Comparative Effectiveness of Two State Payer Strategies to Prevent Unsafe Opioid Prescribing

(PCORI UOP-2017C2-8509)

Study Protocol

November 1, 2022

1. Background

Use and misuse of opioids is now recognized as a major U.S. public health problem, leading to significant morbidity and mortality. While most acute pain episodes (0-6 weeks) resolve, some go on to subacute pain (6-12 weeks), and a minority of individuals develop chronic pain (> 3 months). Musculoskeletal (MSK) conditions were among the top 5 conditions contributing to years lived with disability (YLD) in the U.S. between 1990 and 2010. Common MSK conditions are accounting for an increasingly large fraction of long-term work disability in the U.S. Importantly, these are also the patients who have received disproportionate amounts of chronic opioids, accounting for the largest relative costs to Medicare. Prescribing of both opioids and concurrent sedative-hypnotics for acute and chronic MSK pain increased dramatically from 2001 to 2010.

The body of evidence to date suggests that, among individuals with non-cancer pain: (1) even short-term opioid use early after injury is associated with greater risk of long-term opioid use and disability; (2) opioid use poses risks of serious harms, including overdose death, particularly when prescribed at high doses and/or concurrently with sedative-hypnotic medications; and (3) evidence is lacking concerning effectiveness of long-term opioid therapy for chronic pain. The clearest path to preventing transition to chronic opioid use and associated morbidity or addiction is to reduce unnecessary prescribing during the acute and subacute phases of pain.

Both prior authorization (PA) and other insurer-based drug utilization programs are increasingly being used in an attempt to stem the tide of the opioid epidemic and to reduce unsafe opioid prescribing. Review programs have proven effective in decreasing use and overall costs of more expensive medications. This study focuses on two states, Washington (WA) and Ohio (OH), which have witnessed the devastating consequences of the growing opioid crisis. WA was an early leader in state efforts to combat the opioid crisis; OH's efforts have come more recently. WA and OH offer a unique opportunity to study opioid prescribing interventions because both states have regulatory authority over health care delivery to all injured workers, and are the two largest states with a population-based exclusive State Fund. Further, both states have initiated distinct prescribing guideline-concordant opioid review programs (ORPs), allowing for a unique natural experiment to compare the effectiveness of two substantially different approaches to reducing unsafe opioid prescribing.

2. Research Objectives

Specific aim 1. Examine the comparative effectiveness of prospective prior authorization (PA) with hard stops in WA versus retrospective review (RR) with prescriber notification in OH in reducing unsafe opioid prescribing.
Hypothesis 1. Prospective PA with hard stops (WA) will be associated with statistically significantly less unsafe opioid prescribing compared to RR and prescriber notification (OH).

Specific aim 2. Examine the comparative effectiveness of WA's PA program versus OH's RR program with regard to patient reported outcomes (pain, function, quality of life, return to work), harms (presence of opioid use disorder, opioid poisoning events) and work disability outcomes at 6 weeks, 6 months, and 12 months from date of injury.
Hypothesis 2. Prospective PA with hard stops (WA) will be associated with statistically significantly improved patient outcomes compared to RR and prescriber notification (OH).

Specific aim 2A. For injured workers in WA, examine unsafe opioid prescribing and patient-reported

outcomes and work disability at 6 and 12 months for patients receiving an established, coordinated, stepped care management program during the first 12 weeks following injury plus prospective PA versus patients receiving usual care subject to PA only.
Hypothesis 2A. Specialized care delivered through a stepped care management program plus prospective PA will be associated with statistically significantly lower rates of unsafe opioid prescribing and improved patient outcomes compared to patients receiving usual care and PA only.

Specific aim 3. Using qualitative methods, identify key environmental, programmatic and policy factors that influenced the design, implementation and impact of the PA program in WA and the RR program in OH. This information will lead to the development of an Opioid Review Tool educational module for dissemination to both public and private payers.

3. Study Design

Study type: Observational cohort study, with prospective and retrospective components. Aims 1 and 2 rely primarily on administrative data for a prospective cohort, with longitudinal surveys conducted among a subset of the cohort. Aim 1 also includes a retrospective time series analysis. Aim 3 relies on qualitative research, including individual in-depth interviews and key informant interviews.

4. Study Population and Sample

Study Population and Setting

Workers' Compensation (WC). WC provides no-fault industrial insurance coverage for most employers and workers in WA and OH. Benefits include medical treatment for workers who are injured or develop an occupational disease as a result of their work activities. Workers with an accepted WC claim may be eligible for partial wage replacement benefits (time loss) after 3 lost work days in WA and after 7 lost work days in OH. WA and OH are the largest 2 of only 4 states that have an exclusive State Fund—no private WC insurance companies operate in these states, which makes them particularly well-suited to population-based research. WC covers >97% of jobs covered by unemployment insurance in both states, and the share of all WC benefits paid by the two State Funds (vs. self-insurance) are very similar; 82% for OH and 78% for WA. The populations covered by the WA and OH WC programs are representative of gender, age, race, and ethnicity in the working populations in the two states.

WA Department of Labor and Industries (DLI). The DLI State Fund provides WC insurance for over 2/3 of workers in WA (the remainder work for large self-insured companies and will be excluded due to insufficient available data). Roughly 93,000 State Fund WC claims are accepted annually. Of these, almost 20% involve time loss benefits. Of all accepted WC claims, 32% are women and 68% are men. Overall, about 21% are ≤ 24 years old at injury, 27% are 25 to 34, 24% are 35 to 44, 19% are 45 to 54, and 9% are 55 or older. Race and ethnicity are not recorded; however, in our prior research, approximately 70% of workers were white, 16% were Latino, and 13% reported other racial or ethnic backgrounds. In WA in 2016, there were over 11,000 workers with opioid prescriptions in the first 6 weeks after injury.

OH Bureau of Workers' Compensation (BWC). The BWC is the largest state-fund insurance system in the U.S. and one of the top 10 largest underwriters of WC insurance in the nation, insuring about 60% of OH's workforce. The volume of injured workers in OH is quite similar to WA. The BWC State Fund has about 90,000 accepted claims per year, and about 12% involve time loss benefits. Overall, 36% are

women and 64% are men. About 15% are ≤ 24 years old at time of injury, 23% are 25 to 34, 20% are 35 to 44, 22% are 45 to 54 and 20% are 55 or older. The BWC does not collect data on race or ethnicity. In the BWC State Fund, there is an approximate annual prevalence of 20,000 opioid users.

Inclusion Criteria

Aims 1 & 2. Injured workers in OH and WA who (1) file a new accepted State Fund claim, and (2) fill at least one opioid prescription, paid for by WC, during the first 6 weeks after date of injury. The denominator for both time series described in the Analytical Methods section (Aim 1. Analysis Topic A) has the same inclusion criteria, except that criterion (2) does not apply. The same criteria—including criterion (2)—apply to the numerator for the first time series. The numerator for the second time series described is similar, except that criterion (2) is instead the presence of unsafe opioid prescribing during the subacute phase (6-12 weeks).

Aim 3 key informants. Policy makers and stakeholders who were involved in the creation and implementation of the WA or OH ORP.

Aim 3 provider in-depth interviews. Providers that had at least one patient whose opioid prescription paid for through WC had been reviewed in accordance with the state's ORP.

Aim 3 patient in-depth interviews. Patients who had an opioid prescription for at least 6 weeks paid for by WC or whose prescription payments have been reviewed in accordance with the state's ORP.

Exclusion Criteria

Aims 1, 2, & 3 (patient in-depth interviews only). Injured workers who are under 18 years of age.

Aims 1 & 2. Current cancer diagnosis and (for surveys only) non-English or -Spanish speakers, physically or mentally incapable of completing the survey, incarcerated, or deceased.

Aim 3. Non-English speakers.

Number of Study Groups/Cohorts

The primary analysis involves 2 groups/cohorts of injured workers, 1 from WA and 1 from OH. Secondary analyses involve two subgroups of injured workers within WA, defined by whether the injured worker's attending provider participates in Centers of Occupational Health and Education (COHE) care delivery.

Enrollment/Sample Size

Aims 1 & 2. The time series for Aim 1 will be based on data for all injured workers in OH and WA who file a new State Fund claim from January 1, 2010 through December 31, 2020. For the prospective cohort analysis, we anticipate including 4,636 eligible workers in WA and 779 in OH for a one-year cohort. Using WC claims, pharmacy billing data, and potentially prescription drug monitoring program (PDMP) data from each state, we will track opioid prescribing for each injured worker for a full year after date of injury. The worker survey will largely be drawn from this cohort, depending on the length of time needed to conduct an adequate number of surveys. All workers will be interviewed initially at 4-6 weeks

after injury (baseline). Workers who complete the baseline survey in the first year of recruitment will be asked to complete follow-up surveys at 6- and 12-months after injury. Workers who complete the baseline survey after the first year of recruitment will be asked to *only* do the 6-month follow-up survey due to time constraints. We anticipate that roughly 3,120 workers in WA and 525 workers in OH will complete baseline surveys. We anticipate roughly 1,700 completed 12-month outcome surveys from WA and 234 from OH.

Aim 3 key informants. No more than 12 interviews in WA, supplemented with policy documents to add detail. In OH, we will start with policy documents and use key informant interviews with individuals outside of BWC to complement and supplement the historical account.

Aim 3 individual in-depth interviews. We will conduct 20-30 patient interviews and approximately 10 provider interviews in each state.

Sampling Method

Aims 1 & 2. Consecutive sampling. The entire eligible one-year cohort will be used for analyses based on administrative data, and consecutive sampling will be used to enroll survey participants from that cohort until target enrollment numbers are reached.

Aim 3 key informants. Purposive and snowball sampling. Potential key informants will be identified and invited to participate based on specific characteristics. Snowball sampling from these initial interviews will allow us to expand the sample until the body of interview data achieves theoretical saturation in each state.

Aim 3 individual in-depth interviews. Purposive and quota sampling. Potential interview participants will be identified and invited to participate based on specified characteristics until the body of interview data achieves theoretical saturation in each state. For provider interviews, we will also ask interviewed providers to recommend peers with experience prescribing opioids for WC patients (snowball sampling).

5. Exposures

The primary exposures of interest are the WC-based opioid review programs (ORPs) in each state: (1) prospective prior authorization (PA) with hard stops in WA, and (2) retrospective review (RR) with prescriber notification in OH. Secondarily, the COHE program is an exposure of interest, within WA only.

WA opioid review. Under WA regulatory procedures, payment for any opioid prescription billed beyond six weeks after the injury is denied unless the prescriber has submitted a checklist attesting to completion of all best practices from the regulations/guidelines. For example, the provider must document clinically meaningful improvement in pain and function during acute use. Thus, the WA intervention is prospective and includes a "hard stop" subject to an insurer's decision based on regulatory authority.

OH opioid review. The OH regulations are similar to those in WA regarding best practices, but differ in approach. Rather than a "hard stop" on opioid prescription payments, an automated report identifies new opioid prescriptions beyond the acute phase. OH WC pharmacy and clinical staff review the medical record at 12 weeks to determine whether best practices were met. If not, the prescriber is notified via letter, and cases are reviewed again at 16 weeks. If best practices have still not been met, the prescriber

and worker are notified via letter that opioid coverage will end in 4 weeks. The OH program relies on retrospective chart review and communication of best practices to prescribers.

Centers of Occupational Health and Education (COHE) care delivery, in WA. The focus of the COHEs is to deliver occupational health best practices during the first 12 weeks after injury, during the transition from acute/subacute to chronic pain. The COHE delivery system has been developed over the past decade, and now approximately 50% of workers in WA receive care under these innovative arrangements. Critical elements of the COHE model include organizing care delivery on a population basis, high level executive health system support, ongoing care coordination by health service coordinators (HSCs), and stepped care management. Specific best practices include screening for psychosocial barriers to recovery using the validated Functional Recovery Questionnaire (FRQ); initiation of graded exercise; education regarding psychosocial barriers to recovery; and, more recently, a brief series of cognitive behavioral and reactivation techniques, i.e., activity coaching. COHE is a health care systems intervention, rather than a specific health care service or menu of services, that is primarily focused on improving the coordination of care at the health care community level, as well as with DLI. The COHE model consists of enhanced provider education regarding occupational health best practices and stepped-care features. Both usual care and COHE-based care in the WA workers' compensation (WC) system include the typical mix of health care services delivered for work-related injuries in Washington State, such as chiropractic care, physical therapy, evidence-based imaging services, and guideline-concordant surgery.

Enhanced Care Program (ECP), in OH. Although OH has no program entirely comparable to COHE, the OH BWC did initiate the ECP as a pilot program in 2016, to assess the effect of improving care coordination and treatment planning for injured workers with knee sprains. The pilot was established in selected counties in northeast Ohio. Providers participate on a voluntary basis and agree to use a new treatment planning form for injured workers with knee sprains and to coordinate care for those needing referral for physical therapy or specialty care. Participating providers receive 15% added payment for evaluation and management visits. The pilot is being extended during the next two years throughout OH but will remain limited to injured workers with knee sprains.

6. Outcomes

The primary outcome measure, unsafe opioid prescribing, will be measured as shown in Table 1 using pharmacy billing data from OH and WA, and validated using state PDMP data. Table 2 presents secondary outcome measures, and Table 3 presents exploratory/other outcome measures.

Table 1. Primary Outcome Measures

Title	Description	Timeframe (after injury)
Unsafe opioid prescribing (subacute phase): Days supply	>7 days supply	6-12 weeks
Unsafe opioid prescribing (chronic phase): Chronic	≥60 days supply	3-6, 6-9, and 9-12 months
Unsafe opioid prescribing (chronic phase): Concurrent	Concurrent sedatives/hypnotics	3-6, 6-9, and 9-12 months
Unsafe opioid prescribing (chronic phase): High dose	≥50 MED/day	3-6, 6-9, and 9-12 months
Unsafe opioid prescribing (chronic phase): Composite	Meeting ≥1 of the 3 chronic-phase metrics	3-6, 6-9, and 9-12 months

MED, morphine equivalent dose.

Table 2. Secondary Outcome Measures			
Title	**Data Source**	**Description**	**Timeframe (after injury)**
Pain intensity	Survey	PEG-3 Scale	6 weeks, 6 months, 12 months
Physical function/pain interference	Survey	PEG-3 Scale	6 weeks, 6 months, 12 months
Emotional functioning-Anxiety	Survey	PHQ-4 (Patient Health Questionnaire for anxiety and depression)	6 weeks, 6 months, 12 months
Emotional functioning-Mood	Survey	PHQ-4 (Patient Health Questionnaire for anxiety and depression)	6 weeks, 6 months, 12 months
Global improvement	Survey	Patient Global Impression of Change scale	6 months, 12 months
Disability	Survey	Does health now limit activities during a typical day	6 months, 12 months
Quality of life	Survey	EQ-5D-5L (EuroQoL-5 dimensions)	6 weeks, 6 months, 12 months
Patient experience with opioid review procedures	Survey	Patient experience with opioid review procedures	6 months, 12 months
Perceived outcomes of insurer decisions from patient's perspective	Survey	Perceived outcomes of insurer decisions from patient's perspective	6 months, 12 months
Overall patient satisfaction	Survey	Overall patient satisfaction	6 weeks, 6 months, 12 months
Satisfaction with pain-related treatment	Survey	Satisfaction with pain-related treatment	6 weeks, 6 months, 12 months
Working full-time, part-time or not working	Survey	Working full-time, part-time or not working	6 weeks, 6 months, 12 months
Are wages more, less or about the same as before injury	Survey	Are wages more, less or about the same as before injury	6 weeks, 6 months, 12 months
Work status	WC claims data	Proxy: compensated time loss	6 weeks, 6 months, 12 months
Opioid poisoning events	WC billing data	ICD-10-CM codes	12 months

WC, workers' compensation.

Table 3. Exploratory/Other Outcome Measures			
Title	**Data Source**	**Description**	**Timeframe (after injury)**
Opioid use disorder	Survey	TAPS (The Tobacco, Alcohol, Prescription medications, and other Substance Tool) – opiate pain reliever subset	12 months

7. Analytical Methods: Quantitative Analyses

Note: Because this is an observational study, and because we must submit this study protocol before Ohio data are made available, much of this plan is tentative. Updates will be made once more is known regarding the availability, completeness, and cross-state comparability of various data fields, data definitions, data generating processes, and procedures. A summary of the various planned analyses is provided in Table 4, followed by further detail regarding each analysis.

Table 4. Summary of Quantitative Data Analyses

Aim	Analysis Topic	Analytic Approach	Outcome	Sample
1	A. Compare long-term prescribing patterns across states and identify discontinuities	Time series/ITSA	Any opioid prescription (acute) Unsafe opioid prescribing (subacute)	OH/WA 2010-2020
1	B. PA vs RR	GEE/propensity score & subgroup analysis	Unsafe opioid prescribing	OH/WA cohorts
1	C. PA vs RR	GEE/propensity score	Unsafe opioid prescribing	OH/WA survey samples
1	D. Prescribing data validation	Compare WC billing data with PDMP data	Unsafe opioid prescribing	OH/WA cohorts
1	E. Frequency/outcomes of opioid review decisions	Descriptives (N/percent that are/are not authorized)	Opioid review decisions	OH/WA cohorts
1	F. Subgroup response to opioid review decisions	Subgroup analysis using PDMP data	Opioids obtained from different prescriber or different payer	OH/WA cohorts
1	G. Describe usual care	Descriptives (rates)	Health care utilization	OH/WA cohorts
2	H. PA vs RR	GEE/propensity score & subgroup analysis	Secondary outcomes	OH/WA survey samples
2A	I. COHE vs non-COHE	GEE/propensity score & subgroup analysis	Unsafe opioid prescribing	WA cohort & survey sample
2A	J. COHE vs non-COHE	GEE/propensity score & subgroup analysis	Secondary outcomes	WA survey sample

Admin, administrative data; COHE, Centers of Occupational Health and Education; GEE, generalized estimating equations; ITSA, interrupted time series analysis; OH, Ohio; PA, prior authorization; RR, retrospective review; WA, Washington.

Aim 1

Specific aim 1*. Examine the comparative effectiveness of prospective prior authorization (PA) with hard stops in WA versus retrospective review (RR) with prescriber notification in OH in reducing unsafe opioid prescribing.*

Hypothesis 1. *Prospective PA with hard stops (WA) will be associated with statistically significantly less unsafe opioid prescribing compared to RR and prescriber notification (OH).* ***[See Analysis Topic B]***

Aim 1. Analysis Topic A: Compare long-term prescribing patterns across states and identify discontinuities

This analysis will be based on a time series approach. We will construct data points for each month from January 1, 2010 through December 31, 2020. For each state, we will construct two separate time series. The first is the proportion of WC claims with any opioid prescription in the acute phase (0-6 weeks). The second is the proportion of WC claims with unsafe opioid prescribing (defined earlier) during the subacute phase (6-12 weeks). For each, calendar month denominators for the time series will be assigned based on date of injury, and numerators will be calculated for each one-month set of claims using the pharmacy billing data for up to three months after date of injury.

The resulting four time series will be inspected to identify secular trends and discontinuities/unexpected changes that might indicate a policy or regulatory action, or an external factor that might have affected opioid prescribing pattern. A timeline of opioid-related policy events affecting WA and/or OH (e.g., legislation, regulations, guidelines, large-scale interventions) will be constructed and overlaid on these time series to assess patterns and potential confounding related to the state-based environments. As part of Aim 3 (described below), qualitative methods will be used to understand the causes of unexplained fluctuations.

Finally, we will test whether implementation of the WA PA program (implemented in July 2013) or the OH RR program (implemented in March 2019) was associated with a statistically significant reduction in the rate of unsafe opioid prescribing using standard interrupted time series analysis (ITSA) techniques.[1,2]

Aim 1. Analysis Topic B: Compare PA to RR with respect to unsafe opioid prescribing

This analysis is focused on the primary outcome for this study, unsafe opioid prescribing (defined earlier), using administrative data for the full WA and OH cohorts. We are planning for a one-year prospective timeframe, beginning July 2019 (based on dates of injury). Our cohort size estimates are 4,636 eligible workers in WA and 779 in OH .

Using WC claims and billing data from each state, we will track opioid prescribing for each injured worker for a full year after date of injury in order to test Hypothesis 1: Prospective PA with hard stops (WA) will be associated with statistically significantly less unsafe opioid prescribing compared to RR and prescriber notification (OH).

The primary outcome is the composite unsafe prescribing measure (i.e., meeting one or more of the 3 chronic-phase criteria in Table 1), modeled longitudinally over the three 3-month time windows, in order to assess the comparative effectiveness of PA/RR on the transition from early opioid therapy to longer-term unsafe opioid prescribing. Generalized estimating equations (GEE) panel models will be used to account for outcomes being measured during several time windows within individual patients.[3]

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[1] Linden, A. (2015). Conducting interrupted time series analysis for single and multiple group comparisons. *The Stata Journal, 15*(2), 480-500.

[2] Penfold, R. B., & Zhang, F. (2013). Use of interrupted time series analysis in evaluating health care quality improvements. Acad Pediatr, 13(6 Suppl), S38-44.

[3] Aloisio, K. M., Swanson, S. A., Micali, N., Field, A., & Horton, N. J. (2014). Analysis of partially observed clustered data using generalized estimating equations and multiple imputation. Stata J, 14(4), 863-883.

The working correlation structure will be specified as exchangeable (this may be adjusted later in the Statistical Analysis Plan), and robust variance estimates will be used. (Though using the wrong correlation structure can be inefficient, GEE is not highly sensitive to using the wrong correlation structure, as long as there are at least 100 patient clusters and robust variance estimates are used—we expect to have over 3,000 patient clusters.)

The primary predictor is binary (1 for WA cases, 0 for OH cases). The GEE logit link function will be used to test the Aim 1 hypothesis, with unsafe opioid prescribing specified as a binary dependent variable in each time window. These regression models will provide an estimate of the odds of unsafe opioid prescribing in WA compared to OH, controlling for baseline differences in the two groups. The subacute phase measure, and also each individual component of the composite measure (i.e., chronic use, concurrent sedatives, high dose), will also be tested as distinct outcomes, which will provide information on potential variation in mechanisms and timing of ORP effect across WA and OH. Time will be included in the models (assigning an indicator for quarter since the date of injury; 0, 1, 2, 3), and interacted with state in order to assess (1) change in unsafe opioid prescribing over time and (2) differences in such change by state.

Covariates will be reassessed after more information is available regarding the availability, completeness, and cross-state comparability of various data fields in the OH data. Our initial plan is to include the following covariates for this analysis topic:

- Age
- Gender
- Pre-injury wage
- Marital status
- Number of dependent children
- Injury type
- Occupation
- Industry
- Rural/urban residence
- Provider type, specialty, and COHE or ECP affiliation
- Functional Comorbidity Index (FCI) and cancer diagnosis, based on WC billing data
- PDMP data, if available (see Analysis Topic D), will be used to control for opioid prescriptions in the 3 months prior to injury
- As-yet undetermined utilization-based variables that may help adjust for injury severity and treatment intensity (e.g., hospitalizations, number of emergency department visits in the first 6 weeks, number of provider visits, time until first opioid prescription, presence and timing of physical therapy, imaging, surgery, etc.)
- COHE and/or ECP participation may be included as an additional covariate, depending on findings from exploratory stratified analyses by COHE/ECP participation. We expect small numbers of ECP claims relative to COHE, and have no advance information on relative effect size.

The limited number of independent variables facilitates their full inclusion in the causal model, and restricts the value of propensity score techniques for this analysis topic. However, a propensity score predicting state jurisdiction (WA versus OH) will be calculated for each patient, and propensity score techniques will be used to construct comparable WA and OH samples by restricting cases to the region of common support (i.e., propensity score ranges for WA and OH will be compared, and cases above or below the overlapping range will be excluded). This approach should improve comparability of the samples, i.e., patients with covariate patterns that are typical of only one of the states will be excluded.

Subgroup analysis will be conducted in an exploratory manner. We will include interaction terms (various covariates*state) in sub-analyses to assess whether WA PA compared to OH RR has differential outcomes for particular patient subgroups (e.g., back sprain, other MSK injuries, other injury types).

Aim 1. Analysis Topic C: Compare PA to RR, using survey sample to provide more covariates

This analysis will proceed as described for Analysis Topic B, but include only the subset of the WA/OH cohorts that were included in the survey. Depending on survey eligibility and response rates, up to 100% of survey respondents may be drawn from the underlying WA/OH cohorts (however, it is possible that survey accrual may need to continue beyond cohort accrual). This will allow us to test the Aim 1 hypothesis in a sensitivity analysis that provides additional control for confounding via the inclusion of baseline survey covariates and full use of propensity score techniques, as described for Analysis Topic H below.

Aim 1. Analysis Topic D: Prescribing data validation

We are in the process of confirming the feasibility of obtaining PDMP data (and specifically the payer variable) from each state for the full WA/OH cohorts and all patients included in the survey sample. Presuming we are able to obtain the necessary PDMP data, the following analyses are planned.

We will construct the various unsafe opioid prescribing variables using PDMP data, using the same methods as used for WC billing data. Further, should the payer variable be available to us, we will construct two parallel sets of outcome measures using PDMP data: (1) using all PDMP prescriptions, regardless of payer; and (2) using only prescriptions with WC as the payer. (If the payer variable is unavailable, we will construct only the first measure.) Concordance of the outcome measures by data source (and potentially with and without payer restriction) will be assessed using Cohen's kappa.

Sensitivity of findings to the data source used for the unsafe opioid prescribing outcome measures will be assessed by using the alternate measures in hypothesis tests, as described under Analysis Topics B, C, and I.

Aim 1. Analysis Topic E: Frequency and outcomes of opioid review decisions

To the extent feasible, we will document the frequency of opioid review decisions and their outcomes (patients were or were not authorized to continue using opioids beyond the respective review periods) for each state. We are investigating the existence of these data and feasibility of obtaining them from

each state. This is planned as a simple descriptive analysis (counts and percentages).

Aim 1. Analysis Topic F: Subgroup response to opioid review decisions

Using PDMP data, we will explore whether patient subgroups within the WA and/or OH cohorts respond differently to review decisions ending opioid coverage (e.g., whether opioids were prescribed by a different prescriber or obtained using a different payment source). Patient subgroups of interest for this analysis topic include—but may not be limited to—patients on higher daily opioid doses, those taking opioids longer-term, those with back sprain, those still off work at 6 weeks, gender, age, etc. DEA numbers in PDMP data can be used to determine whether opioids were prescribed by a different provider following an opioid review decision ending opioid coverage. If the PDMP payer variable is available, we can also assess whether opioids were obtained using a non-WC payer following review decisions ending opioid coverage. Subgroups will be exploratory and may also be defined within the survey subset for this topic, so that subgroups constructed using baseline survey variables (e.g., pain level) can also be assessed.

Aim 1. Analysis Topic G: Describe usual care

We will describe usual care by measuring health care utilization indicators (e.g., timing and rates for hospitalization, physical therapy, imaging, surgery, etc.), using WC billing data for the full cohort in both states. Further, we will describe differences in such indicators between COHE and non-COHE patients in WA, and ECP and non-ECP patients in Ohio. Descriptive information about usual care will be stratified by injury type.

Aim 2

Specific aim 2*. Examine the comparative effectiveness of WA's PA program versus OH's RR program with regard to patient reported outcomes (pain, function, quality of life, return to work), harms (presence of opioid use disorder, opioid poisoning events) and work disability outcomes at 6 weeks, 6 months, and 12 months from date of injury.*
Hypothesis 2. *Prospective PA with hard stops (WA) will be associated with statistically significantly improved patient outcomes compared to RR and prescriber notification (OH).* ***[See Analysis Topic H]***

Aim 2. Analysis Topic H: Compare PA to RR with respect to secondary outcomes

This analysis is focused on testing Hypothesis 2 (stated just above). Most secondary and exploratory patient outcomes will be based on survey data, but several will be based on WC data (see Tables 2 and 3).

Surveys will be conducted at approximately 6 weeks (baseline), 6 months, and 12 months after injury. We anticipate that roughly 3,120 workers in WA and 525 workers in OH will complete baseline surveys. Based on estimated response rates, we anticipate roughly 1,700 completed 12-month outcome surveys from WA and 234 from OH. Depending on survey eligibility and response rates, up to 100% of survey

respondents may be drawn from the underlying WA/OH cohorts (however, it is possible that survey accrual may need to continue beyond cohort accrual).

The primary predictor is binary (1 for WA cases, 0 for OH cases). We will specify GEE panel models as described for Analysis Topic B to account for outcome measures at multiple time points for each patient (6 months, 12 months). Appropriate GEE link functions will be specified for each outcome variable, e.g., identity link for continuous variables, logit link for binary variables, and log link for counts (Tables 2 and 3). Comparisons of clinically important improvements in patient pain and functioning will be based on the proportion of patients who achieve clinically meaningful improvement (relative to baseline) on our outcome measures at 6 and 12 months, as defined by 30% or greater improvement. We will include time/state interactions in order to assess (1) change in outcomes over time and (2) differences in such changes by state.

Covariates described under Analysis Topic B will also be included for this analysis, in addition to baseline covariates collected during the survey. Additional survey-based covariates will include the following (this list may be adjusted as the survey is finalized with stakeholder input):

- Education
- Household Income
- Race/ethnicity
- Health status
- Comorbidities (survey-based FCI, current cancer treatment)
- Pain intensity
- Physical function/pain interference
- Emotional functioning-Anxiety
- Emotional functioning-Mood
- Quality of life
- Work status and barriers to work
- Treatment for pain
- Satisfaction with treatment
- Communication with health care provider
- Alcohol and tobacco use

Using these covariates, we will calculate a propensity score. In order to minimize the loss of survey data, we plan to include this propensity score in the causal models along with important covariates. However, if needed to achieve balance on baseline variables, we will restrict the analytic sample to the region of common support and/or implement propensity score matching.

Subgroup analysis will be conducted in an exploratory manner. We will include interaction terms (various covariates*state) in sub-analyses to assess whether WA PA compared to OH RR has differential outcomes for particular patient subgroups (e.g., back sprain, other MSK injuries, other injury types). We

will conduct stratified analysis for strata defined by (a) number and strength of opioid prescriptions during the acute period (0-6 weeks), and (b) continued time loss at 6 weeks.

Aim 2A

Specific aim 2A*. For injured workers in WA, examine unsafe opioid prescribing and patient-reported outcomes and work disability at 6 and 12 months for patients receiving an established, coordinated, stepped care management program during the first 12 weeks following injury plus prospective PA versus patients receiving usual care subject to PA only.*
Hypothesis 2A. *Specialized care delivered through a stepped care management program plus prospective PA will be associated with statistically significantly lower rates of unsafe opioid prescribing and improved patient outcomes compared to patients receiving usual care and PA only.* ***[See Analysis Topics I and J]***

Aim 2A. Analysis Topic I: Compare COHE to non-COHE within WA with respect to unsafe opioid prescribing

This analysis is focused on the primary outcome for this study, unsafe opioid prescribing (defined earlier), using administrative and survey data for the full WA cohort. Our estimate is that we will have about 4,636 eligible workers in WA, and that approximately half will have an attending provider affiliated with COHE.

This analysis will test Hypothesis 2A (stated just above) with respect to unsafe opioid prescribing, using parallel analyses to those described in Analysis Topic B, and including the sensitivity analysis described in Analysis Topic C. The only adjustments are that models will include only the WA cohort, and the binary primary predictor and propensity score calculations will be based on COHE status rather than on state jurisdiction (1 for COHE, 0 for non-COHE).

Aim 2A. Analysis Topic J: Compare COHE to non-COHE within WA with respect to secondary outcomes

This analysis is focused on the secondary and exploratory patient outcomes for this study, using administrative and survey data for the WA survey sample. Surveys will be conducted at approximately 6 weeks (baseline), 6 months, and 12 months after injury. Our estimates are rough and will be updated as survey enrollment proceeds. However, we anticipate that roughly 3,120 workers in WA will complete baseline surveys, that roughly 1,700 will completed 12-month outcome surveys, and that approximately half of those interviewed will have an attending provider affiliated with COHE.

This analysis will test Hypothesis 2A (stated above) with respect to patient outcomes, using parallel analyses to those described in Analysis Topic H. Most secondary and exploratory patient outcomes will be based on survey data, but several will be based on WC data (see Tables 2 and 3). The only adjustments to Analysis Topic H are that models will include only the WA survey sample, and the binary primary predictor and propensity score calculations will be based on COHE status rather than on state jurisdiction (1 for COHE, 0 for non-COHE).

Additional Information Relevant to Quantitative Analyses for Aims 1, 2, and 2A

Subgroups of Interest

Planned subgroup analyses are listed under the relevant analysis topics above. Because all subgroup analysis will be exploratory, non-exhaustive examples of potential subgroups have been specified. New subgroups of interest may be identified via exploratory data analysis and/or proposed ad hoc by the principal investigator, co-investigators, or stakeholders. The total number of subgroup analyses—and all subgroups and outcomes analyzed—will be reported, along with subgroup definitions and procedures used. If indicated, multiple comparisons will be accounted for using p-value adjustment.

Operational Definitions for Eligibility Criteria

These definitions will need to be aligned as much as possible across the two states. The following operational definitions are based on our history of working with WA WC data. They may need to be modified after preliminary OH WC data are available for inspection.

- Inclusion criteria:
    - New State Fund claim: Identified by each state WC agency
    - At least one opioid prescription during the first 6 weeks after date of injury: Based on WC pharmacy billing data
    - Ability to speak English or Spanish (for the survey only): This will be determined by interviewers during the contact/consent process
- Exclusion criteria:
    - Under 18 years of age: Age at injury, calculated as the difference between birthdate and date of injury

Operational Definitions for Key Covariates

Operational definitions will need to be aligned as much as possible across the two states. Thus, key covariates and their operational definitions will need to be determined after (1) preliminary OH WC data are available for inspection and (2) the survey is finalized with stakeholder input.

Clustering

Study objectives and the primary and secondary outcomes for Aims 1 and 2/2A pertain to the individual worker level. Multiple outcome measures for each worker (both administrative and survey based) require accounting for within-person correlation, which motivates the use of GEE. However, provider-level opioid prescribing patterns may induce intraclass correlation among injured workers treated by a particular provider. Each ORP decision is specific to an individual patient; however, providers either request PA in WA or are notified of RR in OH. These experiences may cause providers to adjust their practice for other patients in their care, impacting outcomes for provider-based patient clusters. The vast majority of providers prescribe opioids to very few WC patients. However, there may be some dependence of patient observations within the few higher-volume providers. Injured workers may have multiple prescribing providers over the course of a WC claim, which complicates cluster identification.

The primary predictor for Aim 2A, COHE status, is assigned to injured workers based on provider-level COHE affiliation. COHE program features are determined at the WC system level but its effects may vary depending on provider adherence and individual worker circumstances. In order to obtain accurate standard errors and confidence intervals, we plan to specify models using robust standard error estimates and accounting for potential clustering by primary attending provider. This approach by necessity assumes person clusters are perfectly nested within attending provider clusters; however, attending provider can change over time. In practice such changes are uncommon in WA, and we are uncertain whether such changes can be tracked in OH. If feasible, we will assess clustering based on different approaches (e.g., first attending provider, attending provider in place for the longest period of time during the acute phase, or accounting for clustering only at the person level). We expect these approaches to yield similar results, but in the event they do not, we will proceed with the most conservative approach (highest standard errors).

Missing Data

Assumptions about the nature and prevalence of missing data made below will be assessed once preliminary WC and survey data sets are available. The administrative claims and pharmacy data are virtually 100% complete in WA; we will assess OH data when available, but expect similar completeness for all covariates associated with worker compensation or provider billing.

We expect relatively high survey response rates, based on previous research in these injured worker populations. Barriers to recruitment include being unable to locate and contact injured workers, and injured workers choosing to not participate. The address and phone numbers of injured workers who are receiving WC benefits are largely complete and accurate because contact information is required in order to receive disability benefits. In order to increase the response rate, all eligible workers identified by WA and OH WC systems will be sent an introductory letter 1 week prior to the initiation of the phone surveys. Workers will be able to schedule a time for the survey or can opt out at that point. Workers will be paid $50 for the baseline survey, $30 for the 6 month survey, and $50 for the 12 month survey ($130 total). The University of Washington (UW) Survey Research Division (SRD) will make 10 call attempts. The SRD research staff are extensively trained in standardized interviewing techniques and methods, effective calling strategies, building rapport and interest, and refusal prevention, which all aid in minimizing attrition and maximizing response rates. The survey interviewers are trained to minimize item non-response, while supporting autonomy not to answer individual questions.

Based on these efforts, we anticipate limited amounts of missing data for individual survey items, under 5%. We do expect larger and non-negligible amounts of missing 12-month outcome data relative to 6-month outcome data on the surveys, based on projected attrition.

We will use standard techniques to identify the nature (randomness) of missing data. Where missing data are minimal (<5%) and random (no clear associations with outcomes or predictors of interest), we will use casewise deletion; we expect this approach will be adequate for administrative data and baseline survey data. For the GEE panel models testing survey-based patient outcomes, we will use multiple imputation methods, based on an expected larger amount of missing data and the likely association of missingness with previous unsafe opioid prescribing.[4]

[4] Aloisio, K. M., Swanson, S. A., Micali, N., Field, A., & Horton, N. J. (2014). Analysis of partially observed clustered data using generalized estimating equations and multiple imputation. *Stata J, 14*(4), 863-883.

We will examine predictors of survey non-response and loss-to-follow-up with descriptive statistics comparing the two groups (and potential differences by state), and potential differences will be noted when interpreting results from the analyses of survey data. Non-response adjustment using post-stratification weighting techniques will be implemented, if warranted due to differential non-response. We will record and report reasons for dropout and missing data, run sensitivity analyses if indicated, and account for all patients in reports.

8. Analytical Methods: Qualitative Analyses

Specific aim 3. Using qualitative methods, identify key environmental, programmatic and policy factors that influenced the design, implementation and impact of the PA program in WA and the RR program in OH. This information will lead to the development of an Opioid Review Tool educational module for dissemination to both public and private payers.

Aim 3 will provide important contextual information and insights to enable us to explain why the two states developed different strategies in designing and implementing their respective ORPs, and insight into ORP impact on providers and patients, beyond health outcomes.

Key Informants

During Year 2, we will conduct key informant interviews with policy makers and stakeholders who were involved in the creation and implementation of each state's ORP, including ORP reviewing pharmacists and nurses. Initial key informants in each state have already been identified; these are individuals, as available, who were important in the ORP design and implementation process (however, we will be unable to interview current and former BWC employees due to an ongoing lawsuit in OH). The remainder of the key informants will be identified through (a) snowball sampling, by asking each interviewed informant to name others involved in the policy-making process in their state, and (b) noting the identity of key players in ORP design and implementation mentioned in the policy documents we collect and explore. Each interview is likely to last 60-90 minutes. Key informants will be asked to share a range of information about the policy making process, including the origins of the ORP regulations about which they have expertise; considerations & alternatives explored; inputs to the policy-making process; how the specifics were designed and implemented; how necessary resources were obtained; push-back, setbacks, and decision-making milestones. Interviews will be digitally recorded and professionally transcribed. Once an initial picture of the policy development process has been obtained through key informants, policy documents that could provide additional details will be collected and analyzed. These documents may include reports, transcripts, testimony, position statements, policy drafts, and other materials produced by policy makers, issue stakeholders, executive agencies, and legislative hearings and committees.

Key informant interviews and policy document collection will be designed initially around Aim 3, but expanded to generate the data necessary to address Aim 1 as well. We will employ qualitative methods to understand the causes of unexplained fluctuations in the time series described in Analysis Topic A. Specifically, we will conduct targeted key informant interviews and analyze the specific policy documents most relevant to the time period immediately prior to any observed fluctuations. Interviews and document analyses necessary to complete Aim 1 will be timed to occur in tandem with the larger set of key informant interviews and policy documents necessary for Aim 3.

All qualitative data will be analyzed using a grounded theory approach, aided by Excel spreadsheets and NVivo qualitative data management software. These methods will focus on identifying causal factors that shaped state choices about which ORPs to design, how to implement them, and how these programs should evolve over time. Analytic methods will focus on inductive coding first, in order to facilitate identification of the broadest possible range of causal themes. Analysis will begin as soon as the first key informant interviews are complete; simultaneous data collection and analysis will allow later interviews to be informed by earlier ones, so that the fullest possible picture of policymaking can emerge.

Individual In-Depth Interviews

We will conduct 20 to 30 patient and around 10 provider interviews in each state. Interviewees will be identified from the lists provided to us by each state's WC agencies (and also through snowball sampling in the case of provider interviews). Participants will be recruited from among: (1) patients who had an opioid prescription for at least 6 weeks paid for by WC or whose prescription payments have been reviewed in accordance with the state's ORP, and (2) prescribing providers that had at least one patient whose opioid prescription paid for through WC had been reviewed in accordance with the state's ORP. Patient interviews will explore the impact of the ORPs and related policies on pain management, function, disability, return to work, their relationship with their provider, and their feelings about WC. Provider interviews will explore changes in their use of opioid prescriptions for injured workers, why they made these changes, and the role of ORPs and related policies on their prescribing changes; impact on feelings about clinical autonomy; views of the legitimate role of opioids in pain management; and reflections on consequences and effectiveness of the ORP, whether it should be changed, and whether the ORP affected their attitudes toward the state WC agency or their willingness to treat WC patients.

Interviews will be led by Dr. Padamsee and the qualitative research assistants in WA and OH. Each interview will last approximately 1-1.5-hours. Interviews will be audio-taped and professionally transcribed. Transcripts and notes will be analyzed using a grounded theory approach, aided by Excel spreadsheets and NVivo qualitative data management software.

9. Data Management Plan (DMP)

See Appendix A.

10. Data Safety Monitoring Plan (DSMP)

See Appendix B.

Appendix A. Data Management Plan

Data collection
Data will be generated from the following sources:

1. Washington and Ohio state workers' compensation (WC) systems

   Includes: Contact information (for recruitment), claim descriptors, sociodemographic information, employment information at time of injury, injury information, medical and facility billing data, pharmacy billing data, provider information, time loss days and costs, prescription drug monitoring program (PDMP) data.

2. Survey of participants in the Washington and Ohio workers' compensation system administered by the Survey Research Division (SRD) of the Social Development Research Group at the University of Washington

   Includes: Sociodemographic information, comorbidities, pain intensity, physical function and pain interference, treatment for pain, quality of life, emotional functioning, questions specific to opioid use disorder, disability, work status, wages, patient experience with the opioid review procedures, perceived outcomes of the insurer decisions from the patient perspective, satisfaction with treatment, communication with health care provider, and alcohol and tobacco use.

3. Individual in-depth interviews and key informant interviews administered by The Ohio State University research team

   Includes:
   (patient interviews) the impact of the ORPs and related policies on pain management, function, disability, return to work, their relationship with their provider, and their feelings about WC.

   (provider interviews) changes in their use of opioid prescriptions for injured workers, why they made these changes, and the role of ORPs and related policies on their prescribing changes; impact on feelings about clinical autonomy; views of the legitimate role of opioids in pain management; and reflections on consequences and effectiveness of the ORP, whether it should be changed, and whether the ORP affected their attitudes toward the state WC agency or their willingness to treat WC patients.

   (key informant interviews) origins of the opioid review program regulations, considerations and alternatives explored, inputs to the policy-making process, how the specifics were designed and implemented, how necessary resources were obtained, push-back, setbacks, and decision-making milestones.

Data organization
Raw administrative data (i.e. WC claims data, pharmacy billing data, and PDMP data) will be received from the Washington and Ohio workers' compensation systems. These files will be kept in separate folders for each state and designated as read-only so that they cannot be changed. A log in Microsoft Excel in each folder will keep track of these files as they come in and will include date and time received, size, description, and other relevant meta-data.

Similarly, survey data will be received from the Survey Research Division, stored as a read-only file in a separate folder, and tracked via a log in Microsoft Excel with relevant meta-data.

Merged data files for analysis will be read-only and stored in a separate folder. This folder will also have a log in Microsoft Excel that contains the meta-data in order to keep track of the latest version. This folder will be accessible by team members doing the statistical analysis. All analysis work will be kept in folders separate from the data folders.

Data handling
The Data Manager(s) will be responsible for managing the data, including de-identifying and merging datasets. In both states, each WC claim has a unique Claim ID and a unique Claimant ID, allowing for the identification of multiple claims by one patient. Data files for the WC claims data and pharmacy billing data will be linked using these IDs.

After merging datasets, the Claim ID and Claimant ID will be replaced with Study IDs. A separate linkage file with the Claim ID and the Study ID will be retained and will be stored in a separate folder only accessible by the Data Manager(s), Research Coordinator, and Project Director.

Administrative workers' compensation data will be stripped of most direct patient identifiable information before it is received by this project. For surveys and individual in-depth interviews, some identifiable information (e.g. name, address, phone number) will be necessary for recruitment. The Data Manager(s) will produce deduplicated lists of recruitment targets for the baseline study for the Survey Research Division. The recruitment lists will include the UW-created Study ID, as well as the information necessary for recruitment. Survey data received back from the Survey Research Division will contain the study ID (but not the identifiable information).

As described above, version control for all incoming raw data (i.e. administrative and survey data), as well as the merged read-only analysis files, will be managed using Microsoft Excel logs of the relevant metadata. All files and folders are automatically backed up daily by the Department of Environmental and Occupational Health Sciences computing system. All data transfer and linkage procedures will meet strict Human Subjects (IRB) requirements.

For the qualitative portions of the research (i.e. individual in-depth interviews and key informant interviews), the lead qualitative analysis investigator and qualitative research assistant will be responsible for data management. Data will be stored on a secure server with backup to a separate server. Data will be de-identified after collection, and only these two individuals will have access to the key linking direct identifiers to the Study ID. Other staff responsible for analysis will only have access to the de-identified data.

<u>Linkage of PDMP data</u>
The linkage approach for the PDMP data may vary across states. The process in Washington is as follows:

1) Department of Labor and Industries (DLI) staff routinely send a list of claimant IDs and direct identifiers for WC claimants to the PDMP vendor (Appriss), on a monthly basis;
2) the vendor links the personal identifiers provided by DLI to PDMP records using their internal algorithms/fuzzy logic;

3) the vendor provides DLI with the full history of PDMP records linked to those claimants, with claimant first name, last name, and date of birth attached to each record;
4) DLI staff link claimant first name, last name, and date of birth in the PDMP records to the same fields in the original file sent to Appriss to retrieve claimant ID; and
5) using claimant ID, DLI staff are able to link PDMP records to WC claim IDs and claims data for each individual injured worker.

Thus, in Washington, PDMP data would be delivered to the research team in the same way as other WC administrative data, with claim ID available for linkage to other data files. Ohio does not yet have a routine batch delivery system in place for PDMP data, but they do have statutory authorization to receive PDMP information, and we will be working with them to set this up. However, if a similar system cannot be set up for Ohio, we will obtain data using their current mechanism, whereby Ohio Bureau of Workers' Compensation staff look up and download PDMP records for individual WC claimants, using first name, last name, and date of birth.

Data description
In addition to the logs contained in each data folder, a chronological log will be kept with any data decisions such as deleting a case or the coding of missing values. All code will be held to a documentation standard that includes a header (name of file, author, date, purpose, input data, and output data/analysis/documents) and ample documentation of all steps in the code. In addition, a data dictionary will be created that describes all of the variables used in the study including missing value coding and derived/created variables. There will be separate data dictionaries for each aim of the project.

Data storage and preservation
All raw data and analysis data sets will be stored on a secure server. Data from this server is encrypted and stored on departmental storage daily, as well as backed up daily to a different location. Offsite backup of this location occurs quarterly, with storage of up to one year. Qualitative data is similarly stored on an offsite secure server, with a separate backup server.

Data maintaining
Once the study is complete, all raw data and analysis data sets will be stored on a secure server until after the end of the applicable records retention period, as required by the University of Washington Records Management Services.

Data sharing
The Principal Investigator, the Project Director, the Research Coordinator and the Data Manager(s) will work jointly to oversee and manage any data sharing. Possible sharing will be restricted to analyses of de-identified worker survey data and limited workers' compensation and pharmacy data. At the end of the study, the study team will evaluate whether de-identified worker survey data will be made available. We will request permission to share limited data from the workers' compensation systems (e.g. injury type) to link with the survey data. No data with direct identifiers will be shared and we will not keep any identifiers after the end of the study and relevant retention periods.

The data may also be shared via the University of Washington Data Collaborative (UWDC) (https://datahub.csde.washington.edu/contact-us/) after the study is completed. This system is a highly secure data environment with an infrastructure for screening collaborators. Prior to becoming part of

the UWDC, the data will be de-identified and the appropriate permissions from the Washington and Ohio workers' compensation systems will be obtained.

Appendix B. Data Safety and Monitoring Plan

Study Description
This study has three components (a) analysis of administrative data from the Washington state and Ohio state workers' compensation systems, (b) an observational study (based on surveys) of workers in these workers' compensation systems, and (c) patient and health care provider individual in-depth interviews and a key informant study of opioid policy.

This study has been reviewed as "minimal risk" by the University of Washington IRB and all protocols and requirements set forth by the IRB will be followed.

There are two main issues addressed by this document: (a) minimizing the risk to the study participants, and (b) data security.

A. Individuals who will monitor the research study

Principal Investigator (PI): Gary Franklin
Project Director (PD): Deborah Fulton-Kehoe
Research Coordinator: Andrea Elmore

B. Procedures for monitoring study safety
Data and safety monitoring is ongoing throughout the study. Physical offices and file cabinets are locked and only accessible by authorized study personnel. Computer security includes not keeping identifiable data on local computers but only on secure off-site servers, only used by study team members, and strong passwords (see additional details below). Computer security breaches are monitored by system administrators who will immediately contact both the PI and PD with any concerns. All personnel are trained in human subject protection.

C. Participant risk
The primary risks to research subjects in this study are breach of privacy and confidentiality, and possible discomfort with the data collection process. These risks are being minimized through comprehensive data security and confidentiality measures, in compliance with UW Human Subjects Division requirements, and by informed consent and respect for voluntary responses for worker surveys, individual in-depth interviews, and key informant interviews. This is an observational study to compare the effectiveness of pre-existing and ongoing interventions conducted by each state, which are governed by each state's regulations. The interventions under study (i.e., prior authorization and retrospective review of opioid prescriptions) are mandated by state regulation, and are not subject to change based on study findings, except through the longer-term dissemination and translation process. Consequently, we do not plan to set up a Data Safety Monitoring Board.

1. Expected risks

    a. Participation in Worker Surveys

    (1) a feeling of invasion of privacy because of the researchers having their contact information, (2) possible discomfort with the interview process such as fatigue and/or boredom while completing the telephone assessments, and (3) potential breach of confidentiality. Some participants may also experience mild anxiety, frustration, and/or

stress while answering sensitive questions about depression, pain, and mood. As a result of answering questions about pain, some participants may focus more on their pain, which may lead to a temporary increase in pain intensity.

b. Patient In-Depth Interviews

The risk to participants would be discomfort with the interview conversation and potential breach of confidentiality.

c. Provider In-Depth Interviews

The risk to participants would be discomfort with the interview conversation and potential breach of confidentiality.

d. Key Informant Interviews

The only anticipated risk of participating in this research is that the interviewee may choose to share information that could jeopardize their employment if current or future employers learn of the interview content.

Protection against risks

a. Worker Surveys

Subjects are recruited into the study via a letter describing the study, which will also provide a phone number for them to call to opt out of the study and avoid a phone call. The recruitment mailing and interviewer will state that the workers' compensation agency provided the contact information to the researchers. Research interviews will ask about health status, pain, pain interference with function, quality of life, use of opioid medications, benefits from and problems with use of opioid medications, depressive symptoms, and indicators of potential misuse of opioid analgesics. Subjects will be instructed that they can skip any questions they do not wish to answer. Any concerns related to the research may be addressed by telephoning the investigators, other research staff, or human subjects protection staff at the University of Washington. Also included will be an information sheet that will include phone numbers for the Survey Research Division, the research coordinator, the Principal Investigator, and the IRB. All participants will be informed of their right to withdraw from the study at any point without adversely impacting any of their medical care or relationship with workers' compensation.

b. Patient and Provider In-Depth Interviews

Recruitment letters and phone calls will explain that the state workers' compensation agency provided the study team with the potential participant's contact information. Both will also (a) describe the topics that will be covered during the interview, and (b) emphasize that information provided by the participants will be treated as fully confidential, and that no potentially identifying information will be utilized in any reports or publications that emerge from the study. Both these points will be repeated at the start of the interview. In addition, the interviewer will emphasize that we hope the information revealed by the interview will help lead to better policies and better help for patients in the future.

The interviews will be audio recorded, which may increase the risk of breach of confidentiality. Media will be stored in locked rooms and drawers. The audio recordings will be professionally transcribed in Ohio under Dr. Tasleem Padamsee's (the Lead Qualitative Investigator) direction. Electronic transfers of audio files and transcripts will be encrypted during transmission via a mechanism such as secure FTP, and approved by IT departments of the University of Washington and The Ohio State University. Transcripts will be checked for any potential identifying information that could have come up during the course of the interview; this information will be deleted before the data are analyzed. Only de-identified data will be provided to project staff for analysis. No individuals will be identified in any presentations, reports, or publications that result from this study.

c. Key Informant Interviews

Key informants will be informed that they are not obligated to share anything or answer any questions that might jeopardize current or future employment. Their confidentiality will be protected in the following ways. Included in the consent will be the option for the informant to be identified or choose anonymity. If the interviewee agrees to be recorded, their interview will be transcribed once it is completed. Both the recording and the transcript will be kept in the secure possession of the researcher. If anonymity is chosen, transcriptions of the interviews will be coded so the informant's identity is protected. No identifying information will appear on the transcript of the interview, and both the transcript and recording will be kept physically separate from any information that could identify the participant. No individuals will be identified in any presentations, reports, or publications that result from this study.

Monitoring Participant Safety

Worker Surveys: The Survey Research Division will report any concerns about research subjects to the Research Coordinator. If any particular questions seem to cause repeated distress those questions will be re-evaluated and likely revised.

During the patient and provider in-depth interviews, if something causes discomfort the interviewer will address this directly and provide community resources, if appropriate.

Key informants will be professionals talking about their work-related activities. We do not therefore anticipate any safety risks. Should key informants become uncomfortable during the conversation, the interviewer will volunteer to change the topic or end the interview, allow time for a break, and offer community resources as appropriate.

D. Protecting the confidentiality of participant data

We will take multiple steps to protect participants' privacy. All data collected for data analysis will have direct identifiers (claim ID and name) removed as soon as possible, labeled with a code number that is unique to each participant in the study, and maintained separately from any identifying information excluding exceptions described in more detail below. All of the data collected from participants are for research purposes only.

University of Washington
Department of Environmental and Occupational Health Sciences (DEOHS)

SERVERS/SERVICES

The data will be stored on a secure internal network server. All data will be encrypted when transferred from workers' compensation to the secure internal network server and when viewed on the server. The server is housed in a locked server room to which only our department's IT staff have physical access. The backup system is at the UW Data Center. The room is a shared colocation but the backup system is in a secure cabinet to which only IT staff have access. The IT staff have so-called "root" access that would allow access to the system's data. Assurance of necessary confidentiality is part of the condition of this paid employment. Access to this server is logged and relies on having valid user credentials. Desktop computers used to access the system are likewise restricted to the Department of Environmental and Occupational Health Sciences account holders and measures have been taken to reduce unauthorized access including locked facility and offices and elements such as locking screensavers.

Each member of the research team will have an individual username and password for the secure server; these usernames and passwords will not be shared. Passwords will be required to be of sufficient length and complexity to reasonably protect them from being guessed by humans or computers. Passwords will be changed periodically, and changed immediately if there is suspicion of compromise.

Server operators will take reasonable actions on a regular basis to ensure that the server system is not vulnerable to attack. The server will be kept in a secure location and subject to regular inventory to ensure that loss or theft is identified. Server operators will promptly inform the research team of any suspected breaches. Any actual or suspected loss, theft or improper use of (or access to) the data will be reported immediately to the University of Washington IRB.

The data will be processed completely internal to the server. If it becomes necessary to retain the original data on a disk either for direct use or backup, the data will be encrypted, and such disks stored in a locked drawer, cabinet or other container. Data transferred to the research team over the internet will be encrypted during transmission via a mechanism such as secure FTP.

DEVICES

No data with direct or indirect identifiers will be placed on any desktop computer or portable device including laptop computers, notebook/netbook computers, smart phones, USB or flash drives, portable hard disks, iPads, tablet computers, and DVDs. Local desktop computers will be configured for secure operations, to limit access to the specific person or persons authorized to use the device. Applications being used on these devices will also be configured to protect access and transfer of data. Operating systems and applications will be kept up to date by installing revisions, patches and upgrades. Secure devices will be stored in a way that minimizes the possibility of loss or theft. An established device management and monitoring process will ensure that the devices are appropriately configured, patches to operating systems are installed, devices have not been stolen or lost, and devices are used appropriately.

DIRECT IDENTIFIERS

Only data for the surveys will contain name and contact information when received from workers' compensation. These are needed to recruit study participants. This information will be kept in a separate password protected folder by the Data Manager(s). The Data Manager(s) will receive this weekly data from workers' compensation, remove duplicates, and screen the data for study eligibility. Once identifying the new potential participants, a unique identifier will be added, and this information will be put into a separate folder that is accessible by the Survey Research Division. The key that links direct identifiers to unique study IDs will be kept by the Data Manager(s) and isolated from any other

data. Participant survey data received back from the Survey Research Division to the Department of Environmental and Occupational Health Sciences will only contain the unique study ID and no direct identifiers.

University of Washington
Survey Research Division (SRD)
Social Development Research Group (SDRG)

SDRG's workplace suite is secured with locked, individual password-access doors. Computer networks are secured through a firewall and individual internal access to shared files is controlled through the domain server. Individual computers are password protected.

All surveys will be administered following standard survey administration procedures developed by SDRG and approved by the University of Washington's IRB. To ensure confidentiality, study identification codes will be used. Master lists that link study codes to identifiers are maintained separately and are stored off-line on a CD in locked files. Interviews conducted over the phone by research staff will use computer-assisted interviewing technology that automatically transfers data from each completed interview to a secure server. The resulting electronic data files will be maintained in password protected directories within SDRG's internal computer network.

The Ohio State University

SERVERS/SERVICES
All data will be stored on a secure network server. The Ohio State University secure server has been vetted by the Office of the Chief Information Officer's data risk assessment procedure, and determined to be compliant with HIPAA and to meet all security needs for data containing protected health information. Access to project folders on this server will be locked, and allowed only to IRB-approved project personnel who have completed appropriate Human Subjects and Responsible Conduct of Research certifications.

The server on which data will be stored is housed at the State of Ohio Computing Center (SOCC), an offsite locked facility to which only a limited number of university IT staff have physical access. The backup server is located separately in the SOCC. Server operators take reasonable actions on a regular basis to ensure that the server system is not vulnerable to attack. Server operators will promptly inform the research team of any suspected breaches. Any actual or suspected loss, theft or improper use of (or access to) the data will be reported immediately to the University of Washington IRB.

DEVICES
No data with direct or indirect identifiers will be placed on any desktop computer or portable device including laptop computers, notebook/netbook computers, smart phones, USB or flash drives, portable hard disks, iPads, tablet computers, and DVDs. Only de-identified data will be analyzed on local desktop and laptop computers. These computers are all College of Public Health authorized machines, which are configured for secure operations and limit access to the individuals with strong passwords (as described above). Operating systems and applications will be kept up to date by installing revisions, patches and upgrades. Secure devices will be stored in a way that minimizes the possibility of loss or theft. An established device management and monitoring process will ensure that the devices are appropriately configured, patches to operating systems are installed, devices have not been stolen or lost, and devices are used appropriately.

DIRECT IDENTIFIERS

Identifiable original data from in-depth interviews and key informant interviews will be stored on secure server sites separately from de-identified data for analysis. Only the lead qualitative analysis investigator and qualitative research assistants will have access to the original data, and they will de-identify the data before other staff can access it for analysis purposes. The key that links direct identifiers from in-depth interviews and key informant interviews to unique study ID numbers will be accessible only to those two individuals, and will be kept separately on the secure server from both the original identifiable data and the de-identified data used for analysis. Data transferred between members of the research team over the internet will be encrypted during transmission via a mechanism such as secure FTP, authorized by the IT staff of both The Ohio State University and the University of Washington. Individual in-depth and key informant data will be de-identified as soon as possible after data collection, and only de-identified data will be used for all analytic purposes. Identifying data will be destroyed once all analyses from the study are complete.

E. Identifying, reviewing, and reporting adverse events and unanticipated problems to the applicable IRBs, FDA, and any other and any other applicable governmental agencies or other monitoring bodies, consistent with legal requirements and requirement so of the IRB.

Possible adverse events:

Participant discomfort that the survey staff, individual in-depth interviewers, or key informant interviewers become aware of will be reported to the Research Coordinator. If the discomfort cannot be managed by the identifying staff as described above, the Research Coordinator will report the adverse event to the Human Subjects Division. The Research Coordinator will review these reports with the PI and study staff at regular staff meetings.

Any data security breach will also be reported to the Research Coordinator, the PI, the IRB, and PCORI.

F. For multi-site studies, the procedures for ensuring compliance with the DSMP and requirements for reporting across research study sites.

Tom Wickizer, PI of The Ohio State University study site, will be responsible for ensuring compliance with the DSMP at The Ohio State University and for reporting to the University of Washington site any problems.