Study Title: A Health System Wide Evaluation of Mandated Use and Clinical Decision Support Tools to Improve PDMP Utilization and Patient Outcomes

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Version Date: **3 December 2021**

I. Hypotheses and Specific Aims:

Prior research by this team has shown that when emergency department (ED) prescribers are less likely to prescribe an opioid analgesic to patients at high-risk of overdose or misuse when they consult the Colorado Prescription Drug Monitoring Program (PDMP). Despite extensive work to reduce workflow and accessibility barriers to use of the PDMP, the majority of providers still do not use the PDMP when making prescription decisions. Clinical decision support (CDS) that is embedded in the Electronic Health Record (EHR) has promise as a tool to increase PDMP use, advance presentation of important PDMP data to providers and improve opioid safety without interrupting provider workflow.

This cluster-randomized study is designed to determine if:

- CDS tools that deliver focused, timely clinical information to prescribers can improve use of the PDMP
- The use of focused CDS tools can decrease high-risk opioid prescribing
- The use of focused CDS tools is associated with better patient outcomes: decreasing high-risk, long-term, and aberrant opioid use

Specifically, we will test the hypotheses that:

1. Use of a focused CDS tool will increase the percentage of high-risk patients who are checked in the PDMP in the target populations, compared to those who have not implemented the tool.
2. Use of a focused CDS tool will decrease the percentage of high-risk patients who receive a controlled medication prescription in the target populations, compared to those who have not implemented the tool.

II. Background and Significance:

The opioid crisis is a public health emergency that threatens the wellbeing of our communities. Despite an overall decrease in opioid prescribing[1], 11.4 million US citizens suffer from opioid misuse[2] and opioid deaths continue to rise in the US.[3] Opioid abuse and deaths represent a significant cost to the US economy, with an estimated $78.5 billion spent annually.[4]

Colorado suffered from 1,010 drug-related deaths in 2017, a 9% increase from the prior year and the most ever.[5] Prescription opioid deaths reached 357 in 2017.[6] In the 2016-2017 National Survey on Drug Use and Health Colorado ranked 7th in number of individuals $\geq$12 years old

reporting past year non-medical opioid use (5.03%), with more than 300,000 Coloradans misusing prescription pain medications.[7] Many of those reporting use of illegal opioids such as heroin or illicit fentanyl report inappropriate use of prescription opioids prior to a shift to illegal drugs. Hence, improved prescribing of opioids is an essential intervention in addressing the opioid epidemic.

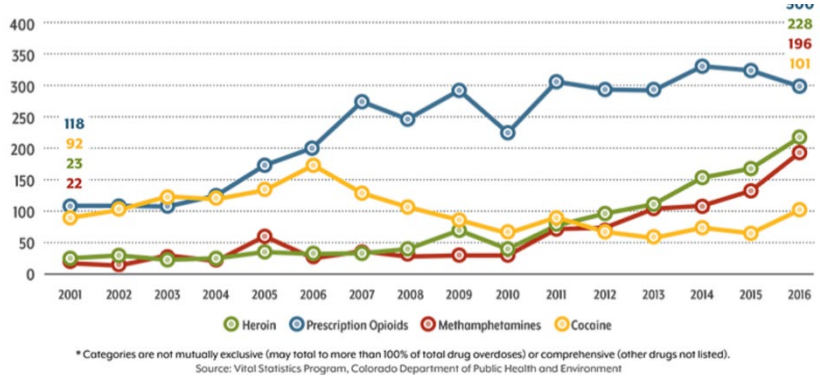


*Figure 1: Number of Drug Poisoning Deaths in Colorado by Drug Type, 2001-2016**

Ten years ago, the Colorado PDMP was established in order to track controlled medication prescribing in an effort to improve patient safety and control misuse and abuse of opioids and other controlled medications. By consulting the PDMP, a prescriber can identify patients with prescription histories that indicate high-risk or inappropriate use. Originally, use of the PDMP required log on, transcription and searching steps on the state web portal which prescribers found the cumbersome and disruptive to their workflow, especially in fast-paced environments such as EDs. Our prior project incorporated PDMP access directly into the UCHealth Electronic Health Record (EHR), which resulted in incremental improvements in PDMP utilization but failed to achieve PDMP usage in a majority of opioid prescriptions.

As a growing part of improving the digital environment in EHRs, CDS is focused on providing the right information to right person in the right format at the right time in the right channel to improve patient care. The overall goal is facilitate decision-making and improve delivery of best practices. CDS tools provide information and alternatives to clinicians to supplement but not replace good clinical judgment. The proposed CDS tools suggest but neither require nor prohibit any particular course of treatment and are not designed to gather information on compliance with state and federal laws governing opioid prescribing. The final decision is always at the providers' discretion.

Given the small progress made by incorporating "one click" PDMP access into the EHR, a logical next step is to investigate if we can improve PDMP use and patient outcomes by designing focused CDS tools for ED, hospital discharge and in primary care clinics. The proposed tool would search the PDMP automatically (saving provider time) and then present providers the PDMP information only when the patient is determined to be high risk. This will improve workflow by increasing the signal to noise ratio for PDMPs.

Our initial studies in incorporating the PDMP into the EHR were carried out in 5 UCHealth EDs across the Front Range. Primary care clinics work under different time constraints and practice patterns, so it is possible that tools which are beneficial in the ED are not easily transferrable to primary care workflows. As such, a key first step in designing effective CDS tools to improve opioid prescribing has been to consult non-ED physicians and prescribers to determine gaps in their knowledge and processes, and learn at what time points additional information and decision support tools would be most effective in their practices. This step was described separately in

study 19-3063, “Prescriber preferences in development of Clinical Decision Support tools to improve PDMP utilization.”

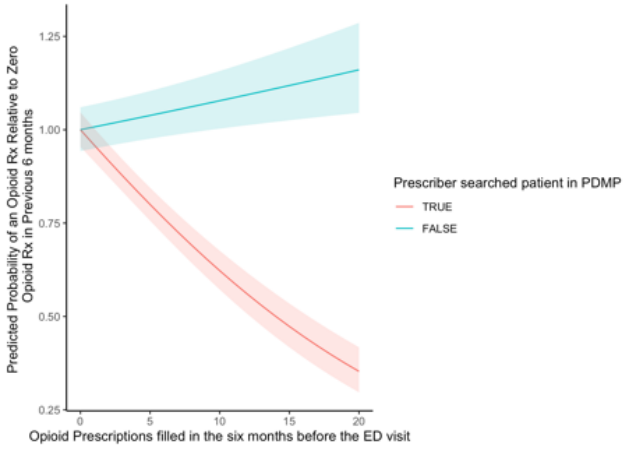
In the current form used by the state, PDMP data is available as a list of prescriptions, but is generally presented in UCHealth system in the form of a NarxCare report. This report includes a proprietary calculated risk score that incorporates aspects of a patient’s controlled medication use history and has been shown to correlate with overdose risk.[8] Individual risk scores are provided for opioids, stimulants, and sedatives (controlled substances tracked by the CO PDMP). These scores will be used to drive CDS tool activations.

III. Preliminary Studies/Progress Report:

In our prior work at UCHealth EDs, we sought to reduce barriers to PDMP use and investigate the effectiveness of improved access to the PDMP and “mandated” consultation of the PDMP prior to signing an opioid e-prescription. We determined PDMP usage rates, prescription rates when the PDMP is used (or not), and patient outcomes. In the setting of already decreasing opioid prescribing, we found that one-click PMDP EHR integration is associated with an increase in the frequency of PDMP searches for ED patients who are prescribed an opioid. Unfortunately, still only a minority of ED patients receiving an opioid prescription were searched even after mandating use through an interruptive “best practice alert”. “Mandated” use for our studies, is a relatively loose term. In order to not disrupt clinical workflows, information is presented as a “best practice alert” (BPA) in a pop-up window but providers can act on or bypass the alert. This design is required in order to ensure the tool does not impede patient care or the exercise of clinical judgment. Additionally, use across different ED sites and providers was highly variable, suggesting inconsistent care and the need for improvement.

After adjusting for site, provider and the patient’s race/ethnicity and age, the predicted probability that a patient who received an opioid prescription would have been checked in the PDMP was only 0.218 (95% CI: 0.202 – 0.234) under the most stringent “mandatory” use criteria in our previous study.

Notably, there was a significant reduction in the probability that an opioid was prescribed as the number of opioids filled in the six months prior to the ED visit increased if the patient was searched in the PDMP (OR: 0.92 [95%CI:0.91-0.94] for every additional prescription). There was no such reduction for patients who were not searched (OR: 1.01 [95%CI:1.00-1.01] for every additional prescription). This suggests that reviewing the PDMP did have an effect on prescribing behaviors for high-risk patients.



We conclude that providing effective information on prior controlled medication use and risk assessment improves patient safety by decreasing high-risk prescribing. However, given poor compliance with “mandatory” consultation of the PDMP, it is clear that improvements are needed in information presentation to facilitate PDMP use. To address this

issue, the current study will focus on designing, testing and implementing CDS tools to ensure delivery of the right PDMP information to prescribers at the right time within their workflow to increase compliance with the recommended best practice of PDMP review.

IV. Research Methods

A. Outcome Measure(s):

Primary outcome:

- Changes in the percentage of high-risk patients (patients who are flagged by the CDS logic) who are checked in the PDMP

Secondary outcomes:

- Changes in the percentage of high-risk patients (patients who are flagged by the CDS logic) who receive a controlled medication prescription
- Overall utilization of the PDMP prior to prescribing for low risk/naïve patients vs. high risk patients
- Percentage of patients who receive a controlled medication prescription who go on to long- term or aberrant use of controlled medication when CDS is used vs. controls

B. Description of Population to be Enrolled:

Two distinct populations will be involved in this study.

1. Health care providers licensed to prescribe opioid analgesics in the UCHealth system. These individuals will use CDS tools provided in the course of normal clinical care and have the opportunity for qualitative feedback on tools. We will collect de-identified data on CDS use and prescribing practices of providers. There will be no attempts to link qualitative responses with measures of prescribing practices, which will be measured system wide as described elsewhere. Oncology, hospice/palliative care, and pediatric practices will be excluded
2. Patients seeking care in the UCHealth system, who may receive an opioid prescription. The population will be limited to non-prisoners 12-89 years of age. Individuals with an active cancer diagnosis, sickle cell disease, or receiving specific end of life care are excluded. Pregnant women and decisionally challenged people will be included but are not considered a target population. No efforts will be made to include these individuals. Patients with limited literacy or limited English fluency will be included but are not considered a target population. Juveniles seen at providers included in the specialties of interest will be included (ages 12-17 inclusive) due to the inclusion of their health care provider. On the advice of pediatric toxicology experts, a cut point of 12 years of age is a clinically relevant age at which misuse of opioid analgesics and other controlled medications becomes a notable risk. However, no efforts will be made to target or enhance inclusion of juveniles. Pediatrics-only specialist offices will not be included in rollout of the CDS tools. Outcomes measures from juveniles will be examined separately from adults but may be included in the overall population if statistically appropriate.

C. Study Design and Research Methods

This will be a 1) cluster-randomized (by practice, as identified by a group of providers who work in the same department or set of departments within UCHealth) study for ambulatory/outpatient providers and 2) a randomized study (by provider) for emergency medicine and inpatient providers, with four study arms:

1. Arm 1: No change in practice
    - Providers are free to access the PDMP when prescribing via the existing integrated PDMP button.
    - This control group will enable monitoring of the secular changes in rates of controlled medication prescription within the UCHealth system.
    - In order to facilitate analysis of patient outcomes, CDS logic as in group 4 will run "silently" in this group such that risks are identified and recorded but not seen by the provider.
2. Arm 2: "Mandatory" use of the PDMP for all opioid prescriptions.
    - A best practice alert (BPA) will be triggered and fire when ordering an opioid prescription. The BPA will not appear (i.e. it will be suppressed) if the provider already reviewed the PDMP within the encounter. The BPA is shown in Figure 2 below.
    - Although this condition is termed "mandatory" use, it is not a hard stop. The provider can easily close the window without consulting the PDMP and the prescription can be signed whether the PDMP has been consulted or not. The BPA will be built to track utilization of the BPA vs. bypass. Note: This has been deemed too interruptive for ambulatory clinics and they will not be included in this arm.

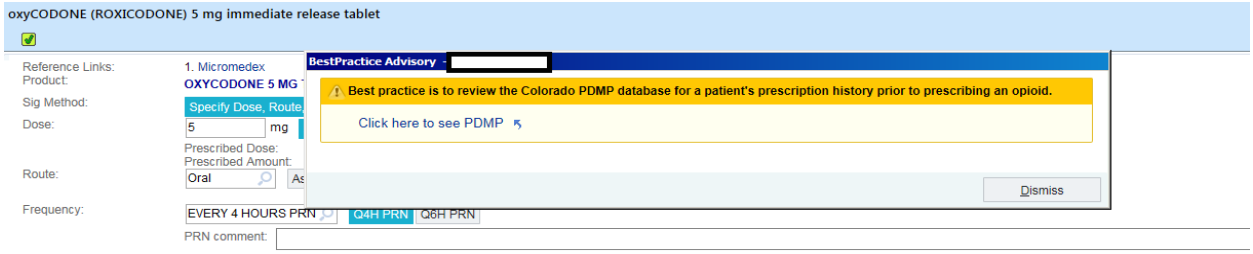


Figure 2: Example BPA used in prior study.

3. Arm 3: CDS for high risk patients based on PDMP data
    - Based on initial interviews with providers (see 19-3063) CDS support will be designed to be supportive of provider workflows via interruptive alerts (BPAs) for high-risk patients only. No alerts will fire for patients without high risk indicators based on data in the PDMP or prescription history as shown in Epic. An example is given below. Exact phrasing may be modified during final testing in order to streamline appearance of the alert.
    - Again, BPA will be triggered upon entry of an opioid or benzodiazepine prescription and will fire only for patients determined to be at risk for controlled medication associated adverse events, misuse or overdose, based on logic built to identify high-risk characteristics. Definition of these risk characteristics is based on CDC guidelines and include: NarxCare opioid or overall overdose risk score (PDMP based) indicating the patient is in the highest ~5% of the population for controlled medication risk, initiating opioid treatment with an extended or long acting release formulation with no opioid usage in the previous 100 days, or information in the PDMP or EHR indicating overlapping opioid use or co-prescribing of a sedative with an opioid.
    - One-click access to the PDMP for all patients will be maintained as in other arms. If the provider reviews the PDMP during the encounter before prescribing, the BPA will be suppressed.

- As in Group 2, this is not a truly mandatory check and can be bypassed. BPA messaging was determined based on work with providers to deliver the most useful and clear information.
- The text displayed in the alert will be specific to the patient. BPA logic and phrasing is included in Appendix A.

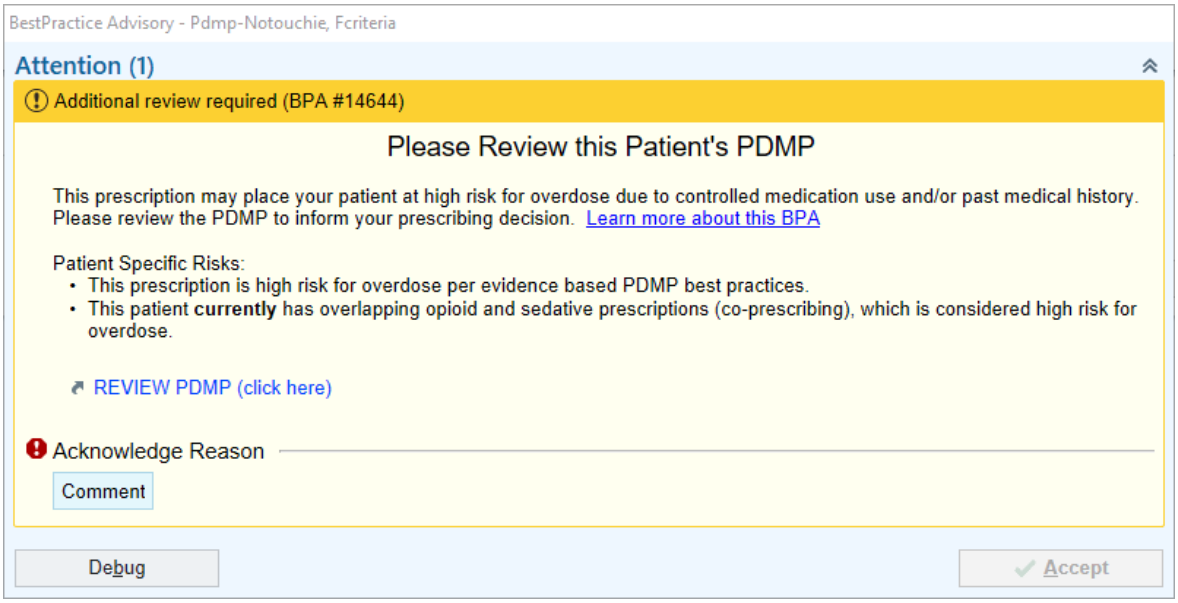


Figure 3: Sample alert.

4. Arm 4: CDS for high risk patients based on PDMP and/or clinical characteristics
   - The CDS will fire based on the same characteristics as in Group 3 OR if clinical history characteristics recorded in the EHR indicate increased high-risk. Again, these risk factors have been determined based on work with providers and include risk factors based on prior published work[9; 10]. Factors included are: history of overdose, an active mental health diagnosis, a history of positive tox screen for illicit drugs, an active or prior diagnosis of a substance use disorder, or multiple recent ED visits which included administration of an opioid.
   - One-click access to the PDMP for all patients will be available as in other arms. If the EHR encounter includes records of a PDMP check, the BPA will be suppressed and not fire.
   - As in Group 2 and 3, this is not a truly mandatory check and can be bypassed.

The exact messaging included in and format of the BPAs were determined based on the results of study 19-3063 and technical feasibility. For high-risk prescribing, each BPA will provide an alert and embedded link to action ("check the PDMP"), a reason ("your patient is at high risk due to XXX") and a link to a website providing more information about the study, the logic used to fire the CDS and resources for prescribers such as the CDC Guidelines. No treatment recommendations will be made as the goal of the CDS is to encourage providers to make effective use of existing resources to inform their prescribing. BPAs will be designed to track provider use vs. bypass.

A series of silent alerts will be used to capture information about patient risks and provider PDMP usage over time. For Arms 2 and 3 as described above, an alert nearly identical to the study alert will fire but not be visible to the provider (2nd level in model). The silent alert will have the same PDMP and EHR criteria but will not filter out patients for whom the provider has already checked the PDMP (suppressed in provider alert). This will allow tracking of provider PDMP behavior change over time since we will have PDMP use due to BPA and PDMP by provider which suppresses BPAs. This is important to identify behavior change regarding PDMP use by providers.

In addition, a second silent alert (3rd level in model) will fire for all eligible patients seen by study providers, using the same criteria as the PDMP + EHR alert described above. As with the previously described alert, PDMP use will not suppress this alert so that all patients can be captured. This alert will allow us to document the same risk information for all study patients so we can describe patient risk information across intervention groups. Much of this information tends to be transient and variable over time. Having a snapshot of the data at that moment will be valuable in the final analysis.

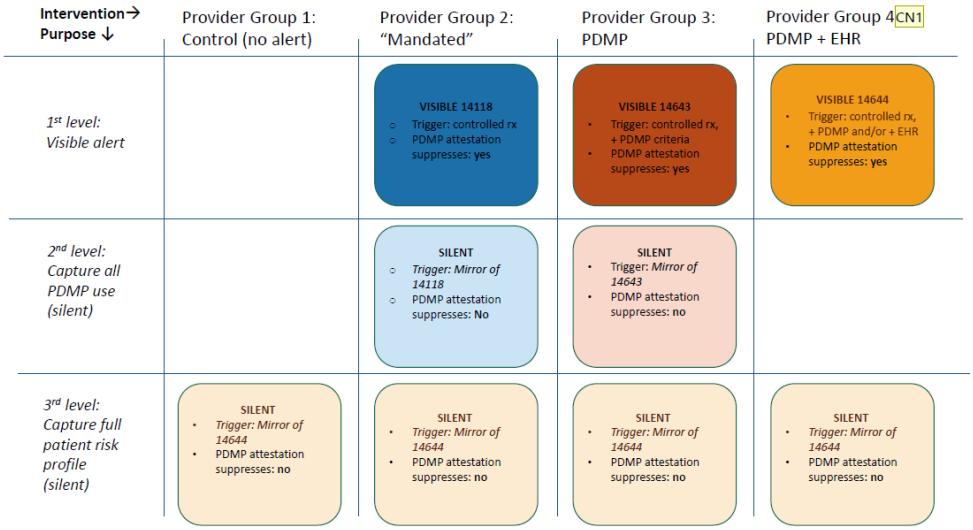


Figure 4: Visible (top row) and silent alerts used in the study CDS

Due to primary care not allowing interruptive BPAs, there will be two units of randomization corresponding to the ED/hospital discharge and the outpatient care setting, respectively.

Prescribers working in UCHealth Emergency Departments and inpatient facilities

- Each ED/inpatient prescriber will be randomized to one of the four study arms described above. Dentists will be excluded.
- Prescribers will be stratified based on primary work site. As a number of facilities within the UCHealth system share staff, "work site" is being defined based on shared staffing as follows:

Emergency Department(s)	**Hospital/Inpatient facilities**
UCHospital at AMC	UCHospital at AMC

Broomfield Hospital; Commerce City, Green Valley, Littleton, Mississippi, Parker, Ralston freestanding EDs	Broomfield Hospital
Highlands Ranch Hospital	Highlands Ranch Hospital
Memorial Hospital North, Memorial Hospital Central, Pikes Peak Regional, Grandview Hospital; Fountain, Meadows, Powers, Woodmen freestanding EDs	Memorial Hospital North, Memorial Hospital Central, Pikes Peak Regional, Grandview Hospital
Greeley Hospital, Longs Peak Hospital, Medical Center of the Rockies, Poudre Valley Hospital, Harmony freestanding	Greeley Hospital, Longs Peak Hospital, Medical Center of the Rockies, Poudre Valley Hospital
Estes Park Hospital	Estes Park Hospital
Yampa Valley Medical Center	Yampa Valley Medical Center

- Prescribers will be randomized at the time of activation of the CDS using permuted block randomization base upon their primary work site and will remain in study for 12 months.
- CDS will only fire for discharge prescriptions (i.e. not for inpatient orders) for prescribers working in hospital-based facilities.
- Providers who work in multiple locations will be assigned to the location where they do the majority of their prescribing.

Primary care and selected specialty practices

- Practices will be randomized into study arms 1, 3, or 4. Due to workflow concerns and the longitudinal physician/patient relationship in primary care, and based on feedback from primary care leadership, inclusion of an interruptive, non-specific alert was considered to be counterproductive in this population.
- Practices will be stratified as small, medium, or large based on the number of opioid and benzodiazepine prescriptions written in the year prior to randomization. Small practices are those with a number of prescriptions in the lowest third, large practices in the highest third, and medium size practice all others.
- Practices with less than 52 total opioid plus benzodiazepine prescriptions in the year prior to randomization will be excluded. With less than one prescription per week, the impact of the CDS on prescribing is anticipated to be minimal and excluding such low providers will reduce the risk of inactive prescribers biasing results.
- Practices will be randomized at the time of activation of the CDS and will remain on study for 12 months.

Practices may be added during the course of the study. Follow up for patient outcomes will continue for 6 months following deactivation of the alerts.

CDS tools will be activated first in EDs, then for inpatient providers, and finally in ambulatory settings. This staged roll out will allow for identification and modification of system bugs and unanticipated problems, as well as allow for increased socialization of the tools and greater buy in by providers.

This study design is chosen for a combination of scientific and pragmatic concerns. This study is effectively an implementation of a novel CDS augmentation, such as would happen routinely in a non-research environment on a practice-by-practice basis. Therefore, to better mimic this real world situation, the most appropriate unit of randomization would be the practice/site. However, pragmatic concerns also inform the design, specifically:

1. **Primary care**: Randomizing by practice will optimize the opportunities for provider education and reduce the risk of cross-group contamination if a single provider or practice treated multiple patients with similar risk patterns but received different CDS alerts. It also ensures that all members of a treatment team working with a single patient or single encounter receive the same information about that patient's risk stratification.
2. **Hospital based**: The small number of EDs and hospitals, especially large EDs, relative to the number of randomization groups translates to a large risk of unbalanced groups. To address this issue, a smaller unit of randomization is appropriate specifically for EDs and hospital discharges. The authorizing provider is ultimately responsible for opioid prescribing and as such is most appropriate as a smaller unit. As residents work under a number of attending physicians, this will also prevent the development of overreliance on automated alerts in a physician in training, in order to minimize the chance of risk to clinical care.

Prior to CDS activation and at the time of activation, training materials will be shared with relevant sites and practices. These materials are included in Appendix #. A link to a provider feedback survey in REDCap will be included in order to collect standardized feedback from system users.

Activation of the alert will be monitored using automated tracking within Epic which identifies providers and patients associated with alert firings. A key feature of the CDS is that the PDMP check must be "attested" to in order to suppress the CDS and prevent re-firing of the alerts, which is interruptive to the provider. This attestation is a workflow change for providers and is essential for CDS success. It can happen prior to prescription entry, in which case the alerts will not activate (suppression), or after activation of the alert.

In the event that providers are being "hit" with CDS alerts multiple times within the same encounter for a single patient because they miss the attestation step, an educational message with a link to the education website will be sent to the provider via email or EHR internal messaging systems to remind the provider to click the attestation button in order to prevent multiple firings. A weekly tally of messages sent will be retained, but no patient information will be retained. No provider will receive more than three educational reminders. The reminder will not include any patient information. This check is intended only to provide an additional personalized education step.

This is important because (1) dissemination of education about new CDS across all of UCHealth is challenging so we will miss providers and (2) we have concerns that if providers find the CDS to be a nuisance (due to a simple knowledge gap of not understanding the attestation requirement) they will not use the CDS.

Similarly, if a provider receives multiple alerts but does not access the PDMP in response, a reminder will be sent that checking the PDMP requires the same number of "clicks" as dismissing the alert and is considered best practice prior to prescribing. As with the contact

described above, these reminders will not contain any patient specific information and are designed as a personalized education step. No provider will receive more than three contacts in this way.

From initiation of educational messages until 9/20/2021, providers who receive one of the above educational messages will receive the message via email. Educational messages sent on or after 9/21/2021 will sent via internal messaging within the EHR. This change in educational message delivery will allow for examination of best practices with providers.

Provider identifying information will be retained in order to determine the effectiveness of the educational outreach. Information retained will include alert firings (including multiple firings/patient) and provider actions over time. In order to better understand the environments in which educational intervention is most effective, provider specialty, primary work site, and basic demographic information (age, gender, race/ethnicity), will be obtained from within the EHR. Method of notification (email or internal messaging within the EHR) will also be tracked to compare provider behavioral changes between educational notifications. Provider work environment (Emergency Department, inpatient or ambulatory) will be determined based on study randomization lists. Data will be deidentified for analysis. Data on CDS and site performance will be monitored continuously during the course of the study (see attached file "Baseline data" for details of data monitored) via automated data extract built by ED Epic analytics team and monitored by study team. No identifiable data will be collected in order to protect confidentiality. De-identified extracts of these data may be exported from Epic to the UCDenver OneDrive system for CDS monitoring and analysis. Baseline data will be gathered retrospectively for the 12 months prior to first deployment of the CDS for each randomization unit. Providers who are not in the system for the baseline will be excluded from analysis.

Validation of the alerts

In order to ensure that the alerts are functioning properly prior to activation, up to 30 individual firings will be identified by study staff and EHR records of the patient will be checked to confirm that a controlled medication was prescribed and the risk criteria identified by the alert system are reflected in the medical record. Records of this validation will be maintained only by alert firing number. Identifying information associated with the alert will not be maintained once the alert firing is validated.

The addition of routine collection of opioid and overall risk scores from the Appriss PDMP interface is a new addition to the UCHealth electronic health record. As such, while the developer can supply data on distribution of scores in their development cohort, no data are available on the distribution of scores in the UCHealth population. Therefore risk scores for patients across the UCHealth system will be collected in order to verify the distribution of scores and number of concurrent controlled medication prescriptions, as reflected in the score. Only risk scores and the department specialty where the patient is being seen will be collected. As most of these data will be from patients whose visit is not relevant to study procedures or study participation, no identifying information will be collected at this step and no attempts will be made to link any given score to a patient, encounter, or specific prescription.

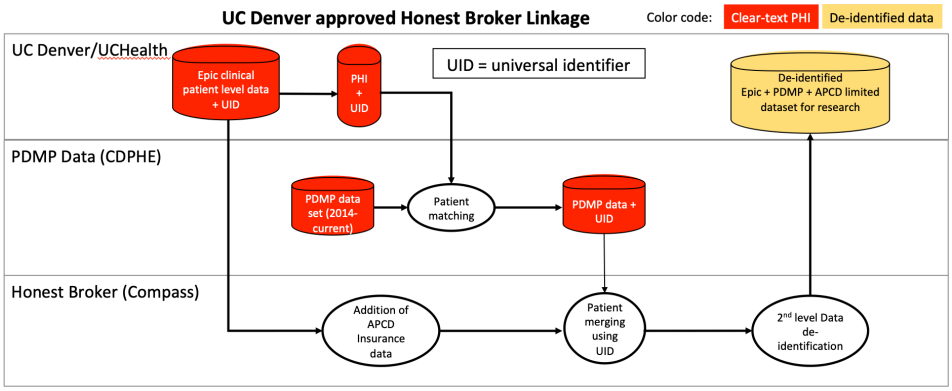
Collection of patient specific data and outcomes:

Data on patient outcomes will be collected retrospectively. These data are crucial to determine the downstream effectiveness of the CDS tools.

Pilot data from selected sites will be pulled by Compass prior to rollout in order to test the data query system. Once the CDS have been activated, data will be pulled shortly after initial deployment, plus up to 2-4 times per year to monitor progress and data integrity. Clinical and demographic data will be extracted from Epic by Compass, based on pre-defined criteria. The list of patients identified will be sent to CDPHE, who will provide PDMP data for all individuals for whom there is a record. PDMP data will provide additional information on controlled substance use by patients from non-UCHealth sites and may be useful to identify aberrant or high-risk use of controlled medications by the patient. Data will be merged with All Payer Claims Data for selected outcomes (ED utilization, hospitalization, death) then secondarily de-identified by Compass acting as an "honest broker" and returned to the study team as a limited data set for analysis.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Procedures: This study does not include any procedures which mandate a particular course of patient care or prescriber behavior. All PDMP information shared is already available through the state portal or integrated Epic PDMP button. It is designed to improve access and data presentation of patient-related information to facilitate safety through risk stratification. Use of the PDMP prior to prescribing an opioid is considered to be a CDC clinical best practice and is required by law in multiple states and in Colorado under certain circumstances[11]. This study is designed to make PDMP access easier and more efficient (increase signal to noise) and measure the impact through both healthcare system and patient outcomes. As such, it represents no greater risk to patients or providers than normal clinical care.



Data collection: CDS activation and provider behavior. Most healthcare system data collection will be automated within the EHR. This is the lowest risk and most accurate method of collecting information on the function of EHR tools and clinical decisions. Collection of feedback from providers will be collected through secure REDCap-based surveys and information collection tools. Providers have the option of answering all questions anonymously. However, there is a small risk of release of information considered private on clinical practices and decision-making processes. Provision of input is fully voluntary, we will not ask for any information on specific patients or any proprietary information from the practice. No information will be provided about statutory compliance to regulatory agencies so there is no risk to the provider around employability or reputation.

Data collection: Patient specific outcomes. This is the only stage of the study which will access PHI, however, there is no direct patient contact by the research team and the study is designed to improve information availability and flow, not dictate a course of treatment. As such, the primary risk of the study is release of private information or a breach of confidentiality around PHI but does not change the patient's risk beyond that of normal medical care. In order to mitigate this risk, UCDenver Compass for Health will act as an "Honest Broker" and provide only a de-identified data set to the study team as they have on 3 prior collaborations with our team. More information on data protections and processes are provided in the COMIRB application document.

Data collection: Provider educational outreach. Provider identifying information will be collected, unassociated with specific patient information. All data will be deidentified by the research prior to analysis. Each provider will be assigned a record number as part of the RedCap database. At the time of analysis, provider name and email will be deleted from the records and the record number will be used to identify the provider. The only risk to the provider from the educational outreach is the possibility of a small breach of privacy around prescribing patterns. All messaging and data storage will be kept within the UCHealth/UCDenver systems in order to maintain privacy. Records including provider names will be stored in RedCap.

E. Potential Scientific Problems:

In our previous work, we noted a temporal trend toward system-wide decrease in opioid prescribing across the EDs examined. If this is ongoing and includes outpatient clinics, it will complicate analysis of the impact of the CDS tools. As such, it is important both to include a control group with no visible CDS and to apply the CDS across as large a range of providers as possible in order to collect enough data to be able to separate temporal and study related differences. To avoid potential data-distorting geographic differences in opioid prescribing, we will randomize clinics by site rather than geographic groupings as was done in our previous study. As we are working only in Colorado, generalizability of the study may be limited if there are unique conditions in this state which cannot be controlled for or statistically managed.

We cannot truly mandate consultation of the PDMP at any point in patient care, therefore we will not be able to definitively determine if prescribing is wholly dependent on the information in the PDMP. However, it is important that clinical care not be disrupted in order to increase acceptance, and therefore impact, of the CDS.

There is a risk that patients will be seen by multiple providers and so be represented in multiple arms of the study. For primary care, this is a small risk as most patients remain with the same clinics for primary care. This is a greater concern for ED or hospital visits where patients are likely to see different providers for subsequent or specialty visits. For provider level outcomes (Aim1) the multiple patient visits can be accounted for with random effects and from a provider prospective the visits can essentially be treated as unique. For patient follow-up outcomes, patients can be censored at the time of a subsequent visit and then followed from the new time point.

At the time of this submission, design and building of the CDS tools is nearly complete and it appears that the required system-level process monitoring data can be collected in an

automated or semi-automated manner, ensuring quality data collection and alleviating previous concerns about potential technical problems with system data collection.

The greatest scientific risk associated with this study is incomplete data. At each stage of the study, it will be possible to bypass study associated BPAs. When this happens, automated data collection fields will remain blank and it will be impossible to determine linkages between the BPAs, use of the PDMP, and prescribing behavior. Epic CDS team have designed CDS and BPAs so bypasses and utilization can be tracked.

F. Data Analysis Plan:

Two categories of data will be collected in conjunction with this study. Hospital system measures will be collected and monitored both at baseline and during conduct of the study. Technical or wording issues in the CDS tools which are identified by this monitoring may be addressed, but the alert logic and conduct of the study will not be changed. Patient level measures will be measured retrospectively.

Hospital system measures will include:

1. Description of practices to include:
   - # of licensed providers
   - # of patients
   - # of visits
   - Specialty/Service
   - Study group
2. Description of prescribing to include the number of opioid and other controlled medication prescriptions written by:
   - Site/practice/prescriber
   - Study arm
   - Month
   - Specialty
   - PDMP button annotation (reviewed/unable to review)
   - PDMP check not recorded
   - To patient with existing sedative prescription
   - Formulation – immediate vs sustained/extended release
3. Description of use of the PDMP and study-associated BPAs, specifically monitoring
   - # of times PDMP activity/website is checked by site/practice/service, monthly, and specialty
   - Frequency of use of the PDMP one-click button per visit and per opioid prescription
   - Frequency of CDS and BPA trigger overall and per opioid prescription
   - Frequency of prescriptions for which the BPA would have fired but the prescriber had already checked the PDMP (look for change over time – do the BPAs lead to learning & change in prescriber behavior)
   - Number of times CDS alert fired, total and per visit (the alert is designed to only fire once during any encounter, thus the per visit rate will be <1)
   - Reviewed (via radio button or via alert)/unable to review/blank

- Resulted in signed Rx (reviewed/unable checked, signed prescription)
- Use of training tools and website. Identifying information on individuals accessing tools will not be recorded.
- Qualitative/semi-quantitative feedback from users as the CDS alerts are implemented

Patient specific measures will include:

- Number of controlled medication prescriptions, both within UCHealth and outside, based on PDMP data (including prescription details to include generic name, dosage, MMEs, days prescribed)
- Use of the PDMP by the prescriber prior to each controlled medication prescription written
- NarxCare risk score at the time of each prescription
- Number of providers/practices used for controlled substance prescriptions
- Number of pharmacies used for controlled substance prescriptions
- Diagnosis of any substance use disorder after the index visit date
- Accidental overdose of controlled substance after the index date (if data available)
- Patient demographics and clinical history characteristics

Educational outreach analysis: Alert firings for providers part of the educational outreach group will be analyzed for percent of non-compliant firings before outreach vs after as well as a comparison between the two different educational outreach efforts (email or EHR messaging system). Non-compliance is defined as 3 or more alerts for a single patient/encounter or >80% of firings closed using the comment/close option rather than using the PDMP link. Firings over time will be tracked as will changes in compliance before and after each outreach attempt. These data will be de-identified prior to reporting. Data will be examined for patterns based on demographics or work environment.

Calculation of sample size:

The number of providers who choose to provide input on CDS design and implementation can only be very roughly estimated. The UCHealth system includes approximately 18,000 individual prescribers, not all of whom will see the alerts. Assuming 5% of individual prescribers choose to provide feedback through the survey available on the website, approximately 900 providers could provide feedback. No minimal response rate is required for significance as no hypotheses will be tested with these data. Survey data will be summarized via descriptive statistics only.

The driving factor in total enrollment is the patient outcome phase. As the tools will be active over the course of approximately 20 months, total patient counts over 20 months, rather than a power calculation, inform our assumptions about enrollment. Of the approximately 2.3 million individuals in the UCHealth system between the ages of 12 – 89, approximately 290,000 received at least one opioid prescription in the last 20 months. Approximately 906,000 individual patients were seen in the UCHealth system in the same time period.

The CDS tools used in this study will automatically query each patient record in order to obtain risk data, but data will only be seen by a provider in a fraction of cases. Based on the advice of privacy officials and COMIRB staff during the design of this study, all individuals queried are included as study participants, even if a provider does not see a study associated CDS alert for all

patients. As such, it is estimated that 950,000 patients will be included in this study. The number of patients queried will be monitored during the course of the study and updated as needed.

Data to be collected:

Variable	Definition	Importance
Prescriber/system data		
Overall controlled medication prescribing rate	Total number of opioid/sedative/stimulant prescriptions divided by total number of visits at each site and the hospital system	Measures the overall impact for each CDS tool
Individual provider controlled medication prescribing rates	Total number of opioid/sedative/stimulant prescriptions divided by total number of encounters for each provider	Measures the behavior and practice variation of individual prescribers for each CDS tool
Overall rate of PDMP use	Total number of times PDMP is accessed when opioid/sedative/stimulant prescriptions are written	Measures how readily providers obtain information for each CDS tool
Provider specific rate of PDMP use	Total number PDMP searches for each provider, changes over time for each provider	Measures provider search behavior and variability changes for each CDS tool
Overall prescription rate after accessing PDMP	Number of times opioid/sedative/stimulant were prescribed after accessing the PDMP	Evaluate the impact of PDMP review on the decision to prescribe controlled mediations
Provider demographics	Age, sex (M/F), years of employment (when available, data saved in EHR)	Evaluate variability in provider acceptance based on information stored in the EHR system.
Provider specific prescription rate after accessing PDMP	Total number of opioid/sedative/stimulant prescriptions divided by the number of times the provider accessed the PDMP for each provider	Evaluate provider variability in interpretation with and without decision support
Patient specific outcomes		
Patient demographics	Age, gender, ethnicity, insurance type	Description of patient population
Visit characteristics	Date of service[#], service location, provider specialty, zip code	Evaluate visit for possible influences on patient and provider outcomes

Opioid prescription	Type, name, strength, number of pills, prescriber	Evaluate the effectiveness of the CDS tools
PDMP search completed	Yes/no	Evaluate the effectiveness of the CDS tools
Patient characteristics	Discharge diagnosis, past medical history, current co-morbid diagnoses, social history, other medications	Evaluate patient variability and other influences on prescribing/risk levels
CDS activation	Activation of CDS alert, which alert	Identify risk factors for patient as presented to prescriber
Prescriptions from PDMP	Type of medication (opioid, sedative, stimulant), date written[#], date filled, [#] medication name, strength, formulation, # of pills prescribed, # of days supply, milligram morphine equivalents (MME), insurance type, pharmacy number	Evaluate patient outcome, needed for complete picture of prescription use
Non-UCHealth visits from All Payers Claims Data	ED visits, hospitalizations	Evaluate overall patient outcome, including unintended consequences of limitation of prescription pain medications
Provider Feedback		
Use of training materials and website	Usage (file access) over time	Measure of effectiveness of educational efforts
Survey responses	See draft included with submission	Provide ideas of aspects of CDS tool considered worthwhile by users. Descriptive statistics only, non-quantitative analysis.

[#]All data will be deidentified prior to release of data to the research team.

G. Summarize Knowledge to be Gained:

As PDMP use improves prescribing decisions, this study will provide immediate, direct benefit to study participants. Further, it will provide greater understanding of the reasons why clinicians use or do not use the PDMP as recommended, and explore several options for improving utilization and maximizing appropriate clinician use of the information provided. Finally, it will explore patient focused outcomes when the PDMP is used (or not), and if patient outcomes are better (defined as less aberrant or long term opioid use) when PDMP CDS tools are better integrated into the provider's workflow and better focused on providing high impact, risk based information

to the provider at the appropriate time. Given the number of patients and providers covered by the UCHealth system, and the geographic dispersion of UCHealth facilities around the state, it is likely that results will be generalizable through the state and other states through the region. The degree to which our findings will be generalizable beyond Colorado and the mountain west regions is uncertain.

H. References:

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[10] Seymour RB, Leas D, Wally MK, Hsu JR. Prescription reporting with immediate medication utilization mapping (PRIMUM): development of an alert to improve narcotic prescribing. BMC Med Inform Decis Mak 2016;16:111.

[11] Colorado Senate Bill 18-022: Concerning clinical practice measures for safer opioid prescribing, 2018.

ATTACHMENT A

Provider/practice specialties included in data

Anesthesiology
Behavioral Health
Brain and Spine
BREAST
Breast Surgery
Burn Surgery
Cardiac Intensive Care
Cardiac Surgery
Cardiothoracic Surgery
Dentistry
Dialysis
EXEC HEALTH
Family Medicine
General Surgery
Gerontology
Gynecology
Hand Surgery
INTEGRATED MEDICINE
Internal Medicine
INTERVENTIONAL CARDIOLOGY
Maternal and Fetal Medicine
Medical Surgical
Neurology
Neurosurgery
Obstetrics and Gynecology
Occupational Medicine
Ophthalmology
Oral Surgery
Orthopedic Surgery
Otolaryngology
Pain Medicine
Physical Medicine and Rehabilitation
Plastic Surgery
Primary Care
Psychiatry
Rehabilitation
Rheumatology
Spine and Rehab Medicine
Sports Medicine
Surgical Intensive Care
Surgical/Trauma
Thoracic Surgery
Transplant
Urgent Care
Urology
VASCULAR
Vascular Surgery
Womens Health
Workers Compensation
Wound Care