**. There was a significant trend across shopping categories for having at least one, two, and three behaviors identified (test for trend p<0.001).

Figure 2. Proportion of patients with misuse, abuse, diversion, and/or addiction related behaviors identified in medical records, by doctor/pharmacy shopping category



Source: PMR 3033-10 Amended Final Study Report Appendix D Study Tables, Figure 3.1

As shown in **Table 2**, compared with no shopping, the crude odds of having at least one, two, and three behaviors identified were significantly elevated in the severe shopping group (ORs 2.8, 4.2, and 8.9, respectively), whereas those for minimal and moderate shopping categories were not. Adjustment for covariates attenuated these associations slightly, but they remained statistically significant for the severe shopping group.

Table 2. Crude and adjusted associations between doctor/pharmacy shopping category and having 1, 2, and 3 behaviors suggestive of misuse, diversion, abuse, and/or addiction

TABLE 7C: SUMMARY OF THE ASSOCIATION BETWEEN DOCTOR/PHARMACY SHOPPING CATEGORY AND EACH OUTCOME												
Shopping Category	Outcome = Yes (N)	Total in Shopping Category (N)	Prevalence of Outcome (%) and 95% CI*			Crude OR[1] (95% CI)			Adjusted OR[2] (95% CI)		
	Outcome = At least one behavior										
None	42	115	36.5	(28.1)	(45.6)	Reference			Reference		
Minimal	59	139	42.4	(34.4)	(50.8)	1.3	(0.8)	(2.1)	1.2	(0.7)	(2.1)
Moderate	65	147	44.2	(36.3)	(52.3)	1.4	(0.8)	(2.2)	1.3	(0.8)	(2.1)
Severe	**116**	**189**	**61.4**	**(54.3)**	**(68.1)**	**2.8**	**(1.7)**	**(4.4)**	**2.4**	**(1.5)**	**(3.9)**
Total	282	590	47.8	(43.8)	(51.8)						
	Outcome = At least two behaviors										
None	14	115	12.2	(7.1)	(19.1)	Reference			Reference		
Minimal	24	139	17.3	(11.7)	(24.2)	1.5	(0.7)	(3.1)	1.4	(0.7)	(2.8)
Moderate	26	147	17.7	(12.2)	(24.5)	1.6	(0.8)	(3.1)	1.3	(0.6)	(2.7)
Severe	**69**	**189**	**36.5**	**(29.9)**	**(43.6)**	**4.2**	**(2.2)**	**(7.8)**	**3.3**	**(1.7)**	**(6.3)**
Total	133	590	22.5	(19.3)	(26.1)						
	Outcome = At least three behaviors										
None	<10	115				Reference			Reference		
Minimal	<10	139				1.7	(0.5)	(5.8)	1.5	(0.4)	(5.2)
Moderate	<10	147				1.8	(0.5)	(6.0)	1.2	(0.4)	(4.2)
Severe	**46**	**189**	**24.3**	**(18.6)**	**(30.8)**	**8.9**	**(3.1)**	**(25.5)**	**6.3**	**(2.1)**	**(18.4)**
Total		590									

Abbreviations: N: number, CI: confidence interval, OR: odds ratio.
1: Odds ratio obtained from a logistic regression model including only the doctor shopping variable.
2: Odds ratio obtained from a logistic regression model the doctor shopping variable and covariates.
*: Exact method (Fisher) was used to calculate the 95% CI for the prevalence.

Source: PMR 3033-10 Amended Final Study Report Appendix D Study Tables, Table 7c

Association between shopping categories and behavior clusters:

Based on cluster analysis, behaviors identified in the medical record were grouped into three clusters:

Cluster 1 incorporated behaviors qualitatively categorized as more explicitly referencing misuse, diversion, abuse, and/or addiction in the medical record:

- abnormal urine/blood screen
- oversedated with opioids/intoxicated from opioids
- third party required to manage patient's medications
- used additional opioids than those prescribed
- saved/hoarded unused medication
- abused prescribed drug
- physician believed patient is addicted

- patient believed patient is addicted
- family believed patient is addicted
- used opioids for purpose other than pain
- concurrent or history of substance abuse
- concurrent or history of abuse of alcohol.

Cluster 2 incorporated behaviors that were most often categorized as suspicious health care utilization:

- canceled pain clinic visits/no show or no follow-up
- requested refills instead of clinic visit
- reported lost or stolen prescriptions
- lost medications more than once
- requested early refills more than once from same provider
- was discharged from practice or placed on a watch list
- resisted therapy changes/alternative therapy
- patient had persistent/non-modifiable pain
- multiple causes of pain were reported
- unauthorized dose escalation
- ER visits to get opioids
- solicited opioids from other providers
- spouse/significant other had a drug abuse problem.

Cluster 3 incorporated two behaviors only:

- use of alcohol for pain management
- excessive visits requesting opioids.

As shown in **Table 3**, only the severe shopping category was significantly associated with having at least one element included in Cluster 1, in both the unadjusted and adjusted analyses. Adjusting for age, gender, number of opioid dispensings, number of pain diagnoses, number of psychiatric conditions, number of hospitalizations, and use of sleep medications, did not substantially change the OR estimates predicting having a behavior in Cluster 1.

Similarly, only the severe shopping category was significantly associated with having at least one element included in Cluster 2, and adjustment for age, gender, number of opioid dispensings, number of pain diagnoses, and use of amphetamines did not substantially change the ORs. Due to sparse data (only two subjects, both in the severe shopping category), ORs for Cluster 3 behaviors were not reported. The sensitivity analysis removing "number of pain diagnoses" from the adjusted model minimally changed these results (data not shown).

Table 3: Association between doctor/pharmacy shopping category and having at least one behavior in each behavior cluster

		Unadjusted			Adjusted		
		OR	**95% CI**		**OR**	**95% CI**	
Cluster 1[a] (N=590)	Doctor/pharmacy shopping group:						
	Minimal versus none	1.6	0.6	4.4	1.5	0.6	4.4
	Moderate versus none	2.2	0.8	5.9	2.0	0.7	5.4
	Severe versus none	**4.3**	**1.7**	**10.5**	**4.1**	**1.6**	**10.4**
Cluster 2[b] (N=590)	Doctor/pharmacy shopping group:						
	Minimal versus none	1.2	0.7	2.0	1.2	0.7	2.0
	Moderate versus none	1.2	0.7	2.0	1.1	0.7	1.8
	Severe versus none	**2.4**	**1.5**	**3.9**	**2.1**	**1.3**	**3.4**
Cluster 3[c]	Doctor/pharmacy shopping group:						
	Minimal versus none	NA	NA	NA	NA	NA	NA
	Moderate versus none	NA	NA	NA	NA	NA	NA
	Severe versus none	NA	NA	NA	NA	NA	NA

Unadjusted analyses model whether at least one behavior that was part of the cluster is associated with doctor/pharmacy shopping group. Adjusted analyses included covariates as follows:

[a] Cluster 1 analysis adjusted for age, gender, number of opioid dispensings, number of pain diagnoses, number of psychiatric conditions, number of ER/inpatient hospitalizations and use of sleep medications.

[b] Cluster 2 analysis adjusted for age, gender, number of opioid dispensings, number of pain diagnoses and use of amphetamines.

[c] Cluster 3 analysis was not feasible given that it was seen only in the severe shopping category.

Source: PMR 3033-10 Amended Final Study Report Appendix D Study Tables, Table 7

Comparison of doctor/pharmacy shopping only, doctor/pharmacy shopping and covariates, and covariates-only models

The performance of doctor/pharmacy shopping only, doctor/pharmacy shopping and covariates, and covariates-only models was compared across of all the study outcomes. For each outcome, the doctor/pharmacy shopping and covariate model outperformed the doctor/pharmacy shopping only model and the covariates-only model **(Table 4)**. The shopping-only models performed similarly to or modestly better than the covariates-only models in predicting each outcome, based on the pseudo R-squared values. C-statistics for the shopping-plus-covariates models were slightly higher than for the covariates only models, and the highest C-statistic (0.779) was for the shopping-plus-covariates model predicting the outcome of three or more behaviors. Almost all of the C-statistics were greater than 0.6, but none were higher than 0.8, indicating that the models predicted the outcome better than chance but are not considered "strong" models.

Table 4. Comparison among doctor/pharmacy shopping-only, doctor/pharmacy shopping and covariates, and covariates-only models

Outcome		Cluster 1		Cluster 2		At Least One Behavior		At Least Two Behaviors		At Least Three Behaviors	
		C-statistic	Pseudo R-squared	C-statistic	Pseudo R-squared	C-statistic	Pseudo R-squared	C-statistic	Pseudo R-squared	C-statistic	Pseudo R-squared
Model Specification	Shopping-Only	0 642	0 028	0 589	0 030	0 602	0 037	0 643	0 052	0 719	0 072
	Shopping and Covariates	0 702	0 055	0 622	0 047	0 632	0 054	0 691	0 076	0 779	0 112
	Covariate-only	0 643	0 031	0 595	0 027	0 597	0 029	0 640	0 041	0 702	0 062

Abbreviations: CI: confidence interval, OR: odds ratio, ROC: receiver operating characteristic

Source: PMR 3033-10 Amended Final Study Report Appendix D Study Tables, Table 7d

Likelihood ratio tests were performed to compare shopping and covariates versus covariate only models, and the contribution of the doctor/pharmacy shopping category was found to be significantly improve model fit across all five outcomes (**Table 5**).

Table 5. Comparison between full model and covariates only model

	Model Specification	Likelihood Ratio Chi-square	Degree of Freedom	Diff Chi-square	Diff DF	P-value
Cluster 1	Shopping and Covariates	33.06	10			
	Covariates-only	18.76	7	14.30	3	<0.01
Cluster 2	Shopping and Covariates	28.31	8			
	Covariates-only	16.11	5	12.20	3	<0.01
At Least One Behavior	Shopping and Covariates	32.59	9			
	Covariates-only	17.20	6	15.40	3	<0.01
At Least Two Behaviors	Shopping and Covariates	46.54	8			
	Covariates-only	24.84	5	21.70	3	<0.01
At Least Three Behaviors	Shopping and Covariates	69.73	10			
	Covariates-only	37.47	7	32.25	3	<0.01

*Chi-square distribution: Chi-square = 11.34, degrees of freedom = 3, p = 0.01

Abbreviations: Diff: difference, DF: degree of freedom

Source: PMR 3033-10 Amended Final Study Report Appendix D Study Tables, Table 7e

Finally, for each outcome, the cut-off point was identified that maximized the sum of sensitivity and specificity and the performance of the shopping-only (unadjusted) and shopping-and-covariates(adjusted) models in predicting each of the five outcomes was calculated (**Table 6**). Sensitivity ranged from 0.41 to 0.73, specificity ranged from 0.61 to 0.77, positive predictive value (PPV) ranged from 0.19 to 0.64, and negative predictive value (NPV) ranged from 0.59 to

0.96. The lowest positive predictive values were observed for the Cluster 1 outcomes (0.19) and at least three behaviors (0.24), the two outcomes with the smallest number of subjects.

Table 6. Metrics of shopping-only and shopping-plus-covariates model performance in predicting five outcomes

	Cluster 1		Cluster 2		At Least One Behavior		At Least Two Behaviors		At Least Three Behaviors	
	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted	Unadjusted	Adjusted
True Positive	36	49	108	143	116	124	69	96	46	49
True Negative	368	342	245	211	235	238	337	277	380	393
False Positive	153	179	81	115	73	70	120	180	143	130
False negative	33	20	156	121	166	158	64	37	21	18
Sensitivity	0 52	0 71	0 41	0 54	0 41	0 44	0 52	0 72	0 69	0 73
Specificity	0 71	0 66	0 75	0 65	0 76	0 77	0 74	0 61	0 73	0 75
PPV	**0.19**	**0.21**	**0.57**	**0.55**	**0.61**	**0.64**	**0.37**	**0.35**	**0.24**	**0.27**
NPV	**0.92**	**0.94**	**0.61**	**0.64**	**0.59**	**0.60**	**0.84**	**0.88**	**0.95**	**0.96**

Abbreviations: PPV: positive predictive value, NPV: negative predictive value

Source: PMR 3033-10 Amended Final Study Report Appendix D Study Tables, Table 7f

Markers of Communication and Triage

The percentage of patients whose medical records indicated that the prescriber was aware of or had referred the patient to at least one other prescriber increased from 20% in the no shopping category, to 56% in the severe category (**Table 7**). The percentage of patients for whom the office-based medical record(s) indicated communication between the ER and office ranged from <10% in the no shopping group to 18% in the severe shopping group.

Table 7: Markers of communication and triage

	No shopping		Minimal shopping		Moderate shopping		Severe shopping	
	N = 115		N = 139		N = 147		N = 189	
	N	%	N	%	N	%	N	%
Number of unique prescribers identified in claims data (mean, median, standard deviation)	2.13, 2, 1.2		3.03, 3, 0.71		4.2, 4, 1.5		6.54, 6, 1.94	
Number of patients with multiple prescribers identified in claims data	82	71.3	139	100.0	147	100.0	189	100.0
Medical record(s) indicate that providers were aware of an additional prescriber	23	20.0	48	34.5	58	39.5	105	55.6
Medical record(s) included consultation notes from an additional prescriber	16	13.9	20	14.4	26	17.7	53	28.0
Medical record(s) indicated referral to an additional prescriber	23	20.0	43	30.9	60	40.8	103	54.5
Medical record(s) indicate communication between the ER and office	<10		19	13.7	18	12.2	34	18.0
Medical record(s) described that emergency care was authorized by a non-ER physician (e.g., primary care provider or pain specialist).	0	0.0	<10		<10		<10	
Number of patients for whom an ER visit was identified in medical record data but not in claims data	0	0.0	<10		<10		<10	

Source: PMR 3033-10 Amended Final Study Report Appendix D Study Tables, Table 9

Claims-identified abuse/addiction: Sensitivity analysis

The proportion of individuals with claims for addiction/substance abuse treatment increased across the specified shopping categories: 2% with no shopping behaviors, 5% with minimal shopping behaviors, 12% with moderate shopping behaviors, and 16% with severe shopping behaviors. Of note, this analysis used substance use disorder claims that mandated exclusion from the medical record review. It did not utilize the abuse and addiction algorithm developed and evaluated in Observational Study #3033-7 and used in Study #3033-8 to develop the shopping categories.

2.5 AUTHORS' STUDY CONCLUSIONS

There was a strong association between increased possible doctor/pharmacy shopping, aberrant drug behavior described in the medical record, and abuse/addiction measured through administrative claims. Some, but not all, prescribing by multiple healthcare providers appears to be consistent with coordinated care.

3 DISCUSSION

a. This study met its stated objectives and fulfills PMR #3033-10. However, it is not, by itself, able to fully evaluate the performance of this specific doctor/pharmacy shopping definition, or doctor/pharmacy shopping measures more generally as an indicator of misuse, abuse, or addiction.

This PMR was considered an exploratory study, intended to augment the findings of PMR 3033-8 and 3033-9 by providing additional insights that might be gained from a manual examination of patient charts. In particular, the study intended to better understand the correlation between shopping category and behaviors identified in the medical record possibly indicative of misuse, abuse, and/or addiction. As such, this investigation met its objectives and fulfills the PMR. It does provide some new information on documented patient behaviors as they relate to pre-defined patterns of opioid prescriber and pharmacy utilization, but it is not a validation study in the traditional sense, as it does not use a "gold standard" outcome measure against which doctor-pharmacy shopping metrics can be evaluated.

b. Severe shopping behavior (>4 opioid prescribers and using >2 pharmacies in an 18-month period) was significantly associated with having potentially aberrant patient behaviors documented in the medical record. However, the inferential value of this finding is limited due to lack of validation of the behavior outcomes as measures of misuse, abuse, and/or addiction.

In this study of commercially insured individuals, excluding those with claims for substance use disorder treatment, only the most extreme category of possible shopping behavior (>4 opioid prescribers and using >2 pharmacies) was significantly associated with potentially aberrant patient behaviors identified in the medical record, as measured by at least one, two, and three behaviors, and data-driven Clusters 1 and 2. The magnitude of association was fairly large, with ORs for the five outcomes ranging from 2 to more than 6. These associations remained significant after adjusting for covariates, including, importantly, the total number of opioid prescriptions filled. Although a gradient was observed for mild and moderate shopping categories, being in these categories was not significantly associated with any of the potentially aberrant behavior outcomes. These findings suggest that in this population, having more than four opioid prescribers and using more than two pharmacies during an 18-month period, regardless of overlapping prescriptions, may indicate a higher

likelihood of problematic opioid use, possibly including misuse, abuse, diversion, and/or addiction.

The inferential value of this finding is limited. The potentially aberrant patient behaviors identified in the medical record, when present, suggest that the patient's use of opioids *may be* problematic. However, these observed behaviors *do not* represent anything close to a gold standard for abuse, misuse, addiction, or diversion. The investigators appropriately provided literature references and rationale for each item's inclusion in the medical record review plan as *possibly* being associated with misuse, abuse, or addiction, and the cluster analysis conducted by the investigators provides some insight into how these behaviors correlate and cluster with one another. However, providers may not be aware of patients' opioid misuse, abuse, addiction, or diversion behavior. They may also hesitate to record potentially stigmatizing information or may fear legal action if they document their concerns relating to a drug they have prescribed. Finally, unconscious biases or incomplete information may lead to incorrect interpretation of observations or events.

c. Doctor/pharmacy category does not discriminate well between people with and without behaviors potentially related to opioid misuse, abuse, and/or addiction. Doctor/pharmacy shopping metrics should not be used as an indicator, or proxy outcome, for opioid abuse, misuse, addiction, or diversion.

Another important finding here was the very low positive predictive value (PPV) of doctor/pharmacy shopping category, even when combined in a model with other potential predictors of abuse, misuse, and addiction. Even in the severe shopping category, more than a third of patients had no aberrant behavior identified in their medical record, and more than three-quarters had two or fewer behaviors identified. The most common behaviors identified in this group were reporting multiple causes of pain, and resisting changes to therapy or alternative therapy (29% and 19%, respectively). It is unknown how likely these behaviors are, either individually or in aggregate, to indicate opioid misuse, abuse, or addiction. ED visits for opioids and unauthorized dose escalation were the next most commonly documented behaviors in the severe shopping category (15% and 11%, respectively). It is unknown whether the intent of these actions was to treat a new legitimate pain condition, versus to abuse or divert medication. Positive drug screens and other overt documentation of abuse were quite rare in this cohort, although an important limitation was the exclusion of patients with drug abuse or addiction identified through administrative claims data at any time, due to privacy rules that do not permit study investigator access to these medical records. Despite this limitation, these findings suggest that even the most extreme shopping category may misclassify a substantial proportion of patients.

It was also notable that a substantial proportion of patients in all the shopping categories, including more than half of those in the severe category, had medical records indicating that the prescriber was aware of or had referred the patient to at least one other prescriber. These findings suggest that some, but not all, prescribing by multiple healthcare providers appears to be consistent with coordinated care.

Based on the likelihood-ratio test, the shopping-plus-covariates model was significantly more predictive than the model with covariates only, but based on the C-statistics, none of the models were strong in their ability to discriminate between those with and without the outcomes.

The results of this study suggest that, especially combined with other information, extreme potential shopping behavior (>4 prescribers AND >2 pharmacies) may help identify some patients at elevated risk for problematic opioid use and substance use disorders, perhaps warranting more careful monitoring, coordination of care, and, if appropriate, screening for

possible substance use disorders. This study does *not* provide evidence that these categories will correctly discriminate between opioid users who are using their prescriptions as directed and those who are misusing, abusing, diverting, or addicted to their opioids. Therefore, it is not appropriate to use such doctor/pharmacy shopping metrics as a proxy outcome measure for abuse, misuse, diversion, and/or addiction. An imperfect, but perhaps helpful, analogy is that elevated LDL cholesterol is associated with coronary artery disease, and is an easily measurable marker that may identify patients at higher risk and needing additional screening or interventions. However, a cholesterol level above a specified threshold does not indicate the presence of coronary artery disease and would never be used as a proxy measure for coronary artery disease itself.

d. This study evaluated only one doctor/pharmacy shopping classification scheme in a single claims-based data environment. It is possible that other definitions of doctor/pharmacy shopping could perform better, either in this or other data environments.

The doctor/pharmacy shopping definition used in this study was based on that developed in PMR-8 based on its ability to distinguish being opioid and diuretic prescriptions and predict algorithmically identified abuse and addiction (AIAA), a claims-based outcome that did not validate well in PMR 3033-7. The classification scheme in PMR 3033-8 was evaluated in a different data environment (IMS Health LRx linked to IMS Health Pharmetrics Plus Database) and used prescriber practice rather than individual prescribers. The similar distribution of patients across potential shopping categories suggests that these categories may be reasonable to evaluate in the HealthCore database in this study. However, it is not clear whether the approach used in PMR #3033-8 was successful in identifying the classification scheme best able to distinguish between those using opioids as directed with therapeutic intent and those misusing, abusing, or addicted to opioids. In particular, the poor performance of AIAA in PMR #3033-7 compared to the "gold standard" of manual medical record review raises questions about the ability of PMR #3033-8 to successfully develop and validate candidate doctor/pharmacy shopping classification schemes. As noted above, manual medical record review undoubtedly misclassifies a substantial proportion of patients as well, and therefore is, at best, a very tarnished gold standard.

e. The generalizability of the study findings was limited.

The inclusion of only commercially insured individuals limits the generalizability of these results. For example, the findings may not apply to analyses using Prescription Drug Monitoring Program (PDMP) or Medicaid data. As previously noted, an important limitation of this study was that patients with a claims-identified history of substance abuse had to be excluded from the medical record review. It was notable that being classified in more extreme potential shopping categories was associated with being excluded due to claims-identified history of abuse or addiction.[g] Although it does not invalidate the association seen in this study population, the exclusion of these high-risk patients reduces the external validity of the study results, in that they may not be applicable to a population that includes these high-risk patients. In addition to the exclusion of these patients, a substantial proportion of charts could not be obtained for administrative reasons, and this proportion was higher in the more severe shopping group, potentially resulting in a detection bias. However, this differential availability of chart information would be expected to bias results toward the null, in that it may differentially miss more behaviors in the more severe shopping group. Finally, results from

[g] The codes used to define a history of abuse or addiction are in Appendix A. Of note, this definition was not the same as the algorithmically identified abuse and addiction (AIAA) definition evaluated in PMR #3033-8.

the time period covered, 2012-2014, may not accurately reflect current dispensing patterns, particularly with regard to doctor/pharmacy shopping. Since 2014, use of Prescription Drug Monitoring Programs (PDMPs) has increased, and additional restrictions on opioid prescribing have been implemented at many levels. Therefore, it is unclear whether the associations observed in this study would be similar in today's prescribing environment.

4 CONCLUSIONS

This study met its stated objectives and fulfills PMR #3033-10. Although the study was not able to validate a doctor-pharmacy shopping classification scheme against a gold-standard measure of clinically-confirmed misuse, abuse, and/or addiction, it provided some valuable insights on the value of these metrics. Being in the most extreme shopping category (>4 opioid prescribers and >2 pharmacies during an 18-month period) was significantly associated with having medical record documentation of behaviors potentially related to misuse, abuse, and/or addiction. However, neither alone nor in combination with other patient and prescription characteristics, did shopping category discriminate well between patients with and without these behaviors. Therefore, although claims-based evidence of use of multiple prescribers and pharmacies may be one factor possibly indicating an elevated risk of misuse, abuse, and/or addiction, it should not be used as a proxy outcome for abuse, misuse, diversion, and/or addiction, as it is likely to misclassify a high proportion of patients. As expected, the study had multiple limitations and will be most useful when findings are interpreted together with those of its sister doctor-shopping studies, PMR 3033-8 and 3033-9.

5 APPENDIX A

List of codes indicating history of substance abuse necessitating exclusion from medical record review:

- Opioid type dependence: ICD-9-CM 304.0x
- Alcohol and/or drug services; crisis intervention (outpatient): HCPCS H0007
- Alcohol and/or drug services; sub-acute detoxification (hospital inpatient): HCPCS H0008
- Alcohol and/or drug services; acute detoxification (hospital inpatient): HCPCS H0009
- Alcohol and/or drug services; sub-acute detoxification (residential addiction program inpatient): HCPCS H0010
- Alcohol and/or drug services; acute detoxification (residential addiction program inpatient): HCPCS H0011
- Alcohol and/or drug services; sub-acute detoxification (residential addiction program outpatient): HCPCS H0012
- Alcohol and/or drug services; acute detoxification (residential addiction program outpatient): HCPCS H0013
- Alcohol and/or drug services; ambulatory detoxification): HCPCS H0014
- Alcohol and/or drug services; intensive outpatient (treatment program that operates at least 3 hours/day and at least 3 days/week and is based on an individualized treatment plan), including assessment, counseling; crisis intervention, and activity therapies or education: HCPCS H0015
- Alcohol and/or drug services; medical/somatic (medical intervention in ambulatory setting): HCPCS H0016
- Alcohol and/or drug services; methadone administration and/or service (provision of the drug by a licensed program): HCPCS H0020

6 APPENDIX B

Table 1: Behaviors suggestive of misuse, diversion, abuse, and/or addiction to be identified through medical record review*			
Behavior	**Justification**	**References**	**Operational details** Note – all behaviors pertain to the 18 month follow-up period unless otherwise specified.
Laboratory findings			
Abnormal urine/blood screen	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1] Witkin, 2013 [2]	Medical record indicates one or more of the following. Each will be captured separately. • Urine or blood screen negative for prescribed chronic opioids. • Urine or blood screen positive for illicit or non-prescribed controlled substances.
Observed clinical consequences of opioid abuse			
Opioid overdose	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1] Witkin, 2013 [2]	Medical record indicates one or more of the following. Each will be captured separately. • Medical record contains at least one reference to an opioid overdose or poisoning. • Medical record contains at least one reference to an overdose or poisoning not attributed to opioids. • Medical record contains at least one reference to an overdose or poisoning where the substance was not described.
Death related to opioid use	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1]	Medical record indicates one or more of the following. Each will be captured separately. • The patient is deceased. • Opioids are suspected/reference in the cause of death (overdose, poisoning, or related terms).
Oversedated with opioids/intoxicated from opioids	Characteristic associated with opioid misuse status in retrospective medical record review study. Characteristic associated with substance use disorder	Cheatle, 2013 3 Fleming, 2007 4	Medical record indicates one or more of the following: • At least one observed instance of oversedation/intoxication where the treating health care provider suspected opioids as the reason for sedation/intoxication. • At least one record of a phone call where the responder noted signs of sedation/intoxication and suspected opioids as the cause.
Suspicious health care utilization			
Cancels pain clinic visits/No show or no follow-up	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Characteristic associated with substance use	Webster, 2005 [1] Fleming, 2007 [4]	Medical record indicates one or more of the following: • At least one cancelled visit (not rescheduled). • At least one no-show visit. • At least one instance of no follow-up (e.g., a patient is instructed to return within 1

	disorder		month but does not return).
Excessive phone calls requesting opioids	Characteristic associated with opioid misuse status in retrospective medical record review study. Aberrant Drug Behavior criteria used in Prescription Opioid Therapy Questionnaire	Cheatle, 2013 [3] Chabal, 1997 [5] Jamison, 2010 [6]	Medical record indicates one or more of the following: • Phone calls requesting opioids. Number of phone calls identified will be recorded. • Notes indicating that the office believes that the number of contacts pertaining to the patient seeking opioids is excessive.
Excessive visits requesting opioids	Committee of the Seattle Veterans Affairs Medical Center consensus item validated in a pain clinic setting.	Chabal, 1997 [5]	Medical record indicates one or more of the following: • Visits where the patient requested opioids. Number of visits identified will be recorded. • Notes indicating that the office believes that the number of visits related to the patient seeking opioids is excessive.
Requested refills instead of clinic visit	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Characteristic associated with substance use disorder	Webster, 2005 [1] Fleming, 2007 [4]	Medical record indicates one or more of the following: • At least one instance where the patient asked for a refill instead of a visit. • At least one attempt to obtain a refill without a visit in phone log or administrative notes.

Reported lost or stolen prescriptions	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Characteristic associated with opioid misuse status in retrospective medical record review study. Aberrant Drug Behavior criteria used in Prescription Opioid Therapy Questionnaire	Webster, 2005 [1] Cheatle, 2013 [3] Jamison, 2010 [6]	Medical record indicates one or more of the following. <u>Each will be recorded separately.</u> • Patient states that the prescription for opioids was lost, misplaced, or inadvertently destroyed (e.g., spilled, thrown away, etc). • Patient states that the prescription for opioids was retrieved from the pharmacy by someone not authorized by the patient. • Patient states that the prescription for opioids was stolen either from the pharmacy or from the patient. • Patient reported never receiving filled prescriptions (e.g. mail order prescription).

Loses medications more than once	Item from a validated questionnaire that was positively associated with addiction status. Aberrant Drug Behavior criteria used in validation of the Opioid Risk Tool. Committee of the Seattle Veterans Affairs Medical Center consensus item validated in a pain clinic setting.	Compton, 1998 [7] Witkin, 2013 [2] Chabal, 1997 [5]	Provide a count of the number of instances where the patient's opioid prescription was lost, misplaced or inadvertently destroyed.
Requested early refills more than once from same provider	Item from a validated questionnaire that was positively associated with addiction status. Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Characteristic associated with substance use disorder	Compton, 1998 [7] Webster, 2005 [1] Fleming, 2007 [4]	Provide a count of the number of instances where the patient requested an early refill.

Was discharged from practice because of egregious aberrant behavior or placed on a watch list	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Aberrant Drug Behavior criteria used in validation of the Opioid Risk Tool.	Webster, 2005 [1] Witkin, 2013 [2]	Medical record indicates one or more of the following: • Practice has discontinued care of the patient due to violation of a Patient-Prescriber Agreement for their opioid medication; • Patient is under probation with the practice or dismissed due to suspected abuse, misuse, addiction or diversion of their opioid analgesics; • Patient is under probation with the practice or dismissed due to abusive behavior towards staff; • Patient is under probation with the practice or dismissed due to other behaviors where an explicit mention of opioids is noted in the medical record. • Engaged in violent or confrontational behavior that let to termination of care by the pain physician.
Resisted therapy changes/alternative	Aberrant behavior indicating abuse of	Webster, 2005 [1]	Medical record indicates one or more of the following. Each will be captured separately.

therapy	opioids used in validation of the Opioid Risk Tool. Characteristic associated with opioid misuse status in retrospective medical record review study. Aberrant Drug Behavior criteria used in Prescription Opioid Therapy Questionnaire	Cheatle, 2013 [3] Jamison, 2010 [6]	• Patient insisted on a particular formulation of opioid analgesic; ○ Insists on a specific product name; ○ Insists on non-abuse deterrent formulations; • Patient insisted on opioid therapy versus alternative pain management forms; • Patient was not compliant with non-opioid pain medication or therapy (e.g., did not follow up on physical therapy referral); • Patient resisted change in opioid product; • Patient resisted change to opioid dose; • Patient resisted change from opioid to non-opioid pain medication. • Reports a bad past experience or no relief by non-opioid or alternative products offered.
Patient has persistent/non-modifiable pain	Characteristic associated with substance use disorders.	Larson, 2007 [8] Liebschutz, 2010 [9] Potter, 2008 [10] Cheatle, 2014 [3]	Medical record indicates one or more of the following: • Pain scores or other markers of patient-reported pain do not change with treatment, time of day, or other factors. • Patient reports that nothing decreases their pain.
Multiple causes of pain are reported	Characteristic evaluated as a marker of abuse in a retrospective medical record review study.	Cheatle, 2014 [3]	Medical record indicates one or more of the following: • More than one painful condition; or • Multiple pain complaints requiring opioids (different pain sites/new injuries).

Third party required to manage patient's medications	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1]	Medical record indicates one or more of the following: • Patient is under the care of a conservator; • Patient is enrolled in a drug treatment program that manages their pain medication; • Pain medication is dispensed to the patient only through a third party (nurse, primary care aid, etc).
Sold prescription	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1]	Medical record indicates that patient sold a prescription/medication or solicited assistance in selling a prescription/medication, either by the patient's own admission, by the statement of a personal contact of the patient, or through records of legal action taken against the patient.
Inappropriate dose, source or route used			

Obtains opioids from a non-medical source	Item from a validated questionnaire that was positively associated with addiction status. Committee of the Seattle Veterans Affairs Medical Center consensus item validated in a pain clinic setting.	Compton, 1998 [7] Chabal, 1997 [5]	Medical record indicates that patient purchased opioids from a non-medical source (e.g., drug dealer, friend), either by the patient's own admission, by the statement of a personal contact of the patient, or through records of legal action taken against the patient.
Forged prescription	Item from a validated questionnaire that was positively associated with addiction status. Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Compton, 1998 [7] Webster, 2005 [1]	Medical record indicates that patient forged a prescription or solicited assistance in forging a prescription, either by the patient's own admission, by the statement of a personal contact of the patient, or through records of legal action taken against the patient.
Injected drug	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1]	Medical record indicates that patient injected opioids, either by the patient's own admission, by the statement of a personal contact of the patient.
Used additional opioids than those prescribed	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1]	Medical record indicates that patient acquired and used an opioid medication not prescribed by this healthcare provider, either by the patient's own admission or by the statement of a personal contact of the patient.

Unauthorized dose escalation	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Aberrant Drug Behavior criteria used in validation of the Opioid Risk Tool. Aberrant Drug Behavior criteria used in Prescription Opioid Therapy Questionnaire	Webster, 2005 [1] Witkin, 2013 [2] Jamison, 2010 [6]	Medical record indicates that patient has used more opioid than was prescribed, either by the patient's own admission or by the statement of a personal contact of the patient.
Emergency Room (ER) visits to get opioids	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Item from a validated	Webster, 2005 [1] Compton, 1998 [7] Cheatle, 2013 [3]	Medical record indicates: • Provide a count of the number of ER visits recorded where the patient requested treatment for pain. • Provide a count of the number of ER visits recorded where the patient requested

	questionnaire that was positively associated with addiction status. Characteristic evaluated (but not associated with misuse) in retrospective medical record review study. Committee of the Seattle Veterans Affairs Medical Center consensus item validated in a pain clinic setting. Aberrant Drug Behavior criteria used in Prescription Opioid Therapy Questionnaire	Chabal, 1997[5] Jamison, 2010 [6]	opioids. • Provide a count of the number of ER visits recorded where the patient requested opioids and there was reference to a primary care provider or pain specialist referring the patient to the ER.
Save/hoard unused medication	Item from a validated questionnaire that was positively associated with addiction status. Characteristic associated with substance use disorder.	Compton, 1998 [7] Fleming, 2007 [4]	Medical record indicates that patient has saved or hoarded unused opioid medications that were prescribed, either by the patient's own admission or by the statement of a personal contact of the patient.

Solicited opioids from other providers	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Committee of the Seattle Veterans Affairs Medical Center consensus item validated in a pain clinic setting.	Webster, 2005 [1] Chabal, 1997 [5]	Medical record indicates that patient has sought opioids from another provider, either by the patient's own admission, by the statement of a personal contact of the patient, or by records of communication between healthcare providers (discharge summary copied in the medical record, specialist visit notes, etc).
Explicit reference to abuse, misuse or addiction			
Abused prescribed drug	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool.	Webster, 2005 [1]	Medical record contains reference to opioid abuse, including: • Illegal use of the drug; • Use of more drug than prescribed for non-medicinal reasons; • Use of quantities or routes (e.g., injection, snorting) of the drug meant to enhance intoxication; • Explicit reference to "abuse"

Physician believes patient is addicted	Item from a validated questionnaire that was positively associated with addiction status.	Compton, 1998 [7]	Medical record states that either • The physician suspects opioid addiction • The physician has referred the patient for addiction treatment services • Physician describes impaired control over drug use, compulsive use, continued use despite harm, and craving
Patient believes patient is addicted	Item from a validated questionnaire that was positively associated with addiction status.	Compton, 1998 [7]	Medical record states that either • The patient suspects opioid addiction, and has shared this with the physician or staff • Patient reports impaired control over drug use, compulsive use, continued use despite harm, and craving
Family believes patient is addicted	Item from a validated questionnaire that was positively associated with addiction status.	Compton, 1998 [7]	Medical record states that either • The family suspects opioid addiction, and this has been shared via telephone or other communication • The family suspects opioid addiction as relayed to the healthcare provider by the patient. • Contacts report impaired control over drug use, compulsive use, continued use despite harm, and craving

Use opioids for purpose other than pain	Item from a validated questionnaire that was positively associated with addiction status. Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Characteristic associated with substance use disorder.	Compton, 1998 [7] Webster, 2005 [1] Fleming, 2007 [4]	Medical record indicates any of the following. Each will be recorded separately. • The patient requested/wanted opioids for anxiety; • The patient requested/wanted opioids for depression; • The patient requested/wanted opioids for sleep disturbances; • The patient was seeking euphoria or intoxication from opioids; or • The patient used opioids for a purpose other than pain.
Risk factors			
Spouse/significant other has a drug abuse problem	Item from a validated questionnaire that was positively associated with addiction status.	Compton, 1998 [7]	Medical record indicates: • The patient's spouse/significant other has a suspected or confirmed drug abuse problem; • The patient's spouse/significant other is seeking treatment for drug abuse.

Concurrent or history of substance abuse	Medical record review study showing that abuse history was associated with aberrant drug behavior.	Michna, 2004 [11]	Medical record indicates: • References to substance abuse either by the patient's own admission, by the statement of a personal contact of the patient, or by records of communication between healthcare providers • Physician recommendation for substance abuse treatment programs • Patient is enrolled in a substance abuse treatment program • Please record current substance abuse and history of substance abuse separately.
Concurrent or history of abuse of alcohol	Aberrant behavior indicating abuse of opioids used in validation of the Opioid Risk Tool. Item from a validated questionnaire that was positively associated with addiction status. Medical record review study showing that abuse history was associated with aberrant drug behavior.	Webster, 2005 [1] Compton, 1998 [7] Michna, 2004 [11]	Medical record indicates: • References to alcohol abuse either by the patient's own admission, by the statement of a personal contact of the patient, or by records of communication between healthcare providers • Physician recommendation for alcohol abuse treatment programs • Treatment with products used off-label for alcohol abuse (topiramate, etc) with explicit reference that the medication is given for alcohol abuse • Current alcohol abuse and history of alcohol abuse will be recorded separately.

Use of alcohol for pain management	Characteristic associated with substance use disorder.	Fleming, 2007 [4]	Medical record indicates one or more of the following. Each will be captured separately. • Patient used alcohol because of pain; or • Patient used alcohol and opioids together.

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