Study Protocol for IRBMED Proposal

Understanding Pain and Medication Use Following Surgery
Department of Anesthesiology, April 2017

Principal Investigator: Chad M. Brummett, MD

Section 1: Introduction and Aims

The United States is currently experiencing a catastrophic opioid epidemic. Since 2000, the mortality rate from opioid overdose has increased by 200%. Between 2013 and 2014 alone, rates of opioid overdose death increased by 14%.[1] Despite these statistics, opioid prescribing continues to accelerate.[2] For instance, health care providers wrote 259 million opioid prescriptions in 2012, enough for every adult American to have a bottle of pills.[3] One of the most common episodes for opioid prescribing is during the perioperative period, and opioids remain the cornerstone of postoperative pain management. Yet, there are no guidelines to direct postoperative opioid prescribing.

The lack of evidence-based guidelines for postoperative opioid prescribing has contributed to a surplus of opioid pills within our patients' homes and communities, increasing the potential for diversion and nonmedical use. A recent study suggests that for outpatient general surgery procedures, roughly 72% of prescribed opioids go unused.[4] Current opioid disposal options are limited to DEA-authorized opioid collectors, including select law enforcement agencies, pharmacies, or organized pill drop events, and many patients remain unaware of these avenues.[5] Several studies have found that few patients have knowledge about opioid disposal options and even fewer dispose of their unconsumed opioids.[5-8]

Unconsumed opioids pose a diversion risk. In the 2011 National Survey on Drug Use and Health, 70.8% of those who used a prescription medication non-medically obtained the medication from a friend or relative, with or without their knowledge. In a separate study of Veteran patients, 34% of participants described engaging in sharing or diversion of opioids at least once.[8] Additionally, nonmedical prescription opioid use is the primary pathway to heroin use.[9-11] For example, a longitudinal study of 12th graders in the United States demonstrates that the lifetime prevalence of nonmedical use of prescription opioids increased from approximately 6% in the early 1990's to 13% by 2009, and the lifetime probability of exposure to prescription opioids in medical or nonmedical contexts among high school students ranges from 22% to 45%.[12,13] Importantly, over 80% of young intravenous drug users report initiation of prescription opioid misuse prior to heroin.[14]

Considering that 40% of the prescriptions written by surgeons are for opioids and patients have limited options for and/or knowledge of opioid disposal, we propose an initiative to provide patients with information and novel options for opioid disposal as part of the surgical care pathway.[2] Our aims are as follows:

Aim 1: To determine whether the use of a novel opioid disposal pouch will increase the rate of safe disposal of opioids after surgery when compared to usual care or an information sheet on the safe disposal of opioids.
Based on the day they undergo surgery, patients will receive either 1) a Deterra® Drug Deactivation System which they can use at home to dispose of their opioids or 2) an informational sheet regarding safe opioid disposal or 3) usual care regarding opioid disposal instructions. We will quantitatively and qualitatively survey patients regarding their postoperative opioid disposal behaviors and satisfaction with these interventions. We hypothesize that the Deterra® Drug Deactivation will prove to be a more efficient and acceptable means for disposal, and will increase the likelihood of disposal and thus, the safety of the patient and their community.

Aim 2: Understand patient characteristics associated with safe disposal. We will collect a brief battery of validated self-report measures of demographics, pain, mood, function, and sleep to assess characteristics of patients that safely do and do not dispose of their medications.

Aim 3: Obtain normative data of postoperative opioid requirements for the surgeries studied. We will obtain data on the number of pills used following surgery to help inform appropriate prescribing for future surgery.

Section 2: Background Information

The Deterra® Drug Deactivation System

This system is a pouch that deactivates prescription drugs, rendering them ineffective for misuse and safe for the environment. It uses a patented activated carbon technology to deactivate drugs, including pills, liquids, and patches, and has been found to be 99% percent effective in studies funded by the National Institute of Drug Abuse (NIDA). Additionally, the pouches are made from environmentally friendly materials and contain active ingredients that are considered non-toxic and pose minimal risk, according to their MSDS.

The Deterra® Drug Deactivation System comes in several sizes – small, medium, large, and extra-large – depending on the number of pharmaceuticals that need to be disposed. Each Deterra® Drug Deactivation System contains a water-soluble inner pod containing a patented activated carbon. Once the pharmaceuticals are placed in the pouch, warm water is added to dissolve the inner pod and release the activated carbon. The warm water then dissolves the pills, patches, or liquids so they can be absorbed by the carbon and rendered inert and irretrievable. The pouch is then disposed of in normal trash. The Deterra® Drug Deactivation System contains clear instructions for disposal, including the amount of pills, liquids, or patches, which can be disposed in the pouch. The company reports that in a survey of 1665 users, 95% of consumers had no problem using the pouch. With the pouch, patients can safely dispose of unused post-surgical prescriptions from their home. Documentation on the Deterra® Drug Deactivation System can be found in Section 44 “Additional Supporting Documents” of the present IRBMED proposal.

Opioid Disposal Information Sheet
The information sheet patients will be provided will include directions on how to use the interactive map developed by our team based on previous research (HUM00116037). This map allows patients to search for permanent DEA-authorized disposal sites within a desired geographical area within Michigan.

Section 3: Study Design and Methods

Subject Selection and Study Design
This pragmatic clinical trial will recruit patients 18 years of age or older who are scheduled for a surgical procedure at Michigan Medicine's East Ann Arbor Ambulatory Surgery & Medical Procedures Center.

Eligible patients will be identified using MiChart and screened for appropriate inclusion and exclusion criteria. In order to conduct this screening, a waiver of informed consent and HIPPA authorization will be requested from the Institutional Review Board at Michigan Medicine (IRBMED).

Eligible patients will be approached in person by a trained member of our research team in the preoperative area on the day of their surgery. Written informed consent will be obtained from each patient. The consent process will include a verbal explanation of the study, including the purpose, time commitment, confidentiality, compensation, and required regulatory information. It will also be explained verbally that participation is voluntary, non-participation will not affect a patient's surgical procedure or medical care in any way, and that patients may cease participating at any time. Patients will also be given the opportunity to ask questions, which will be addressed by a trained member of our study team. The informed consent form given to patients will be approved by the Institutional Review Board at Michigan Medicine (IRBMED).

After informed consent is obtained, the patient will be given the following battery of questionnaires: Opioid and Benzodiazepine Assessment, Marijuana Assessment, Pain at the Surgical Site and Overall Pain, Pain Severity, CSQ:CAT (Thoughts About Symptoms), Fibromyalgia Measure (Michigan Body Map & Symptom Severity Index), the PROMIS Depression, Anxiety, Sleep, Fatigue and Physical Function Measure, Global Impression of Change, Life Satisfaction, PROMIS instrumental and informational questions, Screener/Opioid Assessment for Patients with Pain (SOAPP), Prescribed Opioid Difficulty Scale (PODS), Family Abuse History, Past Nonmedical Use of Prescription Drugs, and Demographics. Patients will complete these questionnaires on paper. If a patient needs physical assistance completing the survey, a member of the research team can record the patient's answers with the patient's permission.

Based on the day of their surgery, patients will be assigned to one of three groups that will receive the following resources at the time of their discharge: 1) an information sheet about safe opioid disposal sites or 2) a Deterra® Drug Activation System or 3) usual care and no interventional materials. We plan to enroll patients over a period of six weeks. If we fail to meet recruitment needed to satisfy our power calculation, we will extend the

study enrollment period beyond six weeks. The research team will communicate to clinical staff which patients have agreed to participate in the study and resources will be presented to the patient by the clinical staff member preforming their discharge.

The usual care group will occur in the first two weeks of the study to avoid any potential contamination of the information sheet and Deterra interventions on the nursing instructions or care. The 4-week period of the information sheet and Deterra bag interventions will randomized by the day.

The usual care group will not receive any specific instructions with respect to safe disposal of opioids, although opioid disposal education from providers may occur based on usual care. In the information sheet group, nurses will be instructed to specifically show the patients the pamphlet as a part of their discharge instructions. Nurses will be asked to state the following as a part of the discharge instructions, "This information sheet goes through a step-by-step process on how to find places in your area where you can safely dispose of any unused pain medications after you have finished using them." In the Deterra group, nurses will show the patients the bag and show them the brief instructions included on the bag prior to discharge. They will state, "This bag offers a way for you to safely dispose of any unused pain medications at home after you have finished using them."

Patients will be surveyed via their preference of an emailed Qualtrics survey or telephone call 4 weeks after their surgery and will continue to be contacted up to 6 weeks following their surgery if they cannot be reached. For patients who requested an emailed survey that do not respond to two emails, we will follow-up by telephone. This message will be communicated to all participants. During the preoperative assessment, patients will be asked for their preferred email address and telephone number and if there is a particular time of day they prefer to be contacted. Researchers will use this contact information or the patient's contact information in MiChart to complete the follow-up survey. The 10 to 15 minute follow-up survey will ask patients about their postoperative pain and prescription pain medication use, disposal of their postoperative pain medication, preferences for controlled substance disposal, and opinions of the disposal resources they received upon discharge.

Each patient's medical record will also be reviewed for clinical events, discharge prescriptions, insurance status, and demographic characteristics. Patients will receive $10 per completed time point (up to $20 total) at the end of their participation in the study.

Data Management and Accuracy

Survey measures completed on the day of surgery will be transferred from paper surveys to Qualtrics® by study team members. The research team member that contacts the patient for a follow-up telephone survey will enter their responses into the online system, Qualtrics® and patients who respond to an emailed Qualtrics® survey will enter their information directly into Qualtrics®.

Statistical Analysis Plan

Based on the day patients underwent surgery, they received either 1) a Deterra® Drug Deactivation System which they could use at home to dispose of their opioids or 2) an informational sheet regarding safe opioid disposal or 3) usual care regarding opioid disposal instructions. Postoperative opioid prescription was recorded, and in the follow-up interview during 4-6 weeks after surgery, number of pills consumed was collected. Prescription size and consumed amount were converted to oral morphine equivalents (OMEs). OMEs were calculated based on the contents of the prescription and the number of pills provided. The study will compare the differences in safe disposal among the three groups of patients.

There are three aims:

Aim 1: To determine whether the use of a novel opioid disposal pouch will increase the rate of safe disposal of opioids after surgery when compared to usual care or an information sheet on the safe disposal of opioids.

Aim 2: To understand patient characteristics associated with safe disposal. We will collect a brief battery of validated self-report measures of demographics, pain, mood, function, and sleep to assess characteristics of patients that safely do and do not dispose of their medications.

Aim 3: To obtain normative data of postoperative opioid requirements for the surgeries studied. We will obtain data on the number of pills used following surgery to help inform appropriate prescribing for future surgery.

Among three intervention groups (usual care, information sheet, and novel bag), for Aim 1, we hypothesize that the Deterra® Drug Deactivation will prove to be a more efficient and acceptable means for disposal, and will increase the likelihood of disposal. Based on the analysis for Aim 1, significant patient characteristics will be identified. To answer Aim 3, amount and percent of opioid prescribed and consumed will be calculated.

Outcome Variable

For Aim 1 and 2, primary outcome variable is binary and represent whether or not a participant that had leftover opioid pain medication to dispose of did so. Participants that were not prescribed an opioid pain medication, that did not fill an opioid pain medication prescription, that took all of their opioid pain medication prescription, or that had an additional procedure or admission during the follow-up period will be excluded from this primary variable assignment and excluded from the primary analysis. For aim 3, the outcome was self-reported use of opioids (number of pills and time to cessation).

Explanatory Variable

The main explanatory variable is group where a participant was randomly assigned as, 1) a Deterra® Drug Deactivation System which they can use at home to dispose of their opioids or 2) an informational sheet regarding safe opioid disposal or 3) usual care regarding opioid disposal instructions.

Patient Characteristics

Patient's characteristics were collected, including age, gender, race/ethnicity, income, education level, and family history of opioid use, chronic pain, alcohol, and drug abuse. Patient's self-report measures of pain, mood, function, sleep, and life satisfaction were also available using the following battery of questionnaires: Opioid and Benzodiazepine Assessment, Marijuana Assessment, Pain at the Surgical Site and Overall Pain, Pain Severity, CSQ:CAT (Thoughts About Symptoms), Fibromyalgia Measure (Michigan Body Map & Symptom Severity Index), the Patient-Reported Outcomes Measurement Information System (PROMIS) for Depression, Anxiety, Sleep, Fatigue and Physical Function Measure, Global Impression of Change, Life Satisfaction, Screener/Opioid Assessment for Patients with Pain (SOAPP), Prescribed Opioid Difficulty Scale (PODS). These measures will be used for the Aim 2 and 3 analyses to understand the patient-level factors associated with opioid disposal and opioid consumption, respectively.

Statistical Analysis
Descriptive statistics will be calculated for demographic variables and self-reported measures of pain, mood, function, and sleep. Differences in demographic variables between the three intervention groups (usual care, information sheet, and novel bag) will be found using bivariate tests. Specifically, for categorical variables such as race and insurance, Chi-square or Fisher's exact tests will be used according to sample sizes. For continuous variables such as age, ANOVA will be used. P-values are 2-tailed, and significance is set at $P < .05$.

Unadjusted odds of leftover opioid pain medication disposal with intervention group will be calculated. Using multivariate logistic regression, adjusted odds of leftover opioid pain medication disposal will be estimated after controlling for patient's characteristics. According to the logistic regression results, patient characteristics significantly associated with disposal will be identified.

To obtain normative data of postoperative opioid requirements for the surgeries studied, we will calculate prescription size and the amount consumed, and report for each of the surgical conditions included to help inform appropriate prescribing.

Section 4: Protection of Human Subjects

Human Subjects Involvement and Characteristics
Women and men will be included in this study. No exclusion criteria will be based on gender, race, or ethnicity. Children under the age of 18 will not be eligible to participate in this study.

Patient recruitment will begin on 06/19/2017. Recruited subjects will consist of all eligible patients meeting the study inclusion criteria.

Research involving human subjects will take place at one site, Michigan Medicine.

Power analysis: We will recruit all eligible patients into the study over a 6 week period at Michigan Medicine's East Ann Arbor Ambulatory Surgery & Medical Procedures

Center. In an unpublished study by our group (HUM00116940), we found that 39 (~21%) of the 187 patients had disposed of their medications in any way. Assuming that the Deterra bag will increase compliance with safe disposal to 50%, we estimate 65 patients per group assuming an alpha of 0.0125 to account for multiple comparisons (3 groups) and a beta of 80%. To account for patients that may not receive opioids and loss to follow up, we will increase the cohort by ~20% to 78 patients/group. As the work plan includes randomizing throughout 6 weeks, we may exceed the target enrollment. Although unexpected, if we fail to meet our target enrollment, we will add additional days or weeks to the recruitment to follow the 6 week period.

The inclusion and exclusion criteria are as follows:

Inclusion Criteria

- Scheduled for a surgical procedure at Michigan Medicine's East Ann Arbor Ambulatory Surgery & Medical Procedures Center
- 18 years of age or older at the time of consent

Exclusion Criteria

- Non-English speaking
- Inability to understand or complete surveys
- Medical or psychiatric conditions that in the judgment of the study team would preclude participation in this study

Sources of Materials

All data collected on study participants will be obtained and managed specifically for research purposes. The types of data to be collected include open-ended and forced-response self-report surveys and medical record data.

Participant information will be stored on a secure server, which will limit access to patient identifying information to only those assigned appropriate permissions, such as the research team. Whenever possible, research investigators will only have access to the de-identified information where the study participant will be identified by their unique study ID number only.

The proposed study will not require any changes to existing surgical practices.

Study personnel and appropriate oversight organizations (including the IRB) will have access to study databases as needed.

Participant confidentiality will be maintained throughout the conduct of this study.

Outcomes

The primary outcome will be the self-reported safe disposal of opioids at the follow up time point. We will further obtain qualitative data regarding patient preferences for opioid disposal and barriers to effective disposal. Preoperative characteristics will be

analyzed to understand factors associated with safe disposal to help build future interventions.

Furthermore, self-reported use of opioids (number of pills and time to cessation) will be for each of the surgical conditions included will be used to help inform appropriate prescribing.

Potential Risks

Due to the sensitivity of some of the survey questions, the risks for participants would be deemed by Michigan Medicine's IRB as having a 'Minor Increase Over Minimal Risk' risk level. Procedures carrying potential risks include the following:

(i) *Extreme sensitivity of survey questions.* A few questions in the day of surgery survey inquire about felonious behavior. Accordingly, the study team plans to obtain a Certificate of Confidentiality from the National Institutes of Health.

(ii) *Breach of confidentiality.* Several measures have been taken to reduce the risk of breach of confidentiality. These include training of the team members, electronic and physical security measures for data capture and storage, and collecting minimum identifiable information from each participant. The study team will take all steps possible to protect the privacy of subjects.

(iii) *Discomfort associated with questions being asked.* There is a possible risk of discomfort associated with the questions being asked. Participants will be able to refuse to answer any question and will be notified that participation is entirely voluntary and that they may cease participation at any time.

(iv) *Potential risks from exposure to the Deterra opioid disposal bag.* Some patients will be given a Deterra opioid disposal bag to take home with them. Similar to opioid medications themselves, the Deterra bag needs to be kept out of the reach of children and pets to avoid accidental exposure to the contents of the pouch. We deem this risk to be minimal, however, because according to the MSDS for the active ingredients in the pouch, the chemicals are only known to cause mild irritation upon skin, eye, or inhalation exposure. There are no known deleterious effects from ingestion of the chemicals.

(v) *Inconvenience of time.* One foreseeable risk of harm to the patients is the amount of time that will be necessary to complete the project. The patients will be asked to participate in a survey on the day of their surgery as well as an electronic or phone survey 4 to 6 weeks after their surgery. Surveys will be kept brief to minimize encroachment on participants' time.

Section 5: Adequacy of Protection Against Risks

Protection Against Risk

The investigators will make every effort to preserve the study subjects' confidentiality. No one but the study personnel will have access to the study subject's record. Precautions will be taken to ensure that the records are kept on a secure server. All completed paper forms containing data will be kept in a secure, locked filing cabinet. Survey responses will not have the subjects name listed on them, but instead a study identification number, which only the research team will be able to link to names. Only tracking logs will

contain the linkage of subject identity, subject ID number, and group assignment. The subjects will also not be identified in any reports of this study. No sensitive information from the surveys will be added to a patient's medical record.

Potential Benefits of Proposed Research to the Subject and Others

The risks to the study subject population are minimal. Although the subjects cannot be promised any direct (personal) benefits for participation in this study, they will have access to more insight about options for disposal of unconsumed opioids. Some participants will also be given a means to immediately and safely remove the unconsumed opioids from their home.

Importance of Knowledge to be Gained

Prescription opioid use is an epidemic in the United States. The present study leverages a unique and experienced study team to evaluate the effectiveness of providing patients with a means to dispose of their unused opioids as part of the surgical care pathway. Unconsumed opioids are a risk for accidental poisonings and diversion for misuse.

Literature Cited

1. Rudd RA, Aleshire N, Zibbell JE, Gladden RM. Increases in Drug and Opioid Overdose Deaths — United States, 2000–2014. *MMWR.* 2016;64(50 & 51):1378-1382.
2. Levy B, Paulozzi L, Mack KA, Jones CM. Trends in Opioid Analgesic-Prescribing Rates by Specialty, U.S., 2007-2012. *Am J Prev Med.* 2015;49(3):409-413.
3. Control CfDCaPNCfIPa. Opioid Painkiller Prescribing: Where You Live Makes a Difference. 2014; www.cdc.gov/vitalsigns/opioid-prescribing. Accessed March 1, 2016.
4. Hill MV, McMahon ML, Stucke RS, Barth RJ, Jr. Wide Variation and Excessive Dosage of Opioid Prescriptions for Common General Surgical Procedures. *Annals of surgery.* 2016.
5. Reddy A, de la Cruz M, Rodriguez EM, et al. Patterns of storage, use, and disposal of opioids among cancer outpatients. *The oncologist.* 2014;19(7):780-785.
6. Egan KL, Gregory E, Sparks M, Wolfson M. From dispensed to disposed: evaluating the effectiveness of disposal programs through a comparison with prescription drug monitoring program data. *Am J Drug Alcohol Abuse.* 2017;43(1):69-77.
7. Tanabe P, Paice JA, Stancati J, Fleming M. How do emergency department patients store and dispose of opioids after discharge? A pilot study. *Journal of emergency nursing: JEN : official publication of the Emergency Department Nurses Association.* 2012;38(3):273-279.
8. Lewis EC, M.; Trafton, J. What Do Patients Do with Unused Opioid Medications? *The Clinical Journal of Pain.* 2014;30(8):654-662.
9. McCabe SE, West BT, Boyd CJ. Leftover prescription opioids and nonmedical use among high school seniors: a multi-cohort national study. *The Journal of*

adolescent health : official publication of the Society for Adolescent Medicine. 2013;52(4):480-485.
10. Voepel-Lewis T, Wagner D, Tait AR. Leftover prescription opioids after minor procedures: an unwitting source for accidental overdose in children. *JAMA pediatrics.* 2015;169(5):497-498.
11. Vaughn MG, Nelson EJ, Salas-Wright CP, Qian Z, Schootman M. Racial and ethnic trends and correlates of non-medical use of prescription opioids among adolescents in the United States 2004-2013. *Journal of psychiatric research.* 2016;73:17-24.
12. Boyd CJ, Esteban McCabe S, Teter CJ. Medical and nonmedical use of prescription pain medication by youth in a Detroit-area public school district. *Drug and alcohol dependence.* 2006;81(1):37-45.
13. Fortuna RJ, Robbins BW, Caiola E, Joynt M, Halterman JS. Prescribing of controlled medications to adolescents and young adults in the United States. *Pediatrics.* 2010;126(6):1108-1116.
14. Lankenau SE, Teti M, Silva K, Jackson Bloom J, Harocopos A, Treese M. Initiation into prescription opioid misuse amongst young injection drug users. *Int J Drug Policy.* 2012;23(1):37-44.