ER/LA Opioid Post-Marketing Requirement Studies:

Observational Study #2065-4A

Cross-sectional study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of abuse and/or addiction

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1. PROTOCOL SYNOPSIS FOR STUDY #2065-4A

Rationale	Conduct a study to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction.
Objectives	To accomplish the requirements set forth for post-marketing requirement (PMR) Study #2065-4, three complementary studies (4A, 4B, and 4C) whose objectives are to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction will be conducted. The primary study objectives for Study 4A 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 abuse/addiction, as defined by algorithms produced by PMR Study #2065-3B. (This entity, which will be a combination of codes available in health insurance databases, is referred to hereafter as algorithmically identified abuse and addiction [AIAA].) Secondary objectives are to: 1. Quantify how well patient characteristics correlate with AIAA among patients exhibiting doctor/pharmacy shopping behaviors. 2. Evaluate the contribution of identified doctor/pharmacy shopping behavior to the prediction of AIAA, after controlling for other patient characteristics.
Data source	Proprietary databases maintained and linked by IMS Health: 1. IMS® LRx, a longitudinal pharmacy database covering 86% of all retail dispensings in the United States (US). 2. PharMetrics Plus™, an insurance claims database that brings together pharmacy, provider, and facility claims and demographics from a number of US health plans with a total membership of approximately 75 million patients in 2013.
Design	Cross-sectional study of period prevalence over 18 months of observation
Population	Adult patients (18 years of age or older) with data in both IMS LRx and PharMetrics Plus, who also have a minimum of two dispensings for IR or ER/LA opioids or two or more diuretic dispensings. The first of these dispensings will have occurred in 2012 and an additional dispensing within 18 months after the first. Dispensings will be determined from the IMS LRx database.
Primary outcomes	1. Examination of candidate definitions of shopping behavior and covariates, and the relation between them.

	a. Numbers and proportions of patients with shopping behaviors under different definitions that incorporate characteristics of opioid dispensings. As a negative control, characterize dispensings of diuretics in the same manner and use this characterization to help create the lower two categories of opioid shopping behavior. The product will be a characterization of potential opioid shopping behavior into probably four categories with sufficient numbers for later analysis. b. Numbers and proportions of patients with different levels of patient characteristics and levels of health care utilization including age, sex, state of residence, concomitant pain and non-pain diagnoses, concomitant dispensing of other drugs, and categories of opioid dispensing (dose, quantity, intervals) that do not form part of the definition of shopping behavior. c. Examination of the degree to which shopping behavior is associated with the measures tabulated in 1b. 2. Relation of AIAA to shopping behavior and covariates a. The numbers and proportions of patients with AIAA in final categories of shopping behavior identified in 1a will be tabulated. b. The numbers and proportions of patients with AIAA at different levels of demographics, medical characteristics, and prescriptions claims characteristics that do not form part of the definition of shopping behavior will be tabulated. 3. Assessment of shopping behavior as an indicator of AIAA a. Sensitivity and predictive value of different levels of shopping behavior. Relative risk of AIAA for all categories against a common reference category consisting of non-shoppers (e.g., patients visiting one pharmacy and one prescriber practice). The c-statistic will be used to summarize discrimination. b. As in 3a, sensitivity and predictive value of patient characteristics (instead of shopping behavior) for AIAA, individually and combined by a logistic regression analysis. The c-statistic will be used for the most discriminative set of categories. c. For the different levels of shopping behavior characterized in 3a, relative risk for AIAA, adjusted by patient characteristics will be estimated from the odds ratio in a logistic regression that includes shopping behavior levels and the selected most discriminative characteristics drawn from demographics, medical characteristics and prescriptions claims characteristics. The change in c-statistic between composite analyses in 3b and 3c will be examined. 4. Ability of patient characteristics to indicate AIAA among patients exhibiting shopping behavior. The purpose is to verify that indicators of AIAA operate

	similarly among shoppers and in the general population. The final analysis identified in 3b above will be repeated among patients with shopping behavior. The sensitivity and predictive value of each of the patient characteristics and the risk and the relative risk for AIAA according to levels of the patient characteristics will be calculated. The relative risk analysis includes a multivariate combination of the patient characteristics. The degree to which this analysis validates doctor/pharmacy shopping behavior as suggestive of abuse/addiction will be taken from the extent of discrimination identified in analysis 3a. The usefulness of shopping behavior as a supplemental indicator of AIAA, beyond patient characteristics, will be examined in analysis 3c. In addition, analysis 4 will examine if certain patient characteristics other than shopping behavior make patients exhibiting shopping behavior more likely to have AIAA.
Final study and report dates	• Study Completion: 8/31/2016 • Final Report Date: 11/30/2016

2. RATIONALE

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, the FDA is requiring that ER/LA opioid analgesic drug sponsors conduct post-marketing studies to assess these risks. The four observational post-marketing requirement (PMR) studies are labeled Study #2065-1, Study #2065-2, Study #2065-3, and Study #2065-4.

The objective of PMR Study #2065-4 is to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction.

Study #2065-4 consists of three sub-studies, Study 4A, Study 4B, and Study 4C. In the current study (#2065 sub-study, Study 4A), the IMS® LRx database, a longitudinal pharmacy database that captures both third-party and self-pay transactions, will be linked to the PharMetrics Plus™ database, which contains provider, facility and pharmacy claims. From these databases, patients with shopping behavior will be identified and evaluated against an algorithm for abuse/addiction that will be developed and validated in PMR Study #2065-3B. Study #2065-3B will review the literature for health information suggestive of abuse/addiction in medical charts and medical claims. Then, through iterative processes that involve experts reviewing claims profiles and medical charts, text searches of medical records using natural language processing and supervised machine learning will identify and create a compilation of codes and health information with the best specificity and sensitivity to identify patients with opioid abuse/addiction. The compilation of codes and health information will be used to develop the algorithm that Study 4A will apply to define abuse/addiction. Restricting the validation of shopping behavior to only patients with diagnoses related to abuse would ignore the population with undiagnosed abuse. By supplementing ICD-9 codes with other information available on

claims (e.g., addiction treatments, emergency visits) to define abuse/addiction, the measurement bias will be decreased and the estimates of the association of shopping behavior with abuse/addiction will be more valid. Categories of doctor shopping will be derived from the population distributions of the multiple variables analyzed for opioid users. The 4 categories will range from no shopping behavior (lowest level) to extensive shopping behavior (most extreme). The specifics of how the categories will be defined will be driven by the data.

The second Study #2065-4 sub-study, Study 4B, will assess the association of shopping behavior with misuse and abuse by surveying patients within specific categories of shopping behaviors. The 4 categories of shopping behaviors identified and defined in Study 4A will be applied to Study 4B. Asking patients directly about their behaviors related to misuse and abuse will provide us with the patient's perspective that is missing in Study 4A. Surveying patients regarding misuse and abuse requires the use of an instrument that has undergone a validation process to ensure confidence that misuse and abuse are being measured. Study 4B will utilize the Prescription Opioid Misuse and Abuse Questionnaire (POMAQ) that will be validated in PMR Study #2065-2A.

The third Study #2065-4 sub-study, Study 4C, will assess the association of shopping behavior with misuse, abuse, and/or addiction by reviewing medical charts in a sample of patients within specific categories of shopping behaviors for behaviors suggestive of misuse, abuse, and/or addiction. The 4 categories of shopping behaviors identified and defined in Study 4A will be applied to Study 4C. Study 4C was designed to utilize an insurance/health plan database (HealthCore Integrated Research Database^{SM} [HIRD]) with access to medical records, to evaluate the association of potential definitions of doctor/pharmacy shopping and behaviors suggestive of misuse, abuse, and/or addiction.

Study 4B and Study 4C will be described in separate protocols.

When designing Study 4A, multiple data sources other than the IMS LRx database that also capture self-pay transactions were considered. Prescription Drug Monitoring Programs (PDMPs) are one of these. PDMPs are statewide electronic databases that collect data on opioid and other controlled substances dispensed in the state [1]. These programs are limited to single states and interstate sharing of data is not well developed. The organization and operation of PDMPs vary among states and each state determines which agency houses the program, and who may access the information [2]. To be able to determine the association between shopping behavior and misuse and abuse, such programs would need to be linked to a database that has access to medical records, has some degree of representativeness, and an adequate number of patients, which is not currently feasible. Study 4A was designed to use the IMS LRx database since this database captures self-pay transactions, is not limited by state boundaries and can be linked to medical diagnosis databases.

The state of residence of study patients will be identified through the IMS LRx database, and it will be determined if the state has an active PDMP, in order to assess whether doctor/pharmacy shopping is affected by the presence of a PDMP, and the analysis will be restricted or modified as necessary in light of this information.

2.1. Advantages of Complementary Studies

At present, there is no single model that adequately describes doctor shopping and its relation to abuse, misuse or addiction. The advantage of conducting three complementary studies is that

shopping behavior can be validated in different settings, and different dimensions of misuse, abuse, and/or addiction can be examined. Study 4A captures transactions across all payer types including self-pay, uses databases that contain numerous health plans across the United States (US) and measures abuse/addiction through diagnosis codes and other health information present in a claims database. While comprehensive, Study 4A does not capture the patient perspective. This is important as doctor shopping can reflect a clinical need based upon inadequate analgesia, so that gaining insights into the patient's motivation are important. Study 4B uses a patient survey to allow for an understanding of the patient perspective. Study 4C uses an insurance/health plan database that covers many states and measures behaviors suggestive of misuse, abuse, and/or addiction as described in the medical records.

In summary, the Study 4 program will provide a comprehensive understanding and validation of a unified definition of shopping behavior with three complementary studies that use a variety of sources of information including medical and pharmacy claims, patient's perspective and medical records to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction. Study 4A will provide a definition of shopping behavior that can discriminate between patients with and without abuse/addiction. Because of the large number of available patients, a comprehensive quantitative validation of shopping behavior and its association with abuse/addiction can be conducted. Studies 4B and 4C will complement Study 4A by providing a more qualitative evaluation and by assessing the association of shopping behavior not only with abuse/addiction but also with misuse and diversion.

Although Study 4A will use an algorithm to identify abuse/addiction that includes more than ICD-9 codes suggestive of abuse/addiction, the algorithm still will be based on claims data alone. Study 4B will ask patients why they visit more than 1 pharmacy or prescriber and therefore it will provide a better understanding of shopping behavior. Patients in Study 4B also will self-report misuse, abuse or diversion. Study 4C further complements Studies 4A and 4B because it assesses the medical records for behaviors suggestive of misuse, abuse and diversion and therefore, it does not rely on self report or on the use of diagnosis codes by clinical providers.

3. BACKGROUND

Shopping behavior

When the term is applied to drugs with potential for abuse, "doctor shopping" refers to a patient's practice of seeking prescriptions from multiple prescribers without their coordination or knowledge[3, 4]. Since it is not possible to assess patient intent or physician knowledge from insurance databases, the term "shopping behavior" as used in this study will refer to patterns of drug dispensing that are presumed to reflect a patient seeking multiple uncoordinated prescriptions for drugs with potential for abuse.

Previous work has shown that an operational definition of shopping behavior should incorporate both the number of overlapping prescriptions written by different prescribers and the number of pharmacies that fill those prescriptions[5]. In the same previous study, shopping behavior defined as groups of overlapping prescriptions written by different prescribers, filled at three or more pharmacies, clearly differentiated opioids from diuretics, a negative control[5].

Risk factors for shopping behavior are age (shopping behavior is much less common in patients 65 years or older than in younger patients) [6, 7], concurrent dispensings of benzodiazepine, and insurance claims diagnoses for mood disorders, back pain and abuse of non-opioid drugs.

Malignancy-related pain appears to be negatively correlated with shopping behavior[7]. Almost 20% of patients who met the above criteria for shopping behavior visited more than one state to obtain their prescriptions, whereas only 4% of non-shoppers did so[8]. Shoppers were more likely to pay fully on their own for prescription opioids than were non-shoppers (44% vs. 18% respectively)[6]. In this document, we refer to a patient's payment for a drug dispensing without using insurance as "self-pay." For the same phenomenon, the designation "cash" payment has also been used in the literature.

Shopping behavior is associated with opioid misuse and abuse[9]. Defined as overlapping prescriptions written by at least two prescribers and filled in at least three pharmacies, shopping behavior is ten times more likely to occur in patients with ICD-9 codes suggestive of opioid abuse than in patients without those codes (odds ratio 9.6; 95% confidence interval, 7.9-11.8)[7]. Shopping behavior so defined and defined with stricter criteria showed large declines after the introduction of a tamper-resistant formulation of extended-release oxycodone[10].

Detecting opioid abuse/misuse in insurance data

A recent study conducted by Group Heath Research Institute and Pfizer, presented at the 33rd American Pain Society Meeting[11] assessed clinician-recorded behaviors suggestive of misuse, abuse and overuse in medical records of patients receiving chronic opioid treatment and compared their prevalence with the presence of ICD-9 codes suggestive of opioid abuse. The sensitivity of ICD-9 codes for identifying clinician-labeled opioid abuse was 64% and the specificity was 95%. This low sensitivity of the ICD-9 codes would likely lead to an imprecise and possibly inaccurate estimate of the association between shopping behavior and opioid abuse. Therefore, to measure the association of shopping behavior with opioid abuse/addiction, the research described in PMR Study #2065-3B will be used to develop an algorithm to define abuse/addiction that will incorporate more information than just the ICD-9 codes suggestive of opioid abuse.

4. OBJECTIVES

The goal of PMR Study #2065-4 is to define and validate "doctor/pharmacy shopping" as outcomes suggestive of misuse, abuse and/or addiction.

The primary study objectives for Study 4A 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 ER/LA opioids.
2. For each candidate definition of doctor/pharmacy shopping, evaluate its association with abuse/addiction, as defined by algorithms produced by PMR Study #2065-3B. (This entity, which will be a combination of codes available in health insurance databases, is referred to hereafter as algorithmically identified abuse and addiction [AIAA].)

Secondary objectives are to:

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

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

5. DATA SOURCE

IMS Health's PharMetrics Plus, an insurance claims database, will provide the source population, characterized through demographic information and full insurance claims records including hospital discharge data. IMS Health's LRx is a longitudinal pharmacy database that will be used to identify all dispensings of drugs and to determine a number of key features of dispensings, as well as prescriber and patient characteristics.

5.1. IMS Health LRx Database

The IMS Health LRx database has information on 234 million patients and covers 86% of all retail dispensing in the US regardless of payment method (insurance or self-pay). IMS LRx includes prescription data from a variety of outpatient pharmacies – chains, food stores, mass merchandisers, and independent stores across the US. From each of the pharmacies in the panel, the database captures all dispensings, both in person and through the mail. This database distinguishes unique pharmacies, unique prescribers and unique practices ("practices" are professionally affiliated groups of prescribers; this information is available for about 45% of prescribers) and can capture records generated by patients who fill opioid prescriptions in more than one state.

The ability to capture self-pay and mail transactions and the lack of state boundaries are advantages of the IMS LRx database over state PDMP databases, which are limited to single states or limited to only the states that share information. Twenty percent of opioid shoppers visited more than one state [8].

IMS LRx's inclusion of prescriber practice groups enriches the possible definitions of shopping behavior. When different prescribers work together in a single practice, considering the prescribers as if they were administratively different entities could lead to the erroneous classification of doctor shopping behavior. The primary definitions of shopping will be based on practice rather than prescriber, and a sensitivity analysis will check the extent to which the study findings would differ in a purely prescriber-based analysis.

5.2. IMS Health PharMetrics Plus Database

The IMS Health PharMetrics Plus database holds pharmacy, provider and facility claims for approximately 75 million patients (in 2013) enrolled in US health plans. Ninety-seven percent of the patients are commercially insured, 2% of the patients have Medicare Advantage coverage, and 1% of the patients have Medicaid coverage. The health plans included have a wide geographic US representation (35% from the South, 27% from the Midwest, 23% from the East and 13% from the West). Rich historical data are available to 2006 and include a much larger number of patients ever insured. PharMetrics Plus also contains hospital discharge data and demographic information. All of these data have been cleaned, linked by patient, and formatted so as to facilitate population research. PharMetrics Plus has been widely used for pharmacoepidemiologic studies.

There are approximately 36 million patients linked between the LRx and PharMetrics Plus databases. This number represents 48% of the 75 million patients in PharMetrics Plus and 15%

of the 234 million patients in LRx. IMS Health estimates that there are approximately 700,000 patients who have at least two dispensings for IR or ER/LA opioids in the IMS LRx database and have claims in PharMetrics Plus in 2012. IMS Health has further indicated that about 54% of the members enrolled in plans contributing data to PharMetrics Plus in 2012 have mental health coverage. Restricting the analysis to patients with mental health coverage will ensure that all claims and dispensings possibly related to AIAA are captured.

5.3. IMS Health Formulary Impact Analyzer (sensitivity analyses only)

The Formulary Impact Analyzer (FIA) provides data on paid and unpaid claims by tracking adjudications between the retail pharmacy, payer, and patient at the point of sale. IMS's FIA suppliers report data for 58 million patients. There are two categories of reasons for which a claim might be unpaid: (1) Reversal – the payer may approve the claim, but the patient reverses it, as for example, if a patient finds the co-pay to be unacceptably high; and (2) Rejection – the claim is rejected by the payer. The patient may obtain the prescribed drug by paying in full out of pocket, or the patient may choose not to have the prescription filled.

Reasons for rejection are captured in nine different categories, including "Prior authorization required," "Plan limitations exceeded," "Refill too soon," "Refills not covered," "Product not covered" and mismatches between product and patient gender or age.

6. PROJECT AND DATA MANAGEMENT

World Health Information Science Consultants (WHISCON) will work with IMS Health to implement the protocol. WHISCON and IMS Health will together create the statistical analysis plan (SAP), detailing data extraction, formation of analytic data sets, and analytic procedures. WHISCON and IMS Health will conduct the protocol-specified analyses, as elaborated in the SAP. WHISCON will be responsible for identifying protocol changes that may be necessary, along with updates to the SAP, and WHISCON will be responsible for implementing notifications about changes in the SAP and for obtaining sponsor approvals for changes in the protocol and SAP. WHISCON will prepare the study report.

IMS Health will select the protocol-specified patients from the IMS LRx database and link these patients to the PharMetrics Plus database. IMS Health will implement the AIAA definitions and other covariate definitions as described here, and it will create analytic datasets at the subject level. Either IMS Health or WHISCON may undertake the protocol-specified analyses and such exploratory analyses as prove necessary to properly implement the protocol.

IMS Health and WHISCON (collectively) will maintain other study documents in a form suitable for sponsor and FDA audit. These include the protocol, SAP, raw study data, extraction and transformation programs, the resulting analytic data sets used to generate study reports, programming logs, meeting minutes and Standard Operating Procedures (SOPs).

The project team is highly experienced. IMS Health has conducted earlier studies of doctor shopping in the same databases that are being proposed for the current study[5, 6,7, 8]. WHISCON staff members have done earlier studies of prescription dispensing patterns[12, 13, 14, 15, 16]. WHISCON and IMS Health have collaborated on research projects, using data from both

PharMetrics Plus and the General Practice Research Database in the United Kingdom (UK)[17, 18, 19].

7. METHODS

7.1. Design

This is a cross-sectional analysis relating period-prevalence measures of doctor/pharmacy shopping and other patient characteristics to combinations of services and codes indicative of the presence of opioid abuse/addiction over 18 months of observation.

Previous work has shown that patients exposed to diuretics do not exhibit the patterns of shopping behavior identified in patients exposed to opioids[5]. Therefore, as a negative control, patients exposed to diuretics are included to avoid categorizing patients as opioid shoppers when the behavior of these so called "opioid shoppers" is usually observed in patients exposed to drugs that are unlikely to be abused.

7.2. Population

The study population consists of adult patients with data recorded in the PharMetrics Plus database for whom (1) a link can be established with IMS LRx and who have (2a) two or more IR or ER/LA opioid dispensings or (2b) two or more diuretic dispensings. The patients exposed to diuretics will be used as a negative control to help define the two lowest categories of opioid shopping behavior.

IMS Health will perform the linkage of the IMS LRx to PharMetrics Plus. The IMS algorithm examines 14 de-identified encrypted patient attributes collected from all IMS suppliers. These include gender, date of birth, last name, first name, address, city, state, zip code and payer identification. The algorithm identifies matching patients at 11 different hierarchical match levels and includes encrypted as well as non-encrypted patient information. The algorithm for identifying matched patients considers the completeness of the attributes as well as the number of levels on which patients match. Data fields with missing elements can be omitted at each match level so that patients with incomplete information can still be matched within the database based on those patient attributes that are present. IMS Health developed this deterministic approach to maintain a low rate of false positivity. By using the known information about the patient to determine matches, IMS Health's system is relatively robust to problems introduced by missing data, typographical data entry error, last name changes, change of patients' addresses and changes in patients' health insurance. Once a link has been established for a given patient, all data from LRx and Pharmetrics Plus for that patient will be included in the analyses. IMS Health estimates a false positive rate of 1-2% of the matched population and a false negative rate (persons who should be matched but are not) of approximately 3.5%.

The LRx data include self-pay transactions, which would not be recorded in PharMetrics Plus. LRx does not include information from non-participating pharmacies, which account for about 14% of US retail dispensings. (See Section 5.1)

The specific qualifications for individuals to enter the analysis will be:

- Linkage for that individual between IMS LRx and PharMetrics Plus
- All PharMetrics Plus non-opioid dispensings also captured in LRx

- Dispensing of an IR or ER/LA opioid or diuretic dispensing in 2012, as recorded in IMS LRx
- Patients aged 18 years or older on the date of first IR or ER/LA opioid or diuretic dispensing in 2012, as recorded in the IMS LRx database. (Shopping behavior is uncommon in patients younger than 18 years of age[8].)
- Dispensing of an additional IR or ER/LA opioid (for patients exposed to opioids) or diuretic dispensing (for patients exposed to diuretics) recorded in LRx within 548 days (18 months) of the first opioid or first diuretic, respectively, dispensed in 2012
- IMS LRx activity for at least one medication at least 12 months prior to the date of the first opioid or diuretic dispensing
- Enrollment in a health plan with mental health coverage contributing to the PharMetrics Plus database in 2012
- Presence in the PharMetrics Plus database for at least 18 months following first opioid dispensing in 2012 or presence in the database for a shorter period, but with an indication of death as the cause for leaving coverage. Possible indications include a hospital discharge with a disposition status of death and outpatient claims sequences indicative of likely death, including at least services associated with ICD-9 codes under the 798 section ("Sudden death, cause unknown"), not followed by provider or facility services on subsequent days.

The requirement for complete capture of PharMetrics Plus non-opioid dispensings in LRx provides assurance that all the pharmacies used by a patient whose data is recorded in PharMetrics Plus also contribute to LRx. If a patient sometimes used a pharmacy not in LRx, the measures of shopping behavior described below would be compromised by the lack of some data on pharmacies and on drug dispensing.

In order to assess whether the requirement for complete capture of PharMetrics Plus dispensings in the LRx data stream has a material effect on the results of this study, there will be a sensitivity analysis that employs a less demanding matching criterion. Persons for whom the capture of PharMetrics dispensings in LRx is less than 100%, but is 75% or greater will be identified. The shopping behavior categories into which these patients fall will be calculated on the basis of known drug dispensings, and the occurrence of AIAA will be tabulated by shopping behavior category in these people. See Section 7.13.

7.3. Patient Characteristics For Patients With Opioid Dispensings

For each patient in the study population with an opioid dispensing, characteristics will be ascertained in the following classes, using data available on the date of first IR or ER/LA opioid dispensing in 2012 and for the ensuing 18 months (548 days):

Demographics

- Age on the date of first IR or ER/LA opioid dispensing in 2012
- Sex
- State of residence at the time of the first IR or ER/LA opioid dispensing in 2012

- If the state of residence has an active PDMP at any time between the dates of the first and second opioid dispensing, and key characteristics of the PDMP, including at least year of first operation
- Types of payment for opioid dispensings (self-pay only, insurance exclusively from the patient's health plan participating in PharMetrics Plus, insurance from more than 1 insurer)

Medical characteristics in the 18 months following first IR or ER/LA opioid dispensing in 2012

- All outpatient diagnoses, coded at the 3-digit ICD-9 level
- All principal hospital discharge diagnoses, coded at the 3-digit ICD-9 level
- All non-principal hospital discharge diagnoses, coded at the 3-digit ICD-9 level

  Note that diagnostic codes will include ones of *a priori* special interest, including major depression, mood and anxiety disorders, abuse of non-opioid medications, and pain-related diagnoses such as arthritis, back pain, fractures, headache, malignancies, musculoskeletal pain, neuropathic pain, reproductive system pain, visceral pain, and wound/injury.

Prescription claims characteristics in the 18 months following first IR or ER/LA opioid dispensing in 2012

- All prescriber identifiers associated with opioid prescriptions
- All practice identifiers associated with opioid prescriptions (when a prescriber cannot be linked to a practice, the prescriber's identifier is substituted here, constituting in effect a single-prescriber practice)
- All drugs dispensed in IMS LRx or PharMetrics Plus, coded at a therapeutic class level (number of dispensings). Note that drugs dispensed will include other drugs of *a priori* special interest, including antidepressants, antipsychotics, hypnotics, anxiolytics and psycho-stimulants.
- Type of opioid (IR only, ER/LA only, IR and ER/LA)

Prescription claims and medical characteristics in the 12 months preceding first IR or ER/LA opioid dispensing in 2012

- Yes/no for IR or ER/LA opioids dispensings and for each class of drugs of *a priori* special interest in IMS LRx
- Diagnosis of opioid abuse using ICD-9 codes

7.4. Patient Characteristics For Patients With Diuretic Dispensings

For each patient in the study population with a diuretic dispensing, characteristics will be ascertained in the following classes, using data available on the date of first diuretic dispensing in 2012 and for the ensuing 18 months (548 days):

Demographics

- Age on the date of first diuretic dispensing in 2012

- Sex
- State of residence at the time of the first diuretic dispensing in 2012
- Types of payment for opioid dispensings (self-pay only, insurance exclusively from the patient's health plan participating in PharMetrics Plus, insurance from more than one insurer)

Prescription claims characteristics in the 18 months following first diuretic opioid dispensing in 2012

- All prescriber identifiers associated with diuretic prescriptions
- All practice identifiers associated with diuretic prescriptions (when a prescriber cannot be linked to a practice, the prescriber's identifier is substituted here, constituting in effect a single-prescriber practice)

7.5. Candidate Components of the Definition of Opioid Shopping Behavior

For each patient in the study population, characteristics of opioid dispensings in the 18 months following the first dispensing in 2012 will be examined.

A key element in previous definitions of doctor shopping has been the idea of overlapping days of sequential dispensings. The definition of "overlap" invokes the number of days of treatment actually listed in each dispensing record, with an overlap occurring when a new dispensing falls within the interval defined by a date of dispensing of an earlier dispensing as the starting point and the number of days' supply as the duration of the interval. The definition is purely administrative, and does not make any assumptions about the number of days of drug actually in the possession of the recipient at the time of the second dispensing.

Three different ways will be used to count variables: at least 1 day of overlap, at least10 days of overlap and no overlap of opioid dispensings. "No overlap" refers to multiple dispensings by same or different practices with no requirement for overlapping days. Overlap is defined as two or more dispensings of prescriptions written by different practices and active on the same day (i.e., a later dispensing occurred during the day's supply of an earlier dispensing). The overlapping dispensings can include the same or different opioids.

"No overlap" was chosen because counting pharmacies and prescribers is commonly used in the literature. Counting pharmacies and prescribers only when there are overlapping prescriptions written by different prescribers was considered because it is a stricter criterion and more likely to represent an unusual behavior. At least one day of overlap was chosen because it was part of a definition that distinguished the behavior of patients exposed to opioids from the behavior of patients exposed to diuretics [6]. In addition, at least 1 day of overlap was used in a definition of shopping behavior that has been associated with opioid abuse [7]. At least 10 days of overlap was chosen because it allows for circumstances such as when patients pick up a prescription before weekends or long holidays. Also, 57.5% of opioid prescriptions had days supply that range from 1 to 14 days. Shorter periods of time of overlap were not considered because previous research shows no difference between 1 day and 4 days of overlap [6].

- Number of distinct practices involved in opioid dispensings
- Number of distinct pharmacies involved in opioid dispensings

- Number of opioid dispensings
- Number of opioid prescriptions written by non-specialists (e.g., family medicine, internal medicine), emergency and urgent care physicians, orthopedic surgeons, other surgeons, oral surgeons and dentists
- Number of opioid dispensings that followed at least one earlier dispensing for which both the practices and pharmacies of the dispensings were not identical
- Number of times opioids were dispensed for self-payment without insurance
- Total morphine-equivalents in mg of opioids dispensed

7.6. Candidate Components of the Definition of Diuretic Shopping Behavior

The analysis of dispensings for diuretics will parallel that for opioids (see Section 7.9 below). For each patient in the study population, characteristics of diuretic dispensings in the 18 months following the first dispensing in 2012 will be examined. As with opioids, three different ways will be used to count variables: at least one day of overlap, at least ten days of overlap and no overlap of diuretic dispensings. The required components will be:

- Number of distinct practices involved in diuretic dispensings
- Number of distinct pharmacies involved in diuretic dispensings
- Number of diuretic dispensings
- Number of diuretic dispensings from prescriptions written by non-specialists (e.g., family medicine, internal medicine), emergency and urgent care physicians, orthopedic surgeons, other surgeons, oral surgeons and dentists
- Number of diuretic dispensings that followed at least one earlier dispensing for which both the practices and pharmacies of the dispensings were not identical
- Number of times diuretics were dispensed for self-payment without insurance

7.7. Outcome Variables

When the algorithm for identifying abuse and addiction (AIAA) becomes available from PMR Study #2065-3B, it will be implemented for each patient of the study population using data for 18 months (548 days) following the first dispensing in 2012. The algorithm may yield a single dichotomous variable, or it may be multileveled or multidimensional. The algorithm output will be attached to each patient record.

7.8. Comparators

Patients in the study population who do not qualify as exhibiting doctor/pharmacy shopping behavior will serve as the reference group for comparative analyses. The reference group will include patients who obtained dispensings from a single pharmacy under prescriptions from a single practice. Patients with low levels of shopping behavior, such as a single dispensing that overlaps with a prior dispensing from a different practice, may be added to the reference category if the occurrence of AIAA is similar to that of patients with no such overlapping dispensings.

7.9. Analysis

1. Examination of candidate definitions of opioid shopping behavior and covariates, and the relation between them.

The candidate definitions of opioid shopping behavior will be developed in a stepwise fashion, looking first at the distribution of the population across different candidate components of the definition and at the relations of candidate components to other characteristics derived from the insurance data such as demographics, medical characteristics and prescription claims characteristics. Finally the relations between the candidate components will be examined. As the example described below in analysis 1a illustrates, the definitions of shopping behavior are anticipated to be closely tied to definitions used in the preceding studies using the IMS LRx data[5,6,7,8].

a. Numbers and proportions of patients with shopping behaviors under different definitions that incorporate characteristics of dispensings.

    1. *Opioid dispensings.* The number of patients at each level of the different opioid dispensing measures listed in Section 7.5 will be tabulated, merging adjacent levels where the numbers are otherwise too small for useful analysis (e.g., fewer than 100 patients). Candidate components for which there is little or no variation in the study patients will be set aside at this stage. Cross-classifications of the opioid dispensing measures listed in Section 7.5 will be examined.
    2. *Diuretic dispensings as a negative control.* The number of patients at each level of the different diuretic dispensing measures listed in Section 7.6 will be tabulated, merging adjacent levels where the numbers are otherwise too small for useful analysis (e.g., fewer than 100 patients). Candidate components for which there is little or no variation in the study patients will be set aside as this stage. Cross-classifications of the diuretic dispensing measures listed in Section 7.6 will be examined.

    By inspection, we will merge adjacent categories of the cross-classified measures in opioid users. The product will be a characterization of potential opioid shopping behavior into probably four categories with sufficient numbers for later analysis. The intent will be to identify a most extreme composite category ("extensive") that contains about 10 percent of shoppers, a second level ("marked") that contains about 30 percent of shoppers, and a lowest level ("minimal") that contains the remaining 60 percent of shoppers. In addition, a large number of the opioid users will exhibit no shopping behavior at all.

    The categorization of the lowest levels of opioid shopping behavior ("no" and "minimal" shopping behavior) may be modified based on the distribution of the candidate components observed in the patients using diuretics. The opioid shopping behavior categories will be constructed so that almost all of the diuretic users would fall into the "no shopping behavior" category.

    After suitable exploration as outlined above, the categories might, for example, be defined by the set of variables with values "[N1, N2, N3]" where N1 is the number of practices involved in overlapping dispensings, N2 is the number of pharmacies involved,

and N3 is the total number of opioid dispensings. Note in this example that the categories are ordered and mutually exclusive, so that they can be combined into smaller numbers of categories or even a single, dichotomous indicator by combination.

No shopping behavior	[0, 0, 0];
Minimal shopping behavior	[2, 2, 2] ; [2, 2, 3]
Marked shopping behavior	Combinations not specified above or below
Extensive shopping behavior	[>3, >3, >3]

b. Numbers and proportions of patients with different levels of patient characteristics and levels of health care utilization as listed in Sections 7.3 and 7.4, including age, sex, state of residence, concomitant pain and non-pain diagnoses, concomitant dispensing of other drugs, and categories of opioid dispensing (dose, quantity, intervals) that do not form part of the definition of shopping behavior.

   This analysis will be identical in form to 1a, with the substitution of covariate levels for opioid dispensing (shopping behavior) categories.

c. Examination of the degree to which shopping behavior is associated with the measures tabulated in 1b.

   Tabulation of the distribution of shopping behaviors across the levels of each of the covariates, with suitable accounting for the number of dispensings. Further cross-classification of covariates will be guided by inspection and by multinomial logistic regression analysis with shopping behavior as the dependent variable and demographics, medical characteristics and prescriptions claims characteristics as independent variables.

2. Relation of AIAA to shopping behavior and covariates

   a. The numbers and proportions of patients with AIAA in final categories of shopping behavior identified in 1a will be tabulated.

   b. The numbers and proportions of patients with AIAA at different levels of demographics, medical characteristics, and prescriptions claims characteristics that do not form part of the definition of shopping behavior will be tabulated.

3. Assessment of shopping behavior as an indicator of AIAA

   a. Sensitivity and predictive value of different levels of shopping behavior. Relative risk of AIAA for all categories against a common reference category consisting of non-shoppers (e.g., patients visiting one pharmacy and one practice) both individually and in a common multivariate analysis by logistic regression with the unit of observation being the individual. AIAA (yes/no) will be the dependent variable. The c-statistic will be used to summarize discrimination.

   b. As in 3a, sensitivity and predictive value of patient characteristics (instead of shopping behavior) for AIAA, individually and combined by a logistic regression analysis. The c-statistic will be used for the most discriminative set of categories.

c. For the different levels of shopping behavior characterized in 3a, relative risks for AIAA adjusted by patient characteristics will be estimated from the odds ratios in a logistic regression that includes shopping behavior levels and the selected most discriminative characteristics drawn from demographics, medical characteristics and prescriptions claims characteristics. The change in c-statistic between composite analyses in 3b and 3c will be examined.

4. Ability of patient characteristics to indicate AIAA among patients exhibiting shopping behavior. The purpose is to verify that indicators of AIAA operate similarly among shoppers as in the general population of opioid users.

The final analysis identified in 3b above will be repeated among patients with shopping behavior. The sensitivity and predictive value of each of the patient characteristics and the risk and the relative risk for AIAA according to levels of the patient characteristics will be calculated. The relative risk analysis includes a multivariate combination of the patient characteristics.

In summary, the degree to which this analysis validates doctor/pharmacy shopping behavior as suggestive of abuse/addiction will be taken from the extent of discrimination identified in analysis 3a. The usefulness of shopping behavior as a supplemental indicator of AIAA, beyond patient characteristics, will be examined in analysis 3c. In addition, analysis 4 will examine if certain patient characteristics make patients exhibiting shopping behavior more likely to have AIAA.

If any of the AIAA events occurs in patients who are later censored because of death, we will note the follow-up time in such patients and the assigned shopping behavior category. We will describe the possible effects of misclassification resulting from the censoring.

7.10. Sensitivity Analysis for Physician/Practice Definitions

The following tabulations including all opioid dispensings will be performed:

- Cross-tabulation of the number of prescribers involved in opioid dispensings by the number of practices involved in opioid dispensings, stratified by the number of opioid dispensings.
- The excess count of prescribers resulting from the subtraction of the number of prescribers involved in opioid dispensings (for a given patient) minus the number of practices involved in opioid dispensings (for the same patient). Cross-tabulate by the number of opioid dispensings.

If the percentage excess count, defined as the total excess count of prescribers (above, summed over all study patients) divided by the total number of prescribers (also summed over all study patients) exceeds 0.1%, the analysis described in 3a will be repeated using the final shopping behavior measures defined on the basis of prescriber instead of practice.

7.11. Sensitivity Analysis for Impact of Rejected Claims

IMS Health estimates that the FIA, which tracks rejected pharmacy claims and reversals, will cover between 40 and 50 percent of the targeted patients in the PharMetrics Plus database. All patients in the study population for whom linkage to the FIA is possible will be identified. For each linked patient, the number of rejected claims for IR or ER/LA opioids in each available category will be identified.

Rejections and reversals will be cross-tabulated by the patients' identified shopping behavior categories. The purpose of this analysis is to determine whether rejected and reversed claims occur sufficiently often among persons with shopping behaviors as to consider incorporating them into the definition of shopping behavior, noting that an analysis on the fully linked data is likely to involve less than half as many people as the planned analysis, with corresponding loss of precision.

7.12. Sensitivity Analysis for the Impact of Self-Payment

In previous studies, persons exhibiting shopping behavior have sometimes obtained dispensings not paid for by their health insurance[6]. Use of the LRx database, which captures these self-paid as well as insurance-paid dispensings, will ensure that self-paid dispensings can be considered in the definition of shopping behavior. Despite their occurrence in the records of persons exhibiting shopping behavior, in the end self-paid dispensings may not enter into the final classification, as they may be highly correlated with other measures that define categories of shopping behavior.

As a sensitivity analysis, if self-paid dispensings enter into the final classification scheme, we will reclassify shopping behavior using the algorithm defined above, but after suppressing all dispensings not appearing in the insurance records, and we will cross-classify shopping behavior using the reduced data against shopping behavior defined using the full data. If more than 1% of all opioid-using patients change their classification status, we will repeat the analysis of Section 7.9.1.a, omitting dispensings not appearing in the insurance record.

7.13. Sensitivity Analysis for Imperfect Capture of Dispensings in LRx

As described in Section 7.2, there will be special treatment for patients whose LRx identity matches an identity in PharMetrics Plus, and whose LRx files capture less than 100% but at least 75% of their recorded PharMetrics Plus dispensings. These patients were set aside from the main analysis, because they are persons who appear to have used a pharmacy that did not contribute to LRx for at least some part of the study period. The concern is that those non-contributing pharmacies would provide no information to the classification of shopping behavior. Any resulting misclassification would be in the direction of reducing the apparent shopping behavior. With possibly high-risk shoppers incorrectly classed as low-risk non-shoppers, the risk gradient between persons in the lower and higher shopping categories would be attenuated.

In order to assess how a less stringent criterion of 75% capture of PharMetrics Plus dispensings in LRx might affect study results, the sensitivity analysis will apply the final shopping behavior categories to the additional persons identified by the 75% criterion, and will repeat in this

additional group the analysis of 7.9.2.a, which tabulates the number of AIAA events in each of the final shopping behavior categories.

8. LIMITATIONS

- The IMS LRx database uses an algorithm for which there are no published validation data. We are therefore requiring that all PharMetrics Plus dispensings for a cohort member have an exact match in the IMS LRx. This is a strong assurance of the validity of the linkage of individuals, as it is very unlikely that different individuals linked in error could have multiple dispensings of exactly the same products on exactly the same days.
- Two factors may have modified shopping behavior during the study period. The first is insurers' implementation of restrictions on opioid use, and the second is the institution of state-specific PDMPs. Rejected pharmacy claims will be considered in a sensitivity analysis. Major differences in shopping behavior will be examined across states. If there are pharmacy-specific policies that limit dispensings, the effect may be to modify apparent shopping behavior.
- This study relies on the portability of the AIAA algorithm between the research setting in which it was developed (Study #2065-3B) and the PharMetrics Plus database. This assumption is not testable in the current study and the number of patients who will be identified as having AIAA is unknown.
- The study was based on patients with commercial health insurance and may not be informative about segments of the US population with other forms of insurance or with no insurance at all.

9. OFFSETTING STRENGTHS

- The IMS LRx database has a large number of patients, an ample coverage of retail pharmacies (86%) and captures self-pay transactions not visible to third party payers. Patients can be followed through different pharmacies and different states (contrary to PDMPs that are state specific), and can be linked to medical diagnosis databases to capture health information data.
- The study will utilize a validated algorithm to identify patients with abuse/addiction that incorporates multiple data elements from claims in addition to ICD-9 codes.

10. HUMAN SUBJECTS

Only primary data holders and their business associates perform record linkages. Parts of the analytic data form a limited dataset, and are subject to Health Insurance Portability and Accountability Act (HIPAA) rules concerning protection. Institutional Review Board (IRB) and Privacy Board approval are not required for data use.

11. ADVERSE EVENT REPORTING

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (i.e. identify a potential causal association between) a particular product and medical event for any individual. Thus, the *minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available* and adverse events are not reportable as individual AE reports.

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