COMIRB Protocol

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Protocol #: 18-2098

Project Title: 24-hour oral morphine equivalent based opioid prescribing after surgery

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I. Hypotheses and Specific Aims:

We have previously shown that 83% of patients after Cesarean section and 71% of thoracic surgery report taking half or less of opioids prescribed; 53% and 45% respectively report taking five or less of the prescribed pills.[1] Such overprescribed opioids are stored in unsecured locations in the 75% of cases.[1,2] These opioids represent a major source of potential morbidity and mortality. The *rationale* that underlies the proposed research is that once we have proven the efficacy of patient-centered pain management approaches, we can improve surgical pain therapy on a large scale.

Specific Aim: *We will utilize the electronic health record to individualize pain therapy in surgical patients after hospital discharge using last 24-hour opioid intake as the decision variable for the amount of opioid pain pills prescribed.* Our preliminary data indicate that current opioid prescription practice after surgery follows a "one size fits all" pattern.[1] In-hospital opioid use 24 hours prior to discharge serves as a strong indicator to correctly estimate needs for analgesic medications at home.[3] We will test our hypothesis that this tool will reduce the amount of opioid medications prescribed while maintaining patient post-operative pain control. We will test this tool prospectively for 44 post Cesarean section patients anticipated to use about half or less of the usually prescribed amount of opioid pain pills randomized equally to prescription tool intervention or no intervention (prescription as usual).

This protocol addresses only Specific Aim #3 of the original grant. Specific Aim #1 and #2 are addressed under a separate COMIRB protocol #14-1938.

II. Background and Significance:

Prescription opioid overdose has emerged as a leading cause of death in the general population.[4,5] Opioid-based therapy represents a corner-stone of post-operative pain management.[6] With increasing emphasis on robust pain therapy, sales of opioid medications have increased four-fold in the last decade.[7-12] Parallel to this rise, opioid-associated deaths have also quadrupled.[7] We have shown that long-term opioid use occurs in up to 22% of patients following surgery.[13] Over-prescribed opioids after surgery can create a reservoir of opioids that become available for non-medical use.[14,15] Effective strategies to maximize non-opioid pain therapy and to limit such a reservoir are lacking. Thus, there is an *urgent need* to individualize post-operative pain therapy and reduce our reliance on opioids.

Converting knowledge on actual need for opioid pain medications after surgery into tangible benefits can prevent over-prescription of opioids that become available for non-medical use.[16] The *objective* of this aim is to prescribe pain medications after surgery in a patient-centered fashion. We will use the average amount of opioid medications (in oral morphine equivalents - OME) taken in the last 24 hours prior to discharge to inform and design a clinical decision support tool. This tool will reduce the amount of opioid medications prescribed while maintaining patient post-operative pain control. The calculated "last 24 hour OME dose" will be applied to generate a recommendation for the prescription of a cumulative opioid dose that will be shared with the provider when the post-discharge pain medication is made, e.g. via displaying the last 24-hour opioid use in the electronic health record (EHR). The *rationale* is that testing of such a decision-making tool will lay the groundwork to translate the findings of this project into more secure and efficient opioid prescribing practices to a system-wide level. Upon completion, we *expect* to have developed an effective decision-making tool to help providers estimate required pain medication following patient discharge.

III. Preliminary Studies/Progress Report:

Preliminary Studies. In a cohort of 652 patients who had undergone surgery at UCH Metro clinicians chose the same cumulative opioid dose (300 oral morphine equivalents) in more than 75% of patients for the discharge opioid prescription (Figure 1). These data indicate that opioids following inpatient surgery are not prescribed in an individualized fashion, but rather that most patients receive a very similar regimen for post-discharge pain management. Using the same EHR (Epic) database that generated the data above, we are able to generate information on types and doses of pain medications that are administered to patients, who are still in the hospital in real time (Dr. Lin, Chief Medical Information Officer and Dr. Jean Kutner, CMO at UCHealth strongly support this project). We have previously shown that 83% of patients after Cesarean section and 71% of thoracic surgery patients report taking half or less of opioids prescribed; 53% and 45% respectively report taking five or less of the prescribed pills.[1] Hence, a "one size fits all" approach to pain management after discharge is common in clinical practice and leads to frequent over-prescription of opioids. Based on our own preliminary data and recommendation published by others, opioids taken 24 hours prior to discharge inform the amount of opioids that are likely to be used at home and hence the following prescriptions amounts have been suggested for patients taking equal or less than 22.5 MME in the 24 hours prior to discharge:

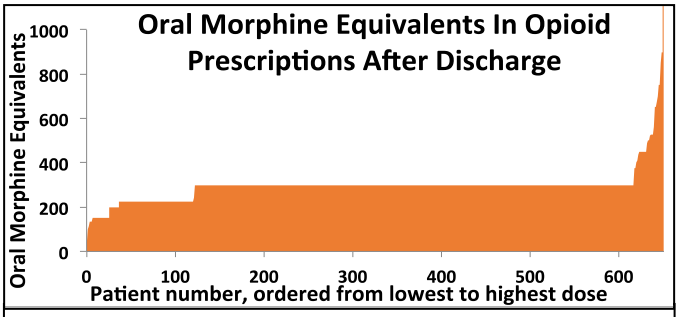

Figure 4: Cumulative opioid dose in oral morphine equivalents (OME) prescribed to 652 patients upon hospital discharge after surgery. Clinicians chose the same cumulative opioid dose (300 OME) in more than 75% of patients.

- no opioids for home use for patients having taken no opioids in the last 24 hours prior to discharge
- 75 morphine milligram equivalent (MME), e.g. 10 oxycodone 5mg tablets, for home use for patients having taken equal or less than 22.5 MME, e.g. 1-3 oxycodone 5mg tablets in the last 24 hours prior to discharge.[17]

IV. Research Methods

A. Outcome Measure(s):

Study measurements will include 24 hour prior to discharge opioid and other medication intake, prescribed post-discharge opioid doses in morphine milligram equivalents from the EHR, self-reported analgesic medication requirements (post-discharge intake of opioid medications, left-over opioids, intake of other pain medications, such as acetaminophen and non-steroidal anti-inflammatory drugs – NSAIDs), NIH PROMIS[18] outcomes for Pain Intensity and Pain Interference, side effects, reasons for not taking opioids, as well as basic demographic information. We will also collect information about need for additional opioid prescriptions, and reported medication disposal for left-over opioids, length of hospitalization, repeat vs. first C-section and other relevant perioperative variables. For this study, we will be using REDCap for data collection after Cesarean section to administer four weekly surveys following the day of discharge.

We will seek follow-up with providers about the usefulness and acceptability of the EHR-based intervention. Providers will be surveyed with a REDCap survey using a modified version of the GUIDES checklist, which provides a tool to improve the successful use of guideline-based computerized clinical decision support.[21]

B. Description of Population to be Enrolled:

Survey population:
Inflating enrollment by approximately 25% to account for drop out and result in 44 patient completers, we will consent 60 adult patients receiving a Cesarean section procedure. After completing an observational study in three surgical groups (thoracic surgery, gastrointestinal surgery, C-section), we chose to evaluate this intervention first in C-Section patients based on their unique characteristics: low procedural variability, low incidences of chronic opioid use, and low level of comorbidities. Also, the issue of having potentially unsecured opioids in a household with young children is of special relevance for opioid safety research in the Cesarean section cohort.[19]

Inclusion Criteria: 1) Women ages at least 18 years of age having undergone Cesarean section surgery at the University of Colorado Hospital are eligible. 2) Willingness to complete weekly surveys for 4 weeks after discharge. 3) Anticipated to need half or less of the usually prescribed amount of opioids based on the amount of opioids taken in the last 24 hours prior to the opioid medication being written for discharge (only patients who took 22.5 MME or less opioids in the last 24 hours prior to the day of discharge will be eligible for this study). Inclusion and exclusion criteria (including the amount of opioids taken in the last 24 hours prior to discharge) will be evaluated in the morning in patients scheduled to be discharged later that day.

Exclusion Criteria: 1) Patients under the age of 18 years, 2) Patients returning to institutional settings (e.g. prison, jail, mental health facility), 3) Pregnant women (patients will be approached after their C-section), 4) Decisionally challenged patients, 5) Blind or illiterate patients.

Based on our prior research factors such as emergency status, prior opioid use, repeat vs primary C-section, and associated procedures were not associated with post-discharge opioid use once we adjusted for last-24 hour inpatient opioid use. Hence, these patients will not be excluded.

We will perform a randomized clinical trial (RCT) of an EHR-based recommendation to prescribe opioids at discharge according to the recorded last 24-hour inpatient use according to current recommendations and evaluate its effect on the amount of opioids prescribed as well as pain control after discharge.

The medical provider of each patient enrolled (up to n=60) will also be surveyed using an online REDCap survey. Inclusion criteria: 1) Medical provider of a patient enrolled in the study, 2) Willingness to use the Prescription Tool and complete an online survey. No exclusion criteria.

Total number of participants counting both patients and providers will be114; up to 60 patients and 54 providers enrolled in the study.

C. Study Design and Research Methods

Using the UCH Epic/Clarity database, we will continuously identify all patients who underwent Cesarean section surgery at University Hospital. Patients will be approached regarding interest in the study prior to hospital discharge. A trained PRA, Perinatal CTRC staff or other trained provider will explain the study to prospective participants using standard language. Participants will be told that they are being asked to be in this research study because they recently had surgery at the University of Colorado Hospital.

If the patient is interested in participation the study PRA, Perinatal CTRC staff or trained provider will review the consent/HIPAA form with the patient and answer any questions the patient may have. Study staff will also provide them with a hard copy of the consent/HIPAA form.

- OR –

During the SARS-CoV-2 (COVID-19) pandemic or as required by UCHealth, we will minimize in-person contact with patients and complete study visits remotely whenever possible. Perinatal CTRC staff will obtain informed consent from patients using the procedures detailed below.

Consent-HIPAA authorization will be obtained remotely via phone or HIPAA-compliant videoconference application (Zoom) following COMIRB guidance (CG-85, Version April 9, 2020).

- A trained provider with appropriate PPE, who is already providing standard care to the patient, will give the patient a hard copy of the consent/HIPAA form so they have an approved copy of the consent form “in hand” at the time of the informed consent discussion.
- Perinatal CTRC staff will call the patient to initiate the informed consent discussion.
- The discussion will begin with identification of who is participating on the call; Perinatal CTRC staff will confirm the potential subject has a hard copy of the consent-HIPAA form before beginning the discussion.
- Perinatal CTRC staff will review the consent/HIPAA form with the patient and answer any questions.

- The patient will sign the consent-HIPAA form and give it to the trained provider already providing standard care. The provider will give the signed form to Perinatal CTRC staff who will also sign the form noting that consent was obtained by phone. A copy of the signed consent-HIPAA form will be given to the patient.

We will seek a waiver of written consent for surveying providers who are given the dosing suggestion via the EHR-based Prescription Tool. At their convenience, these providers will complete an online postcard consent and survey via REDCap.

After consent, demographics and the best contact information will be collected (remotely by phone during the COVID-19 pandemic or as required by UCHealth) from those enrolled patients who indicate they are interested in completing the surveys after their hospital discharge.

We expect 44 patients to complete all four weekly surveys and we define the intent-to-treat sample as patients who complete one or more surveys (providing at least one observation to be used in analyses). To conservatively allow for increased variability due to attrition, 60 patients will be randomized equally electronically to intervention (prescription tool) or no intervention (prescription as usual). We will use an electronic randomization scheme created so that the principal investigator and statistician can remain blind to assignment.

At the time of writing the prescription for a patient the provider will be informed that a patient may be considered for a lower post-discharge opioid dose (No opioids for patients who did not take any opioids in the last 24 hours, and 10 oxycodone 5mg tablets, for patients having taken less than 22.5 MME, e.g. 1-3 oxycodone 5mg tablets in the last 24 hours). No dosing recommendations for patients having taken more than 22.5 MME will be made as these patients are not eligible for this study. Final dosing decisions and drug choices will remain at the discretion of the treating provider and decisions will be tracked.

For this pilot study, the provider information (best practice alert – BPA) will be operationalized via a written recommendation on paper handed to the provider by study staff in a sealed envelope or emailed with a read receipt that the provider will be asked to open and read. Alternatively, the BPA may be presented electronically using a screen. Providers will be asked to acknowledge that they read the BPA by closing the window or opening the envelope or email.

<u>For the intervention group:</u>
For patients receiving no opioids in the last 24 hours prior to an oxycodone or oxycodone/acetaminophen discharge prescription being written:

BPA: “In the last 24 hours, your patient received NO opioids. Consider not prescribing any opioids for pain management after discharge.”

For patients receiving >0 MME up to <u>≤</u>22.5 MME in the last 24 hours prior to an oxycodone or oxycodone/acetaminophen discharge prescription being written (example BPA is for 15 MME – 2 oxycodone 5mg tablets):

BPA: "In the last 24 hours, your patient received opioid medication equivalent to 2 oxycodone 5 mg tablets by mouth. Consider writing for a total of 10 oxycodone 5 mg tablets for pain management after discharge."

Note, oxycodone-containing medications are the opioid prescribed in >96% of cases after Cesarean section at our hospital. We will make equivalent recommendations if hydrocodone is used. Based on our data, no other opioid medications have been prescribed for use after discharge following Cesarean section.

For the control group:
BPA: "Consider prescribing the usual medications for pain management after discharge."

One week after hospital discharge interested patients will be contacted and asked to complete the first of four surveys. Participants will receive a $10 gift card, or equivalent money order if requested, for each of four weekly surveys, for a total of $40. All enrolled patients will complete the weekly post-discharge surveys within REDCap or by hard copy or phone if they do not have internet access.

Providers will not be paid to use the Prescription Tool or complete the short, one-time online survey.

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

Discomforts and other possible risks include:

Common Risks:

- Tiredness or boredom when completing study assessments.

Uncommon Risks:

- Tension or nervousness may occur from completing the study assessments. Participants can talk with the researchers about such problems, and can terminate the study if they wish.

- Problems with pain management.
  Only patients who are predicted to require approximately half or less than the usually prescribed opioid dose (i.e., those taking equal or less than 22.5 MME in the 24 hours prior to discharge) will be eligible. Patients will be randomized to have their provider receive a suggestion for a reduction of opioid dose versus standard of care. Providers may still choose to prescribe a higher dose as clinically indicated. The prescription tool will only make a suggestion. We will track the recommendation made as well as the actual dose prescribed.

  We will follow up with all patients at half of their usual follow-up period (usually 2 weeks) via a REDCap survey, phone, email, or in clinic to assess how they are doing and if they are likely to run out of opioid medications despite still requiring them for acute surgical pain. For patients, who are running low on opioid pain medications, we will arrange for additional pain medications to be prescribed as deemed appropriate by their providers using the electronic prescription route if needed. We will monitor the study progress closely and reassess our study design

if more than 5 intervention group patients require prescriptions prior to scheduled clinic follow-up.

All patients are routinely given a phone number where they can reach a surgical provider 24 hours a day, seven days a week, in case pain therapy is inadequate.

The study team will monitor need for secondary prescriptions from providers to ensure that no significant under-prescription of opioid medications after surgery occurs.

These recommendations are in accordance with current quality improvement efforts by the system-wide Pharmacy and Therapeutics (P&T) Opioid Subcommittee charged with addressing UCHealth actions to meet the new Joint Commission Pain Assessment and Management guidelines. This committee is co-chaired by the Co-I of this study (Karsten Bartels) and Dr. Clark Lyda, Pharm.D. The PI is also an active member of the system-wide UCHealth Opioid and Pain Management Steering Committee that is chaired by Dr. Jean Kutner. This committee also supports this application. Lastly, the PI holds an active funded 5-year NIH K23 grant "*Improving Opioid Prescription Safety After Surgery*" that provides material and personal support, statistical support, and regulatory support for this application.

Rare But Serious Risks:

- Breaches of confidentiality.

Confidentiality is maintained throughout the study's entirety and protected health information will not be disclosed outside the University of Colorado. The study therefore does not involve any more than minimal risk to patients, namely loss of confidentiality. While there is no direct benefit to subjects, knowledge gained from our study will help to tailor prescription of analgesic medications after surgery to patients' actual needs.

Strict safeguards for data protection will be followed including storage on protected servers, password protection and monitored access to authorized users. Please see the Data and Safety Monitoring Plan section for additional details. Patients are provided with the PI's office phone number, COMIRB's phone number, and the PI's email address and phone number should they have any questions. Patients may withdraw from the study at any time.

Data and Safety Monitoring Plan:

Each participant will be assigned a corresponding study ID number. ID numbers will be assigned in the order of patient enrollment. A master list connecting the enrollment number with the patient's medical history number will be maintained only for the duration of the data collection. Only PI-approved study personnel who have current COMIRB-required human subject protection training will have password-protected and monitored access to the data. Following the interpretation of the data, the master list will be destroyed and no patient identifying information will be maintained.

Demographic data, information on prescribed and non-prescribed medications, and clinical outcome values relevant for pain management will be obtained from the Epic database and stored in a secure fashion using REDCap.

E. Potential Scientific Problems:

Concomitant provider education may itself lead to a change in pain management practices. To address this, a future larger pragmatic clinical trial could include cluster randomization based on study site. Few prognostic models actually are in clinical use, often because they have not been externally validated and because of the data collection burden. Our local Clinical Decision Support Program has confirmed the feasibility of our proposal to integrate a future decision-making tool into the electronic medical record and order entry system.

F. Data Analysis Plan:

The intent-to-treat (ITT) sample is defined as those who complete at least one survey. In our prior observational study, 100% of the C-section patients satisfied this criterion. If there is a subsample that does not complete at least one survey, we will compare that group to the ITT group on relevant demographic and clinical characteristics. Outcomes not requiring any response to the survey will be compared for all patients enrolled, regardless if they completed at least one survey.

The prescription tool and prescription as usual (PAU) groups will be compared on baseline demographic and clinical characteristics using Mann-Whitney tests, independent t-tests and chi-square tests as appropriate for continuous and categorical data; when necessary (i.e. when variables have distributions violating assumptions), nonparametric procedures will be substituted. We expect randomization to ensure group equivalence; should variables be different they will be evaluated as covariates in the analyses described below as appropriate.

Our primary analyses will compare the prescription tool group with the PAU group on oral morphine equivalent dose left over (not used) from the total amount of prescribed opioids. Based on our preliminary data, we will assume the control group to receive an opioid prescription for 20 oxycodone 5mg tablets (150MME), leading to a mean MME of 101.8 (SD 60.5) left over. Conservatively estimating a 50% adoption rate of the decision support tool by prescribing clinicians, we would expect a mean MME of 55 (SD 37.6) left over opioids in the intervention group. Assuming statistical comparisons will be made using Mann-Whitney test a sample size of n=22 per group (44 total using 1:1 allocation) will yield 90% power with an assumed one-tailed alpha of 0.05 (G-Power, version 3.1.9.2).[20]

For the primary weekly opioid use variable and for secondary longitudinal variables of interest (i.e. weekly scores for pain interference and pain intensity), trajectories will first be visually compared between the two groups. Mixed models will then be used to analyze each outcome that will include fixed group, time, and group by time interaction effects and random patient effects. Covariates will only be included if they differ by group at baseline and are related to the outcome of interest. The test of the group by time interaction will indicate if each outcome differs over time by groups. Overall means for each outcome will be estimated and compared between groups as will week 1 and week 4 means of each outcome will be separately compared between groups. These analyses on the ITT sample will then be repeated on the subset of patients who complete all 4 surveys and any differences between results will be reported.

Important secondary summary variables that will be compared between groups using chi-square, t-test, nonparametric, and covariate-adjusted (i.e. ANCOVA) methods as appropriate are: need for additional opioid prescriptions (yes, no), and amount of opioid and non opioid analgesic drugs taken (total mg). Reported medication disposal by group will additionally be described.

G. Summarize Knowledge to be Gained:

We expect to have designed and demonstrated the feasibility of implementation of a decision-making support tool to better estimate individual patient needs for pain therapy after surgery. The instrument will be parsimonious in nature, as it will rely on information that is readily available in the patient's medical record and it will not require any special action by the clinician to obtain a dosage recommendation. Creating such a tool will be critical to translate the findings of this line of research into safer opioid prescribing practices for our patients. Given that the tool can be integrated into a nationally used electronic medical record and order entry system (Epic), usage and further testing of its performance will be possible in many diverse environments. Eventually, public health will be promoted through improving non-opioid analgesia and by decreasing prescriptions of unneeded opioid pain medications. This will lead to a subsequent decreased availability of opioid medications for non-medical use. Further, the data obtained from this aim will be used for a subsequent grant application.

H. References:

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