STUDY PROTOCOL

PROTOCOL TITLE: RELIEVING ACUTE PAIN: A PILOT STUDY

PROTOCOL NUMBER: HP-00078742

PRINCIPAL INVESTIGATOR: Luana Colloca, MD, PhD, MS
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NCT ID: NCT03426137

DOCUMENT DATE: January 21, 2020

PREPARED BY: Nathaniel Haycock, MS (Research Coordinator)
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UNIVERSITY of MARYLAND
THE FOUNDING CAMPUS

Date: Thursday, March 5, 2020 3:12:55 PM

View: v2_Introduction Page

Introduction Page

* Abbreviated Title :
Relieving Acute Pain (RAP) Study

2 * Full Title:
Relieving Acute Pain: A Pilot Study

3

* Select Type of Submission:

- **IRB Application**

Q Humanitarian Use Device (for FDA approved Indication & non-research purposes ONLY)

Q Emergency Use

Q Unsure if this proposal requires IRB review (Not Human Subject Research)

Note: The Type of Submission cannot be changed after this application has been submitted for review.

4 Original Version #:

ID: VIEW4DF8709A33COO
Name: v2_Introduction Page

View: v2_Research Team Information

Research Team Information

* Principal Investigator - Who is the PI for this study (person must have faculty status)? ***Faculty status is defined as being a full-time (>51 % effort) faculty member holding one of the following titles at UM: Professor; Associate Professor; Assistant Professor.***
Luana Colloca

1.1 * Does the Principal Investigator have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

2 Point of Contact - Who is the alternative point of contact for the PI? This person can be a study coordinator or any other study team member. In case the IRB cannot contact the PI, this person is a secondary person to contact:
Nathaniel Haycock

2.1 Does the Point of Contact have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

Name	Edit Submission	cc on Email	Research Role	Has SFI?

[redacted]

IMPORTANT NOTE: All research team members (including PI) must have current CITI and HIPAA training completed.

[redacted]

ID: VIEW40F85C16F2800
Name: v2_Research Team Information

View: v2_Resources

Resources

If this study is a collaborative UM/VA study, please clarify which resources are being used at each institution.

• Describe the time that the Principal Investigator will devote to conducting and completing the research:
The PI, Luana Colloca, will devote 15% of her time to conducting and completing the research, estimated at 9 hours/week.

2 • Describe the facilities where research procedures are conducted:
Research procedures will be conducted at the following University of Maryland Facilities:

1) The University of Maryland Medical Center - Shock Trauma Center (STC)
Clinical Facility: The R Adams Cowley Shock Trauma Center (STC) cares for nearly 8,000 injured patients each year. The STC is a free-standing dedicated trauma hospital and provides the highest level of care for critically ill and injured patients in the state as the primary adult resource center for Maryland's emergency medical

services system. The STC is also the specialty referral center for the State of Maryland for neurotrauma and orthopedic surgery. Computed tomography scan and MRI are available 24 hours per day. There are six dedicated trauma operating rooms (ORs), with the capacity to immediately accommodate any surgical emergency at any time. The Program in Trauma at the STC is distinctive in that multiple disciplines are represented, all of which are dedicated 100% to care for STC patients. Divisions of Trauma Surgery, Trauma Critical Care Medicine, Trauma Anesthesiology, Trauma Neurosurgery, Hyperbaric Medicine, Infectious Diseases, Orthopedic Traumatology, Trauma Plastic Surgery, Trauma Radiology, and Wound Healing are each composed of fellowship or subspecialty-trained experts in these fields. Clinical coverage is provided all times/all shifts by an in-house trauma surgeon, trauma intensivist , trauma radiologist , and trauma anesthesiology attending; two trauma/critical care fellows and a trauma surgery fellow; and general surgical, emergency medicine , and anesthesiology house staff. Trauma orthopedic coverage is provided by an in-house trauma orthopedics fellow and trauma orthopedics resident. Neurosurgical coverage is provided by in-house senior trauma neurosurgery resident.
The University of Maryland Spine Program offers comprehensive, state-of-the-art evaluation and non-surgical and surgical treatment of all spinal disorders. Furthermore , as part of an academic medical center, our physicians are all on the University of Maryland School of Medicine faculty.The Spine Program, which is a part of the Department of Orthopaedics, provides a comprehensive, multidisciplinary approach to the evaluation and treatment of patients with spinal disorders affecting the cervical, thoracic, and lumbar spine.

2) Shock, Trauma and Anesthesiology Research Center (STAR): STAR coordinates the infrastructure for all research projects conducted at the STC. A dedicated staff of research nurses, research assistants, and research project coordinators are available in-house to provide continuous, all times/all shifts, research staffing. All patients admitted to the STC are screened by the research staff and evaluated for possible inclusion in ongoing studies. The research staff determines eligibility for protocols, obtains informed consent, and provides study coordination and data collection. Additional research staff members provide statistical support, regulatory document preparation , and post-award grants management. The recent creation of the Organized Center for Shock, Trauma and Anesthesiology Research has added a further wealth of resources and expertise from which our program project will benefit. Other important resources include multiple National Institutes of Health (NIH) pre-doctoral and post-doctoral training programs, multiple seminar series, and the proximity to the NIH and to the Johns Hopkins University School of Medicine.

3) School of Nursing (SON): The School of Nursing shares a 61-acre campus in downtown Baltimore with the University of Maryland (UM) six other professional schools - Dentistry, Law, Medicine, Pharmacy, Social Work, and the Graduate School-and is in close proximity to the University of Maryland Medical Center, University of Maryland Biotechnology Institute, University of Maryland BioPark, and the Baltimore VA Medical Center. A national leader in health sciences research, public service, and patient care, UM was awarded $529.1 million in extramural funding in fiscal year 2012. The School of Nursing is currently ranked #6 in the nation for NIH funding among schools and colleges of nursing (2015). The School is dedicated to creating a research intensive environment that will advance the science and clinical care through research and scholarship of the highest quality.

Clinical Laboratory Facilities - SON: The clinical laboratory facilities, under the direction of Prof. Luana Colloca, are located on the 7th fioor of the School of Nursing. These laboratories provide state of-the-art pain assessment and testing equipment for clinical studies-such as the one proposed in this grant application. There is over 1700 square feet available for this study. This includes a spacious intake area, clinical exam suite, pain-testing suite, office space for record retention, and both refrigerators and freezers for sample collection, all of which are kept locked and secured by video surveillance. Both research team members and security guards have keys to access these areas, but records within these secured areas will be kept in locked filing cabinets that will only be accessible by research team members.

Computer Resources:
The School of Nursing has a well-established state-of-the-art network that provides a wide range of data services and is tightly integrated with the UMB campus network.

The primary network authentication is through Microsoft Windows 2003 Active Directory. Disk space is provided for storage of personal and group data. E-mail and collaboration services are provided through Exchange 2003. SON services are also integrated with campus directories in order to foster wider collaboration. Extensive support for all SON computing resources is available from the School's Computer Network and support staff, including database systems and programs, access methods, access time, file structure, device allocation, statistical methods and security. Significant security and password protocols are in place to protect all data and electronic information from access by unauthorized individuals.
SON Information Technology and support team secure all of the computers used for this proposal with antivirus software and firewalls that are continuously updated for maximum protection.
There are seven Dell T3400 workstations with monitors and network connectivity located throughout the laboratory to operate experimental and behavioral instruments.

The computers are equipped with standard word processing, database and spreadsheet programs as well as statistical analysis (SPSS v17, STATA v10, JMP v8) and specialized data analysis programs specific to the instrumentation. The university provides free Ethernet connections to other campus computers and rapid access to the internet, UMB library and e-mail. Research File Server: Ors. Colloca and Dorsey have access to 10 terabytes of data capacity for storage of research data including the genomic data that will be collected during this project period. This server is also available by VPN access to enable Dr. Dorsey to access research data from off-site computers. Data Backup System: The SON provides a tape backup of all data for secure off-site permanent storage. There is a full back up every Friday night and a differential backup on each of the other nights.

Office Space and Computational Capacity:
Dr. Colloca has approximately 120 square feet of office space adjacent to the laboratory. She has a Dell Precision T7500 dual quad core processor 64-bit Windows XP workstation with 2TB of storage and 12 GB of RAM and a 2.7 GHz Mac Pro with 12 processors and 64GB RAM-suitable for genomic analysis and bioinformatics. She has one 32" 4K Sharp monitor. Her office is equipped with a networked color laser printer and numerous external Raid hard drives for data storage. Research staff has a 40 square foot office equipped with a Windows-based desktop computer and monitor, phone and shared networks laser printer. Currently, Dr. Colloca team includes a Research Coordinator, a Post-Doctoral student, a Lab Manager, a few PhD students and

3 • Describe the availability of medical and/or psychological resources that subjects might need as a result of anticipated consequences of the human research:

All staff involved with the protocol will be fully trained on it and will be given study team member emergency contacts in case of incident. If participants experience any adverse events because of their participation , participants can report their adverse events and receive medical care if necessary immediately from a referred doctor.

If for any reason, participants experience psychological distress because of participating in this study, they will be referred as soon as possible to their PCP or a psychologist. If participant's scores on the BDI indicate severe depressive symptoms, including suicidality, the PI will immediately communicate these results with the participant and refer them to their PCP and psychologist for a follow-up, although it will also be noted to the participant that the BDI is intended for research use only and not clinical diagnostic use. Similarly, in the event of distress due to a response of neglect and abuse on the EPM and ACE-IQ questionnaires , participants will be referred to psychiatry or social work as inpatients.

4 • Describe the process to ensure that all persons assisting with the research are adequately informed about the protocol, the research procedures, and their duties and functions:

All persons involved in working on this research study will be adequately trained to perform the tasks that were delegated in the Regulatory Binder's Delegation of Responsibility Log. All research personnel will be sent a copy of the IRB approved protocol and auxiliary documents to learn about the protocol and study procedures. The PI will conduct individual and group meetings with all team members to ensure that they have been trained on the duties they are expected to perform and the study procedure and protocol. Before the launch of this study, there will be a study initiation meeting with all research personnel to complete any final trainings and to answer any questions relevant to completing study duties. After all research personnel are adequately trained and before the launch of this protocol, they will be required to sign the Training Log, also kept in the Regulatory Binder, to indicate that they feel entirely confident in their ability to complete their delegated tasks because of the training they received.

ID: VIEW4DF83CB976400
Name: v2_Resources

View: v2_Sites Where Research Activities Will Be Conducted

Sites Where Research Activities Will Be Conducted

* Is this study a:

Q Multi-Site

- **Single Site**

2 * Are you relying on an external IRB (not UM) to be the IRB of Record for this study?

Q Yes. **No**

3 * Are any other institutions/organizations relying on UM to be the IRB of Record for this study?

Q Yes. **No**

3.1 Attach the applicable regulatory documents here (i.e., IRB Authorization Agreement (IAA), FWA, local ethics approval, other IRB approvals, etc.). Final UM approval will be contingent upon final execution of all required regulatory approvals:

Name	Created	Modified Date

There are no items to display

4 * Is UM the Coordinating Center for this study? (Applicable for multi-site studies. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project.)

Q Yes. **No**

5 Is VA the Coordinating Center for this study? (Applicable for Collaborative studies between the VA, UM and other sites. A Coordinating Center is responsible for overall data management, monitoring and communication among all sites, and general oversight of conduct of the project)

Q Yes Q No

6 * Institution(s) where the research activities will be performed:

m **University of Maryland, The Founding Campus**

D VAMHCS

0 University of Maryland, Upper Chesapeake Kaufman Cancer Center

0 UMB School of Medicine

0 Marlene and Stewart Greenebaum Cancer Center

0 University Physicians Inc.

m **Shock Trauma Center**

0 General Clinical Research Center (GCRC)

0 Maryland Psychiatric Research Center (MPRC)

0 Johns Hopkins

0 International Sites

0 UMB Dental Clinics

0 Center for Vaccine Development

0 Community Mental Health Centers

0 Private Practice in the State of Maryland

0 Institute of Human Virology (IHV) Clinical Research Unit

0 Joslin Center

0 UMB Student Classrooms

0 National Institute of Drug Abuse (NIDA)

0 National Study Center for Trauma and EMS

0 Univ of MD Cardiology Physicians at Westminster

0 Nursing Homes in Maryland

0 University of Maryland Biotechnology Institute
0 Department of Health and Mental Hygiene (DHMH)
0 Mount Washington Pediatric Hospital
0 Capitol Region PG Hospital
0 Maryland Proton Treatment Center
0 Other Sites
a **University of Maryland Medical System (Select below)**

* UMMS Sites:

a **University of Maryland Medical Center**
0 UMMC Midtown Campus (formerly Maryland General Hospital)
0 UM St. Joseph Medical Center
0 UM Baltimore Washington Medical Center
0 UM Charles Regional Medical Center
0 UM Shore Medical Center at Easton
0 UM Shore Medical Center at Chestertown
0 UM Shore Medical Center at Dorchester
0 UM Shore Emergency Center at Queenstown
0 UM Shore Regional Health
0 University of Maryland Rehabilitation & Orthopaedic Institute (formerly Kernan Hospital)
0 UM Upper Chesapeake Health
0 UM Upper Chesapeake Medical Center
0 UM Harford Memorial Hospital
0 University of Maryland Community Medical Group

10: VIEW40F8700F2COOO
Name: v2_Sites Where Research Activities Will Be Conducted

View: v2_Funding Information

Funding Information

* Indicate who is funding the study:

0 Federal
0 Industry
0 Department / Division / Internal
0 Foundation
0 Private
a **State Agency**

2 * What portion of the research is being funded? (Choose all that apply)

a **Drug**
D Device
a **Staff**
D Participant Compensation
D Procedures
D Other

3 Please discuss any additional information regarding funding below:

Drs. Colloca and Murthi received funding from the Mpowering the State Grant to conduct clinical research related to new approaches to taper opioids for the management of acute pain. These funds will be used to hire a research coordinator, manufacture the study drug (specifically, to purchase oxycodone and placebos, package them identically, and cover any additional expenses deemed appropriate .

ID: VIEW4DF85DF452400
Name: v2_Funding Information

View: v2_State Agency Sponsor Information

State Agency Sponsor Contact Information

You indicated that this is a State agency funded study.

* Agency Name:
University of Maryland Strategic Partnership (SM) and MPowering State Grant (LC)

* Address 1:
University of Maryland Blended Reality Center

Address 2:
University of Maryland School of Nursing

* City:
Baltimore

* State:
MD

* Zip Code:
21201

* Contact Person:
Sarah Murthi and Luana Colloca

* Phone Number:

ID: VIEW4OF8955CCF0OO
Name: v2_State Agency Sponsor Information

View: v2_Research Protocol

Research Protocol

* Do you have a research protocol to upload?

0 Yes

- No, I **do not have a research protocol and will use the CICERO application to enter my study information**

2 If Yes, upload the research protocol:

Name	Created	Modified Date

There are no items to display

ID: VIEW4E00563F8D0OO
Name: v2_Research Protocol

View: v2_Risk Level

Risk Level

What is the risk level of your study? (Ultimately, the IRB will determine the appropriate risk level and your designation is subject to change.)

* Choose One:

0 Minimal - The probability & magnitude of harm/discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations /tests.

- **Greater Than Minimal - Does not meet the definition of Minimal Risk.**

ID: VIEW4E02805225800
Name: v2_Risk Level

View: v2_Type of Research

Type of Research

• Indicate **ALL** of the types of research procedures involved in this study (Choose all that apply):

Use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol.

0 Evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition .

0 Use of device(s) whose use is specified in the protocol

Psychological/Behavioral/Educational Method or Procedure (i.e., survey, questionnaires, interviews, focus groups, educational tests).

Sample (Specimen) Collection and/or Analysis (including genetic analysis).

Data Collection or Record Review (i.e., chart review, datasets, secondary data analysis).

0 None of the above.

2 • Is this study a clinical trial OR will this study be registered at ClinicalTrials .gov?
A clinical trial is a research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.

- **Yes** Q No

ID: VIEW4E0280569E0OO
Name: v2_Type of Research

View: v2_Lay Summary

Lay Summary

• Provide a summary of the background and purpose of the study in language that can be understood by a person without a medical degree.

The United States (US) faces a crisis of pain management. According to the 2012 National Health Interview Survey, almost 50 million adults in the US reported having significant chronic or severe pain (Nahin 2015). Doctors in the US still prescribe opioids across the board for pain despite a growing recognition of an epidemic of opioid overdose and use disorder. Few solutions have been successfully proposed and implemented. Placebos represent a novel and potentially fruitful means of addressing this issue. However, clinicians often use placebos deceptively and with little rationale or evidence of benefit, making their use ethically problematic. In contrast with their typical current use, a provocative line of research suggests that placebos can be intentionally exploited to extend analgesic therapeutic effects. Recently, we reviewed a database of placebo studies including 22 studies in both animals and humans hinting of evidence that placebos may work as a dose extender of active painkillers. Placebos given after repeated administration of active treatments can acquire medication-like effects based on learning mechanisms.
Here, we will test if dose-extending placebos are effective in relieving clinical acute pain in patients taking opioids for trauma or elective cervical or lumbar spinal surgery. Patients will be randomized to three arms. Arm 1 will be a Full Dose (FD) group, which will receive all NSAIDs as described in the Guidelines for NSAID use in Orthopedic Patients (see attachment) and Oxycodone (5mg). Arm 2 will be a Partial Reinforcement (PR) group, which will receive NSAIDs, Oxycodone (5mg), and placebos to reach a 50% reduction of the total intake of opioids. Finally, Arm 3 will be a Control (C) group receiving NSAIDs and placebos. Patients will be assigned to one of three arms according to a 1:1:1 schedule of randomization. Study IDs will be generated by the pharmacy and blinding will occur by ensuring that oxycodone and placebos look, smell, and taste identical. Rescue therapy will be provided as needed. Patients within the elective spinal surgery population who choose patient controlled analgesia will have the option to participate only in the optional samples and followup.
This novel prospect of placebo use has the potential to change our general thinking about painkiller treatments, the typical regimens of painkiller applications, and the ways in which treatments are evaluated.

ID: VIEW4E02805CF7000
Name: v2_Lay Summary

View: v2_Justification, Objective, & Research Design

Justification, Objective, & Research Design

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

• Describe the purpose, specific aims, or objectives of this research. State the hypothesis to be tested:

Primary Aim: To establish an alternative method of prescribing opioids that would reduce overall intake, decrease physiological or psychological dependence on medication, and yet be equally as effective in terms of pain relief and prevention of pain interference with daily functioning. To do this, patients will be randomized to three arms. Arm 1 will be a Full Dose (FD) group, which will receive all NSAIDs will be dosed in accordance with the Guidelines for NSAIDs (see attachment) and Oxycodone (5mg). Arm 2 will be a Partial Reduction (PR) group, which will receive NSAIDs, Oxycodone (5mg) and placebos to reach a 50% reduction of the total intake of opioids. Finally, Arm 3 will be a Control (C) group receiving NSAIDs and placebos. Patients within the elective spinal surgery population who choose patient controlled analgesia will have the option to participate only in the optional samples and followup.

Secondary Aims:
1) To assess the feasibility of recruiting trauma and elective spinal surgery patients and having them successfully participate in the trial, including 2 week, 1 month, 3 month, and 6 month follow-ups for pain and opioid use.
2) To inform and determine appropriate power for a larger randomized controlled trial in the future.

Hypotheses:

H1: Patients in the PR and C treatment arms will perform significantly better in terms of all outcomes (see Sample Size and Data Analysis Section 2) as patients in the

FD arm.
H2: Patients in the C arm will not experience significantly different outcomes than patients in the PR arm.

2 * Discuss the research design including but not limited to such issues as: probability of group assignment, potential for subject to be randomized to placebo group, use of control subjects, etc. :

We will screen 5000 patients from the Shock Trauma Center Trauma Program to recruit a total of 159 (53 per arm) to participate in a pilot study aimed at reducing use of opioids. We will also screen 5000 patients from the Shock Trauma Center Spine Program to recruit a total of 212 (53 per arm plus 53 in the PCA/followup only group) to participate. In sum, we will enroll 371 patients.

Participants will meet all of the eligibility criteria and none of the exclusion criteria. After enrollment, participants will be blindly allocated to one of three randomization arms by means of de-identified Study IDs corresponding to treatment arms. Study IDs will be generated by the pharmacy and blinding will be ensured by creating study drugs that look, smell, and taste identical. The pharmacy will create and dispense identical study drugs in terms of appearance, smell, and taste. Only the blinding coordinator will know the identity of patients in each treatment arm. Arm 1 will be a Full Dose (FD) group, which will receive NSAIDs, dosed in accordance with the Guidelines for NSAIDs (see attachment) and Oxycodone (5mg). Arm 2 will be a Partial Reinforcement (PR) group, which will receive NSAIDs, Oxycodone (5mg), and placebos to reach a 50% reduction of the total intake of opioids. Finally, Arm 3 will be a Control (C) group receiving NSAIDs and placebos. Patients will be assigned to one of these three arms according to a 1:1:1 schedule of randomization. The patient will start receiving study medication as part of his or her pain management as soon as possible after admission to the hospital and enrollment in the study (ideally as their first dose of pain-management medication). Rescue therapy will be provided as needed. Patients within the elective spinal surgery population who choose patient controlled analgesia will have the option to participate only in the optional samples and followup.

All enrolled patient will receive an Adult Pain Management Service (APMS) consult. APMS will work with the study and clinical teams to ensure that all treatment protocols are met, and be available to address any issues that may arise. The APMS provider will work with the primary service to determine the most effective NSAID as described in the Guidelines.

Other than the study medication (Oxycodone and placebo), all participants will be treated in accordance with the current standard of care at Shock Trauma. This includes Toradol IV q 8 hrs for 24 hrs followed by oral NSAIDs round the clock until pain is minimal. The timing of administration will be the same for participants in all three arms - they will receive their arm's treatment (Oxycodone, Oxycodone alternating with placebo, or no additional medication beyond standard of care NSAIDs) RTC for the first 24 hours followed by q4 hours for the remainder of hospitalization. Drug administration will occur as close as possible to q4 hours and the pain assessments will within 20-90 minutes of that time. All patients will receive 0.4-1 mg q1 hr i.v. or 1-4mg q1 p.a. Dilaudid for rescue/break through pain. Adjuncts (e.g. lidocaine patches and other medication) can be given as rescue therapy. The rescue therapy will be managed clinically by the Acute Pain Management Service (APMS) and the team will document use of Dilaudid rescue therapy and any given additional medication will be appropriately documented by the APMS team.

The two instances in which APMS will contact IDS for treatment allocation information (and thus become unblind) are
o Patient being withdrawn from the study because he required more than 3 doses of rescue medication in a row.
o At the end of Phase 1 when APMS will recommend appropriate treatment for pain management.
APMS will contact IDS at the end of Phase 1 (after projected minimum 3 days hospitalization). At the end of Phase 1 (discharge timepoint), APMS team will obtain treatment assignment from the IDS, and the information will be documented on EPIC ONLY in case of patients' withdrawal or at the discharge. The PI or designated individual who will be responsible for data integrity, data collection, and analyses will only access EPIC during Phase I (hospitalization) and before the discharge therefore will not see any discharge summary or other notes entered by APMS that may unblind the data analysis.
Once Phase I is complete, patients will be monitored via REDCap/MetricWire (not EPIC) guaranteeing that the PI will continue being blind to the treatment allocation.

Discharge: In addition, based on the severity of their pain and drug assignment during the hospitalization (Phase I), patients will be discharged on either no opioid prescription, Oxycodone 5mg q4 PRN, Oxycodone 5mg q6 PRN, or Oxycodone 10 mg q6 PRN in addition to adjuvant therapies such as baclofen, flexeril, lidocaine patches, NSAIDs, tylenol, gabapentin/lyrica. In order to do this at the discharge, APMS will contact the IDS for the study allocation to prescribe the adequate treatment. APMS will monitor patients for safety during the Hospitalization (Phase I).

In Arm 2, the first four doses of study drug will be Oxycodone (5 mg) to condition them to its effects. Afterwards, they will receive alternating Oxycodone (5 mg) and Placebo according to one of four repeating sequences (please refer to Figure 2 - Administration Schedule under "Additional Documents" for a visual depiction of these four sequences). During data analysis, we will test whether the sequence of administration has an effect on outcomes. As seen from the Figure 2, participants in Arm 2 will never receive more than 2 doses of placebo in a row. This administration schedule will be repeated for the remainder of hospitalization. Patients who miss or ask to skip a dose will resume treatment with the skipped dose. Thus, a patient who skips dose #4 will receive dose #4 when they resume medication.

The duration of the trial is the two to three days of hospitalization following enrollment {Phase I) and a 2 week, 1 month , 3 month, and 6 month follow-up (Phase II). Primary outcomes will be: pain self-reports, requests of rescue intervention, and reduction of opioids. Secondary outcomes will be: long-term prescriptions of opioids over the follow-up period, psychological questionnaires, and pain.

3 * Describe the relevant prior experience and gaps in current knowledge. Describe any relevant preliminary data:

Opioid therapies should not be first-line treatment for the management of all chronic noncancer pain (CNCP) disorders, as recent research is increasingly demonstrating (Pedersen and Fredheim 2015, Reuben, Alvanzo et al. 2015, Chou 2016, Dowell, Haegerich et al. 2016, Wen and Lloyd 2016, Wersocki, Bedson et al. 2016). There is a lack of high-quality evidence demonstrating opioid efficacy, effectiveness and long-term safety. Indeed, opioid therapy may actually be complicate chronic pain management (Chou, Turner et al. 2015) by causing the development of opioid use disorder (Bohnert, Valenstein et al. 2011) and by increasing the risk of opioid-overdose death(Ray, Chung et al. 2016). Nonetheless, the prescription rates of opioids have increased by 300 percent over the past 20 years in the United States.(Sullivan and Howe 2013) This is particularly true for a large population of patients who suffering from pain, addiction, and comorbid mental disorders who are treated daily with high morphine equivalent doses (MEDs)(Bair and Bohnert 2015). These unintentionally unwise prescription rates have generated a large population of opioid users taking moderate-high MEDs on a daily basis.

In Canada and in the United States, the per capita use of opioids for the treatment of chronic low back pain is double than in the United Kingdom ; three times more than in the Netherlands; and 26 times more than in Japan (Zerzan, Morden et al. 2006, Deyo, Von Korff et al. 2015). Racial and cultural differences only partially account for this variety of attitudes regarding the prescription of opioids, and there is a lack of professional consensus on use of opioids (Burgess, Crowley-Mataka et al. 2008, Lembke 2013, Burgess, Phelan et al. 2014).

The new Centers for Disease Control (CDC) Guideline for Prescribing Opioids for Chronic Pain have been issued in an attempt to reverse this epidemic of opioid overprescribing (Dowell, Haegerich et al. 2016, Dowell, Haegerich et al. 2016). A decrease of 10% of the original dose per week, a slower taper of 10% reduction per month when patients have been taking opioids for years, and an individualized tapering plan based on the patient's goals and concerns have all been suggested{Dowell, Haegerich et al. 2016, Dowell, Haegerich et al. 2016). However, the fact that there is no published comparative effectiveness research (CER) for the appropriate pace of opioid tapering in patients with long-term opioid treatment for CNCP brings about a huge clinical dilemma (Berna, Kulich et al. 2015). In addition, opposing and biased beliefs influence opioid tapering outcomes among both patients(Frank, Levy et al. 2016) and healthcare providers (Wen and Lloyd 2016).

Recent evidence differentiating neuropathic and non-neuropathic pain conditions suggests one potential solution. These two types of pain conditions have different pharmacological indications for successful pain management,(Vardeh, Mannion et al. 2016) Thus, phenotyping patients with respect to the nature of their pain could serve as a basis for personalized pain treatment(Reimer, Helfert et al. 2014, Edwards, Dworkin et al. 2016, Edwards, Dworkin et al. 2016, Haroutounian 2016, Lewandowski Holley, Wilson et al. 2017). The strongest evidence showing that profiles of symptoms and signs can indicate proper pain treatment is a trial in which patients who were defined as having an "irritable nociceptor" phenotype had a larger decrease in pain with the anticonvulsant oxcarbazepine versus placebo than those without this phenotype (Deman!, Lund et al. 2014). Phenotyping could also be used to test whether certain patients have a more robust response to non-pharmacologic treatments, for example psychological and integrative interventions ,{Edw ards, Dworkin et al. 2016) as well as to identify which patients are most likely to respond to combinations of treatments (L., T. et al. 2017). Despite the fact that opioids do not form part of the recommended first-line treatments for chronic pain (Finnerup, Attal et al. 2015), there are no studies linking opioid tapering success or failure to the nature of the underlying chronic pain disorder(s).

Knowledge of the placebo response could be utilized to reduce overall intake of opioid medications. Analgesic effects can be induced with pharmacological conditioning, which is effective in extending the analgesic response to opioids and nonopioids in both animals and humans (Amanzio and Benedetti 1999, Benedetti, Pollo et al. 2007, Guo, Wang et al. 2010). For instance, Guo et al. performed a 4-day experiment in female Imprinting Control Region (ICR) mice using a hot-plate test and pharmacological conditioning with opioids and nonopioids (Guo, Wang et al. 2010). Cues were paired with either the opioid agonist morphine hydrochloride or non-opioid aspirin, and opioid and non-opioid-like responses that were either naloxone-reversible or naloxone-insensitive, depending on the drug used in conditioning procedure, were observed. A hot-plate test was used to measure response latencies according to the method described by Hargraves and Hentall (Hargraves and Hentall 2005) and targeted the involvement of supraspinal mechanisms (Le Bars, Gozariu et al. 2001). After conditioning with morphine, mice were treated with saline solution, exposed to the conditioned cue, and then tested for pain tolerance (Guo, Wang et al. 2010). Saline solution induced enhanced pain tolerance compared with control levels, indicating that the previous morphine conditioning was sufficient to evoke a morphine-like analgesic effect. Pre-treatment with naloxone blocked this placebo-induced analgesia. The same procedure described above was repeated after pharmacological conditioning with aspirin. Interestingly, similar placebo responses were observed except that the pre-treatment with naloxone did not block the conditioned analgesic response established by prior conditioning with the non-opioid aspirin, suggesting that opioid and non-opioid endogenous pain modulation mechanisms may exist independently of one another and may both contribute to placebo analgesic effects.

Morphine conditioned analgesic responses also affect behavioral despair tests and hormonal secretions in mice (Guo, Yuan et al. 2011). Male Sprague-Dawley rats were trained with 10 mg/kg morphine for 4 days to establish a placebo analgesia model similar to the one used in Guo et al.[50] Animals were microinjected in the rostral anterior cingulate cortex with D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH(2), a selective μ-opioid receptor antagonist; naltrindole, a highly selective 5-opioid receptor antagonist; or nor-binaltorphimine, a highly selective K-opioid receptor antagonist. Only the μ-opioid receptor antagonist , not K-opioid or 5-opioid receptor antagonists, reduced the pain threshold of the rats, indicating a modulatory role of μ-opioid receptors in conditioned placebo analgesic responses (Zhang, Zhang et al. 2013).

Similar results have been shown in a rat model of conditioned analgesia in an operant pain assay. Specifically, rats were conditioned to associate a placebo manipulation with the analgesic effect of 1mg/kg morphine on facial thermal pain. Conditioned (placebo) responsiveness was characterized by three aspects that have been reported in human research: (1) inter-animal variability in the response, (2) suppression by the opiate antagonist naloxone (5mg/kg), and (3) a positive predictive relationship between the unconditioned analgesic effect and the conditioned (placebo) effect (Nolan, Price et al. 2012). This research suggests that animals learn to associate contextual cues with elevated pain tolerance, which produces conditioned analgesia.

Learning from prior positive experience can create strong memory-based analgesic responses, and likewise prior negative experiences can elicit pain intolerance. We designed a study in which one group received a treatment perceived as efficacious (actually, the intensity of painful stimulations was surreptitiously decreased) and a second group received a treatment perceived as ineffective (verbal negative suggestions were used to create the expectation of ineffectiveness without actually manipulating the intensity of painful stimulation). When tested for placebo analgesia, the first group reported significant reduction of pain (49.3%), while the second group reported a smaller pain reduction (9.7%) (Colloca and Benedetti 2006) After four to seven days, both groups were retested for placebo analgesia. We found that the placebo responses following the effective procedure were significantly higher than that observed after the ineffective treatment (29% versus 18% pain reduction). Therefore, placebo effects are shaped by learning (either positive or negative prior experience) and the effect of initial treatment exposure influences the response to subsequent placebo responses with obvious clinical implications (Colloca and Benedetti 2006).

Intentional use of placebos has been recently documented in survey studies spanning different countries including USA (Sherman and Hickner 2008, Tilburt, Emanuel et al. 2008, Kermen, Hickner et al. 2010), Canada (Raz, Campbell et al. 2011, Harris and Raz 2012), Germany (Meissner 2005, Linde, Friedrichs et al. 2013), Switzerland (Fassler, Gnadinger et al. 2009), Denmark (Hrobjartsson and Norup 2003), UK (Howick, Bishop et al. 2013), Israel (Nitzan and Lichtenberg 2004), India (Shah, Panchal et al. 2009), Saudi Arabia (Hassan, Fauzi et al. 2011), and New Zealand (Holt and Gilbey 2009). A systematic review of 22 studies from 12 different countries reported that between 17 and 80% of clinicians interviewed have administered such placebo treatments as sugar pills or saline injections during their careers (Fassler, Meissner et al. 2010).

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4 • Provide the scientific or scholarly background, rationale, and significance of the research and how it will add to existing knowledge:

Background:

Despite the fact that opioids are an important component of effective pain management, there is increasing attention on the greater harm that they may cause to patients, particularly if prescribed in larger doses over a longer period of time. The opioid crisis is a public health disaster resulting in 16 deaths/day in the USA (Chou, Turner et al. 2015, Chou 2016). The majority are patients who are misusing/abusing prescription pain killers dispensed to them to manage acute perioperative pain. One 1 out of 550 chronic opioid users dies within approximately 2.5 years of their first opioid prescription that is given to treat acute pain (Kaplovitch, Gomes et al. 2015).

Opioids are often prescribed for the management of any type of pain despite the lack of high-quality evidence demonstrating efficacy, effectiveness and safety of long-term opioid therapy for the management of chronic noncancer pain (Furlan, Chaparro et al. 2011, Sehgal, Colson et al. 2013, Sullivan and Howe 2013). Long-term opioid use is associated with risks and likely results in greater harm than good (Sullivan and Howe 2013). The per capita use of opioids in North America is double that of the United Kingdom, three times of that in the Netherlands, and 26 times of that in Japan (Zerzan, Morden et al. 2006, Deyo, Von Korff et al. 2015). Opioids can induce drug tolerance (and the need for escalating doses), hyperalgesia (increased pain sensitivity), and addiction (Zerzan, Morden et al. 2006, Kroenke, Krebs et al. 2009).

In comparison with standard regimens of medication, dose-extending placebos - placebos and/or subclinical dose of painkillers that are blended with treatments in accordance with reinforcement learning principles can be effective in improving pain management while the total drug intake is reduced. First, extending the effects of a medication by interspersing placebos rather than using only medication for a treatment of equal duration may reduce the overall intake of painkillers. Side effects associated with the medicine are likely to be reduced as well (Sandler, Glesne et al. 2008, Sandler and Bodfish 2008), although there is some the risk of conditioned side effects (Colloca and Miller 2011). Second, in cases in which the medicine is habit-forming, dose-extending placebo use may decrease physiological or psychological dependence on medication. Third, using dose-extending placebos for part of the course of treatment rather than using medication for the entire course will presumably lower costs. Dose-extending placebos in pain medicine catalyze the body's capacity for endogenous pain modulatory systems (Colagiuri, Schenk et al. 2015). Recently, we reviewed the literature related to placebos given along with painkillers and no-pain related treatments to see if there is any evidence of benefit. We found that animal and human research studies reported a modulation of clinical pain when placebos are given to extend the analgesic effects of painkillers.

Extensive research on placebo analgesia over the past several decades has expanded knowledge of a fascinating psycho-neurobiological phenomenon underlying endogenous pain reduction (Colloca, Klinger et al. 2013, Klinger, Colloca et al. 2014). This provocative line of research involves the use of placebos to enhance therapeutic outcomes through learning paradigms that produce behavioral and biological responses mirroring those induced by active drugs (Colloca and Miller 2011, Doering and Rief 2012, Enck, Bingel et al. 2013). In particular, studies indicate that placebos given after repeated administration of active treatments (e.g. morphine) acquire a drug-like effect (e.g. pain reduction) in both animals and humans. Moreover, it is apparent that the effect of this modality is greater than that obtainable through the use of placebo alone (Amanzio and Benedetti 1999, Colloca and Benedetti 2006, Klinger, Soos! et al. 2007, Fiorio, Recchia et al. 2012, Fiorio, Recchia et al. 2014). Based on research on placebo effects derived from pharmacological and non-pharmacological conditioning, we recently published the first systematic analysis of dose-extending use of placebos and factors that need to be considered before incorporating such use into clinical practice. Some of this research uses the term "partial reinforcement" instead of "dose-extension" based on Pavlovian and non-Pavlovian learning principles, but subtle differences are unheeded here due to the fact that conceptual (Colloca and Miller 2011, Doering and Rief 2012, Schedlowski, Enck et al. 2015) and empirical (Au Yeung, Colagiuri et al. 2014) research on partial reinforcement has been previously published.

We searched PUBMED for articles using the search term "placebo" to select papers dealing with the placebo effect. For the approximately 100,000 citations retrieved in 2004, we screened their titles and abstracts retrospectively and excluded papers describing placebo-controlled trials of individual drugs and other medical interventions that only assessed differences between drug and placebo for evaluation of therapeutic benefits of the therapy. We also excluded meta-analyses of placebo-controlled trials and reviews. After exclusion of letters and editorials, we were left with approximately 1,000 papers (or approximately 1% of all papers screened) that discussed different aspects of the placebo response and/or placebo effects in different medical and psychological subspecialties. These were predominantly experimental data (exploring the different mechanisms of the placebo response) and reviews, systematic reviews, re-analyses and meta-analyses of RCT data. For 2004 until 2015, this search was repeated weekly for updates. This database currently (Dec 31, 2015) contains 3,023 papers addressing various aspects of the placebo and nocebo responses in medicine and beyond. For this review, this database was searched using the terms "Pharmacological conditioning" (22 hits) and "conditioning" (225 hits). We identified 22 experimental studies that fulfilled selection criteria including pain- (10) and no-pain-related (12) studies. We reviewed the identified pivotal studies that provide the scientific rationale for placebos to be administrated in a learning-based way and we found that placebos can act as booster agents mimicking the action of active painkillers in both animal and human research. However, there is a lack of research in clinical settings involving patient populations. We carefully analyzed ethical

and clinical requirements for such an approach and herein we propose to perform a pilot clinical study exploring the use of dose-extending placebo in the clinical acute pain.

Conditioned cues were paired with either the opioid agonist morphine hydrochloride or non-opioid aspirin, and opioid and non-opioid-like responses that were either naloxone-reversible or naloxone-insensitive, depending on the drug used in conditioning procedure, were observed [for a review see (Colloca 2014)].

Robust analgesic responses have been documented in human research studies. Amanzio and Benedetti performed a complex experiment in which pharmacological conditioning was done in humans. Either morphine or ketorolac was administered for two consecutive days and then replaced by a placebo on the third day. Naloxone was also given to study to what extent the conditioned effects were antagonizable. All drugs were administered 10 min before infiating a sphygmomanometer cuff to induce ischemic pain. The time interval from cuff inflation to the last squeeze was 1 min and the time interval from drug administration to last squeeze was the same in all subjects (11 min). The pharmacological conditioning was induced by means of either the opioid agonist morphine hydrochloride or the nonopioid ketorolac tromethamine. Conditioning with morphine induced robust placebo analgesic responses that were naloxone-reversible. By contrast, ketorolac conditioning elicited smaller placebo effects that were naloxone-insensitive (Amanzio and Benedetti 1999). Opioid-related placebo analgesic responses can be antagonized by cholecystokinin-2 receptor agonist pentagastrin, indicating a fine balance between cholecystokin and opioid systems in conditioned placebo analgesic effects (Benedetti, Amanzio et al. 2011, Benedetti, Amanzio et al. 2011).

Different schedules of pharmacological conditioning worked in eliciting morphine-mimicking effects, at least in the range of days and weeks. Benedetti and colleagues also performed pharmacological conditioning with two morphine administrations that were given one week apart. Despite the long interval, strong placebo analgesic effects were elicited, indicating that the morphine conditioning has long-lasting effects (Benedetti, Pollo et al. 2007). Therefore opioid-mediated placebo analgesic responses can be re-evoked and learned analgesic effects have practical implications and applications. Using learning principles and pharmacological agents elicits responses that are mediated by opioidergic and non-opioid systems. Notably, these laboratory studies designed to explore the possibility of eliciting beneficial effects by giving placebos after pharmacological conditioning may change therapeutic regimes.

Significance:

The opioid crisis persists despite multiple strategies being introduced to prevent it. Novel approaches are urgently needed for managing acute perioperative pain.

Pharmacological conditioning has been used to study the mechanisms underlying placebo effects in the context of motor (Benedetti, Colloca et al. 2004) and endocrine (Benedetti, Pollo et al. 2003) systems. However, there are interesting studies in which conditioning is considered a viable strategy to harness therapeutic conditioned effects. One of the first studies adopting dose-extending placebos explored decrements in peripheral leukocyte counts in 10 patients treated for multiple sclerosis with four intravenous cyclophosphamide treatments paired with a conditioned stimulus. Eight of 10 patients showed a decreased peripheral leukocyte count when a placebo was given after cyclophosphamide (Giang, Goodman et al. 1996).

In a pre-clinical trial, Goebel et al. gave healthy subjects cyclosporine A (2.5 mg/Kg) along with a green-colored, strawberry-fiavored milk drink (CS) (Goebel, Trebst et al. 2002). The effects of conditioned immunosuppression were assessed by measuring interleukin-2 (IL-2) and interferon gamma (IFN-gamma) mRNA expression, in vitro release of IL-2 and IFN-gamma, and lymphocyte proliferation. A placebo given with the flavored drink significantly suppressed immune functions in terms of interleukin-2 (IL-2) and interferon gamma (IFN-gamma) mRNA expression, in vitro release of IL-2 and IFN-gamma, as well as lymphocy1e proliferation , revealing for the first time the mechanisms underlying conditioned immune responses (Goebel, Trebst et al. 2002).More recently, a study explored the duration of such a conditioned response , observing that the suppression of T-cell function extinguished after 14 unreinforced exposures to the CS drink. Notably, administering sub-therapeutic dosages of cyclosporine A (0.25 mg/Kg) along with the CS drink prevented the extinction of the conditioned immunosuppression(Albring , Wendt et al. 2014). A similar approach was used to produce antihistamine-like effects in patients with allergic rhinitis (Goebel, Meykadeh et al. 2008) and condition behaviorally the acute response to interferon (IFN)beta-1a (Goebel, Hubell et al. 2005).

Notably, Ader and colleagues demonstrated that placebos given in a certain context to elicit conditioned responses can be used with corticosteroids in patients to reduce the symptoms of psoriasis (Ader, Mercurio et al. 2010). Patients were treated under a partial schedule of pharmacologic (corticosteroid) reinforcement in which a full dose was given 25% to 50% of the time and substituted by placebos the other times as compared to a dose control group, in which patients received the full dose 25-50% of the time but not placebos, and a group receiving active corticosteroids every time. The partial schedule of pharmacotherapeutic reinforcement with corticosteroid administration given one quarter or half as frequently as currently prescribed along with dose-extending placebos was sufficient to treat psoriasis. Indeed, the frequency of relapse under partial reinforcement (26.7%) was lower than in the control group (61.5%) and clinically comparable to the reduction in symptoms induced by a full-dose of corticosteroids (22.2%) (Ader, Mercurio et al. 2010).

More recently, Perlis and colleagues applied a similar therapeutic schedule to medically manage chronic insomnia in the long term using a partial reinforcement strategy with nightly dosing strategies including 10 mg zolpidempill use with 50% active medication and 50% placebos for 12 weeks. The partial reinforcement group showed the same clinical benefit as the other three groups randomized to 10 mg or 5 mg or intermittent 10 mg nightly dosing (Perlis, Grandner et al. 2015).

A recent study in children with Attention Deficit Hyperactivity Disorder (ADHD) indicates further therapeutic potential (Sandler and Bodfish 2008). Children were randomly assigned to 1 of 3 schedules of 8-week treatments. Children in arm 1 received a placebo pill paired with a 50%-reduced dose of amphetamine. The same reduction of treatment was performed in arm 2 but without a controlled conditioned cue (control group). Children in arm 3 received a full dose of amphetamine treatment. In a novel methodological twist, use of placebos was described to both parents and children transparently, thus offering a model for pre-authorized placebo use in which patients are explicitly informed that placebos (e.g. lactose or talc pills) will be given to extend medication effects. Pairing a conditioned stimulus with amphetamines produced placebo conditioned responses that allowed children with ADHD to be treated effectively with a lower dose of stimulant medication.

Based on these clinical studies on ADHD, insomnia, psoriasis, we designed the current pilot study to provide evidence that learning mechanisms and dose-extending placebos can be used to reduce opioids intake while acute pain is well managed clinically. Moreover, we will test how reduction of opioids during the hospitalization impacts future use of opioids within a 2 week, 1 month, 3 month, and 6 month follow-up.

ID: VIEW4E02805EA0COO
Name: v2_Justification, Objective, & Research Design

View: v2_Supporting Literature

Supporting Literature

• Provide a summary of current literature related to the research: ***If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.***

Please see references in the attached PDF "Supporting Literature". Additionally, we uploaded very recent studies pointing out to a potential of gabapentin to reduce opioids and the evidence that opioid over-prescriptions occur regularly after surgery among almost all surgical specialties.

We also added a review "Howard, Waljee, and Brummett (2018)" looking at the effectiveness of creating opioid prescription guidelines based on patient use as opposed to standard dosage.

For Amendment 5, we uploaded a paper (Brummett 2017) and report (NSDUH 2017), which are cited in the Opioid Brochure and provide evidence that spinal surgery patients may be at greater risk for developing opioid dependence and that Maryland's death rates from opioid-related overdose has been consistently above the national average since 1999, respectively.

2 If available, upload your applicable literature search :

Name	Created	Modified Date
Brummett et al 2017 JAMA	12/14/2018 4:31 PM	12/14/2018 4:31 PM
NSDUH 2017	12/14/2018 4:30 PM	12/14/2018 4:30 PM
Howard, Waljee, and Brummett 2018 Reduction in Opioid Prescribing Through Evidence-Based Prescribing Guidelines	4/10/2018 2:37 PM	4/10/2018 2:37 PM
Overprescription of opioids after surgery among all surgical specialties	12/16/2017 6:36 PM	12/16/2017 6:36 PM
Potential opioid reduction with gabapentin	12/16/2017 6:34 PM	12/16/2017 6:35 PM
Supporting Literature	12/15/2017 8:36 PM	12/15/2017 8:36 PM

ID: VIEW4E02805A7E400
Name:v2_Supporting Literature

View : v2_Study Procedures

Study Procedures

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below. (If this study is a collaborative UM/VA study please list each procedure that is being conducted and the locations where it is being conducted.)

• Describe all procedures being performed for research purposes only (these procedures would not be done if individuals were not in the study) and when they are performed, including procedures being performed to monitor subjects for safety or to minimize risks:

Prior to patients' enrollment: The intent of this study is to enroll 159 patients with trauma and 212 patients undergoing elective cervical or lumbar spinal surgery requiring inpatient opioid medication into this study to compare strategies to reduce opioid use during the management of acute pain. Patients will be screened on admission to the Shock Trauma Center and/or UMMC. Patients with trauma will be considered for enrollment and be flagged for screening. A plan by the primary service to adhere to The Shock Trauma Protocol for NSAID use (see "Additional Documents") is also a requirement for enrollment. Eligible patients will meet all of the inclusion criteria and none of the exclusion criteria as specified on the "Eligibility Checklist - STC" and "Eligibility Checklist - SSU", respectively (please see Section 9: Study Population , subsection "Eligibility"). Eligible participants will be informed and have the opportunity to discuss the nature of the study, potential for treatment allocation, and risk/benefits. For those who agree to participate, the approved "Informed Consent Form" and "HIPAA" authorization form will be signed. The research staff will explain to the participant what tasks they are expected to complete during this study, answer any questions they may have, and ensure comprehension by completing the "Informed Consent Checklist," which asks participants to verbally report their understanding of the study purpose and procedures, among other key points.

Allocation to treatment group: After the participant discusses and signs the consent form, a staff member will call the pharmacy to inform them of the participant's de-identified Screening number. The pharmacy will then randomly assign that participant a Study ID corresponding randomly to one of the three treatment groups and handle drug logistics (sourcing, processing, and administration) for the remainder of Phase I. Arm 1 will be a Full Dose (FD) group, which will receive all NSAIDs as described in the Guidelines for NSAID use in Orthopedic Patients (see attachment) and Oxycodone (5mg). Arm 2 will be a Partial Reinforcement (PR) group, which will receive NSAIDs, Oxycodone (5mg), and placebos to reach a 50% reduction of the total intake of opioids. Finally, Arm 3 will be a Control (C) group receiving NSAIDs and placebos. Patients will be assigned to one of three arms according to a 1:1:1 schedule of randomization. All staff involved with the protocol will be fully trained on it and will be given study team member emergency contacts in case of incident. Patients within the elective spinal surgery population who choose patient controlled analgesia will have the option to participate only in the optional samples and followup.

Blinding:
Oxycodone and Placebo will be identical in terms of appearance, taste, and smell so as to keep both the investigators and participants blind to their treatment allocation. Oxycodone and placebo oral suspensions will be manufactured by the IDS. Oxycodone solution will be made from tablets according to the compounding procedure detailed under "Additional Documents" to make ensure blinding. In this way, both oxycodone and placebo will look identical for taste, color, and smell. This will help not only to blind the study, but also facilitate study drug administration given that patients may be intubated. All research personnel , aside from the pharmacists and team members responsible for final review and write-up of the study, will be blinded to participants' treatment groups. The pharmacy will dispense medications for each participant that will correspond with their allocated treatment group. For participants in the Partial Reduction group (Arm 2), the pharmacy will dispense the study drug such according to the administration schedule depicted in Figure 2 under "Additional Documents." In summary, participants in Arm 2 will receive four doses of Oxycodone (10 mg) followed by one of four repeating schedules of administration alternating between Oxycodone (5 mg) and placebo. Patients who miss or ask to skip a dose will resume treatment with the skipped dose. Thus, a patient who skips dose #4 will receive dose #4 when they resume medication.

Hospitalization window (Enrollment - the following two to three days hospitalization): Pain ratings will be recorded as usual using the tool in EPIC (uploaded under "Additional Documents") within 20 to 90 minutes after each study drug administration. Also, participants will be given the option to complete a psychological battery (see below Sect. Questionnaires) during the time in the hospital or by the time of their first follow-up visit on paper, over the phone, or electronically via MetricWire or REDCap , which are both secure HIPAA-compliant tools. Questionnaires unrelated to pain will be optional. Although we cannot change the wording of our validated pain questionnaires, we specified in the protocol sections that staff will be trained to use the phrasing suggested by Dr. Fouche (e.g. "how well they are able to perform their daily activities, how well they are able to interact with visitors/family, and how well they are sleeping") whenever possible, and that surveys/questions during the follow-up phase will also take this non-pain-centric approach.

Discharge: Participants will be monitored for subsequent use of opioids at the first post-discharge visit (at approximately 2 weeks) and within month 1, 3, and 6 for follow-ups. The research team may communicate with participants via calls, letters, emails, or texts. REDcap/Qualtrics/MetricWire will be used to facilitate communication. The team member will ask the participant questions about their health and medication use. In addition, a phone application may be developed or the data collection systems used to gather information about participants' medication use and health during the follow-up period. Although the wording of the validated Pain Questionnaires (Please see Section 5.0, Surveys/Questionnaires) we will use during hospitalization cannot be changed, during the follow-up phase we will aim to frame questions about pain intensity and interference with function in such a way as to avoid nocebo effects (i.e. asking how well they are able to perform their daily activities, how well they are able to interact with visitors/family, and how well they are sleeping instead of how much pain are they experiencing).

Duration of the Clinical Trial: Phase 1 (the hospitalization window) will begin with enrollment and last for the following two to three days hospitalization. Enrollment should occur as soon as possible after admission and be within 72 hours of admission. Phase 2 (follow-up) will occur at approximately 2 weeks (coinciding with their first post-discharge visit with their clinician), and months 1, 3, and 6.

Rescue plan: All patients will receive 0.4-1 mg q1 hr i.v. or 1-4mg q1 p.o. Dilaudid for rescue/break through pain. Adjuncts (e.g. lidocaine patches and other medication) can be given as rescue therapy. The rescue therapy will be managed clinically by the Acute Pain Management Service (APMS) and the team will document use of Dilaudid rescue therapy and any given additional medication will be appropriately documented by the APMS team. Discharge: Inaddition, based on the severity of their pain and drug assignment during the hospitalization (Phase I), patients will be discharged on either no opioid prescription, Oxycodone 5mg q4 PRN, Oxycodone 5mg q6 PRN or

Oxycodone 10 mg q6 PRN in addition to adjuvant therapies such as baclofen, flexeril, lidocaine patches, NSAIDs, tylenol, gabapentin/lyrica. In order to do this at the discharge, APMS will contact the IDS for the study allocation to prescribe the adequate treatment. APMS will monitor patients for safety during the Hospitalization (Phase I).

The two instances in which APMS will contact IDS for treatment allocation information (and thus become unblind) are
o Patient being withdrawn from the study because he required more than 3 doses of rescue medication in a row.
o At the end of Phase 1 when APMS will recommend appropriate treatment for pain management.
APMS will contact IDS at the end of Phase 1 (after projected minimum 3 days hospitalization). At the end of Phase 1 (discharge timepoint), APMS team will obtain treatment assignment from the IDS, and the information will be documented on EPIC ONLY in case of patients' withdraw or at the discharge. The PI or designated individual who will be responsible for data integrity, data collection, and analyses will only access EPIC during Phase I (hospitalization) and before the discharge therefore will not see any discharge summary or other notes entered by APMS that may unblind the data analysis.
Once Phase I is complete, patients will be monitored via MetricWire and/or REDCap (not EPIC) guaranteeing that the PI will continue being blind to the treatment allocation.

Primary and secondary outcomes. To be measured daily during hospitalization

1.) Acute clinical pain / acute pain improvement; opioid intake; rate of request of rescue therapies.

Primary and secondary outcomes. To be measured daily during the follow-up.

1.) Use (frequency and intensity) of opioid prescriptions
2.) Development of dependence / addiction problems

2 • Describe all procedures already being performed for diagnostic or treatment purposes (if not applicable to the study, enter "N/A"):
N/A

J • Describe the duration of an individual participant's participation in the study:
Phase 1 (the hospitalization window) will begin with enrollment and last for the following two to three days hospitalization. Enrollment should occur as soon as possible after admission and be within 72 hours of admission. Phase 2 (follow-up) will occur at approximately 2 weeks (coinciding with their first post-discharge visit with their clinician), and months 1, 3, and 6.

4 • Describe the amount of time it will take to complete the entire study:
The entire study is projected to last 2 years, with the final participant being enrolled 6 months before the end of enrollment.

5 • Describe any additional participant requirements:
There will be no additional participant requirements.

ID: VIEW4E02805858400
Name: v2_Study Procedures

View: v2_Sample Size and Data Analysis

Sample Size and Data Analysis

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

• Provide the rationale and sample size calculations for the proposed target population:
This study will enroll a total of 371 inpatients (159 from the Trauma Program and 212 from the Spine Program, both at Shock Trauma Center and UMMC) with 53 participants assigned to each arm in each location, and 53 additional participants in the Spine Program included in the Optional Samples/Follow-up Only group if they choose to receive PCA.

This is a pilot study and the statistical power will be calculated at the end of the data collection to inform future larger scale studies. We predict in the FD group that patients will take a maximum of 90mg (5mg q4 hrs x 3 days) and in PR group that patients will take a maximum dose of 45 mg (5mg q4 hrs x 24 and then estimated q6hrs for 2 days) with an overall reduction of opioids in the hospitalization window of approximately 50%. We expect a small change in pain report (0.25%), and account for 20% participant withdrawal. Therefore, at each location, we would need to recruit 159 participants with an n=53 per group to achieve a significant difference across groups (alpha set at 0.05 and F equal to 3.054, See Figure 1). An interim analysis for each location will be conducted when 25 participants for each arm is reached at that location.

2 • Provide the plan for data analysis. Include in the description the types of comparisons that are planned (e.g., comparison of means, comparison of proportions, regressions, analysis of variance, etc.), which is the primary comparison/analysis, and how the analyses proposed will relate to the primary purposes of the study:
Primary and secondary outcomes. To be measured daily during hospitalization

1.) Acute clinical pain / acute pain improvement; opioid intake; rate of request of rescue therapies.

Primary and secondary outcomes. To be measured daily during the follow-up.

1.) Use (frequency and intensity) of opioid prescriptions
2.) Development of dependence / addiction problems

Collection of variables: pain reports (PEG and Functional Pain scales) and other validated scales (e.g. PROMIS); Use of medication (date- and time-of administration); continuous monitoring by collecting self-reports (HIPAA compliant REDcap/Qualtrics/MetricWire) over the 6 month follow-up period.

To test H1 and H2, mixed effect ANOVAs will be used to test differences in the primary and secondary outcomes among the three groups accounting for sex, age, race, and socioeconomical status as well severity of baseline pain and duration of pain.

ID: VIEW4E02806052800
Name: v2_Sample Size and Data Analysis

View: v2_Sharing of Results

Sharing of Results

• Describe whether results (study results or individual subject results, such as results of investigational diagnostic tests, genetic tests, or incidental findings) will be shared with subjects or others (e.g., the subject's primary care physicians) and if so, describe how it will be shared:
No results will be shared with participants or other non-research personnel. Participants may be informed about BDI scores if they indicate present suicidality.

10: VIEW4E02808CBOBOO
Name: v2_Sharing of Results

View: v2_Research with Drugs or Biologics

Research with Drugs or Biologics

You indicated on the "Type of Research" page that your study involves use of unapproved drug(s)/biologic(s) or approved drug(s)/biologic(s) whose use is specified in the protocol AND/OR evaluation of food(s) or dietary supplement(s) to diagnose, cure, treat, or mitigate a disease or condition.

• List all drugs/biologics to be administered in this study. Be sure to list each drug/biologic with its generic name only.

Drug Name	FDA Approved	IND Number	PI IND Holder
View Oxycodone	yes		no
View ketorolac	yes		no

2 • Attach the drug package insert or investigational drug brochure for the drugs being administered in this study:

Oxycodone insert	12/15/2017 8:40 PM	4/10/2018 6:22 PM
Placebo Insert	12/16/2017 6:52 PM	12/16/2017 6:52 PM
Ketorolac insert	12/16/2017 6:51 PM	12/16/2017 6:51 PM

3 If more than one drug is administered, discuss the risk implications of drug/therapy interactions:
Based on limited studies in acute pain but numerous studies in cancer pain, it seems that there is no evidence of harmful interactions between NSAIDs and Opioids. In a Cochrane review of 42 trials involving 3084 patients, McNicol et al (2005) found a statistically insignificant trend toward a "slight but statistically significant advantage (9 out of 14 papers), compared with either single entity" (1). In a mouse model, Zelcer et al (2005) found that ketorolac did not influence hydrocodone analgesic action during a radiant heat tail-flick test.
This lack of interaction makes biological sense, as in a review Vanegas, Vazquez, and Tortorici (2010) describe how NSAIDs interact with cannabinoid and opioid receptor systems to create analgesia - if both ketorolac and oxycodone have convergent mechanisms of action, then instead of activating opposing systems they would instead both act to saturate the same receptors and reach an analgesic maximum. These papers have been uploaded under "Additional Documents"

4 • Will you be using Investigational Drug Services?
e ves Q No

ID: VIEW4E0916E6E1400
Name: v2_Research with Drugs or Biologics

View: v2_Placebos

Placebos

• Is this study placebo controlled?
e ves Q No

10: VIEW4E0514EECCC00
Name: v2_Placebos

View: v2_Placebo Use

Placebo Use

You indicated that this study is placebo-controlled.

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.

1.1 • Justify the use of the placebo study design and how the benefit to society outweighs the risks to the participants:
There is strong scientific evidence that dose-extending placebos may be used to prolong the effects of active treatments while reducing the overall intake of the drug (see "Supporting Literature" and "Justification, Objective, and Research Design"). As risks of using dose-extending placebos are minimal, and their intake may in fact decrease the risk of abuse and addiction to opioid medications, their potential benefit justifies research such as this into their comparative effectiveness.

1.2 • Is the placebo being used in place of standard therapy?
e ves Q No

1.3 • Is the standard treatment considered effective?
e ves Q No

Psychologi

View: v2_Psychological/Behavioral/Educational Methods and Procedures

cal/Behavioral/Educational Methods & Procedures

ID: VIEW4E0514O798400
Name: v2_Placebo Use

You indicated on the "Type of Research" page that your study involves a psychological/behavioral/educational method or procedure such as a survey, questionnaire, interview, or focus group.

• Select all behavioral methods and procedures which apply to this study:

- m **Surveys/questionnaires**
- 0 Key informant or semi-structured individual interviews
- 0 Focus groups or semi-structured group discussions
- 0 Audio or video recording/photographing
- 0 Educational tests or normal educational practices (education instructional strategies, techniques, curricula, or classroom management methods)
- 0 Individual or group behavioral observations
- 0 Psychosocial or behavioral interventions
- 0 Neuropsychological or psychophysiological testing
- 0 Deception
- 0 Other psychosocial or behavioral procedures

ID: VIEW4E09416F57800
Name: v2_Psycho/ogica//Behavioral/Educational Methods and Procedures

View: v2_Surveys/Questionnaires

Surveys/Questionnaires

You indicated that this study involves surveys and/or questionnaires .

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

• List all questionnaires/surveys to be used in the study, including both standardized and non-standardized assessments:
The Psychological/Emotional Questionnaire battery includes the list of tools below:

Interpersonal Reactivity Index (IRI)
Life-Orientation Test-Revisited (Lot-R)
Neuroticism - Extroversion - Openness Inventory (NEO)
Mood Anxiety Sensitivity Questionnaire (MASQ) - short form
Depression, Anxiety and Stress Scale (DASS 21)
State and Trait Anxiety Inventory(STAI-Y1, STAI-Y2)
Beck Depression Inventory (BDI)
Mood/Depression Assessment
Behavioural Inhibition and Behavioural Activation Scale (BIS/BAS)
Fear of Pain Questionnaire (FPQ)
Positive and Negative Affective Schedule (PANAS)
Tridimensional Personality Questionnaire (TPQ)
Quality of Life-R
Pittsburgh Sleep Quality Index (PSQI) (short version)
Insomnia Severity Index
Last night sleep questions
Adverse Childhood Experiences International Questionnaire (ACE-IQ)
Early memory pain
Adapted Credibility/Expectancy
Edinburgh Handedness Inventory
Chronic Pain Coping Scale

Pain Questionnaires:
• PEG
• Fear of Pain Questionnaire (FPQ)
• Pain Catastrophizing Scale (PCS)
• Pain Detect Questionnaire (PDQ)
• Neuropathic pain (Neur pain)
• Functional Pain Scale

PROMIS (Patient-Reported Outcomes Measurement Information System) - Short Forms
• Pain intensity
• Pain interference
• Pain behavior
• Prescription pain medication misuse
• Sleep disturbance
• Depression
• Anxiety

2 • Upload a copy of all questionnaires/surveys:

Name	Created	Modified Date
PROMIS Scales Combined	10/22/2018 3:38 PM	10/22/2018 3:38 PM

Name	Created	Modified Date
Functional Pain Scale	6/18/2018 4:27 PM	6/18/2018 4:27 PM
Psychological /Emotional Questionnaires	12/14/2017 6:20 PM	3/7/2018 7:02 PM
Early Pain Memory	3/7/2018 5:36 PM	3/7/2018 5:36 PM
Last Night Sleep	3/7/2018 5:36 PM	3/7/2018 5:36 PM
ACE-IQ	3/7/2018 5:35 PM	3/7/2018 5:35 PM
ISi	3/7/2018 5:35 PM	3/7/2018 5:35 PM
PSQI	3/7/2018 5:35 PM	3/7/2018 5:35 PM
CPCI	3/7/2018 5:25 PM	3/7/2018 5:25 PM
Nociceptive vs neuropathic pain assessment scales	12/16/2017 6:55 PM	12/16/2017 6:55 PM
Pain_PEG scale	12/16/2017 6:54 PM	12/16/2017 6:54 PM

J * What is the total length of time that each survey is expected to take?

Psychological/Emotional Questionnaires:

Interpersonal Reactivity Index (IRI) - 1 minute
Life-Orientation Test-Revisited (Lot-R) <1 minute
Neuroticism - Extroversion - Openness Inventory (NEO) - 2 minutes
Mood Anxiety Sensitivity Questionnaire (MASQ) - 1 minute
Depression, Anxiety and Stress Scale (DASS 21) - 2 minutes
State and Trait Anxiety Inventory(STAI-V1, STAI-V2) - 2 minutes
Beck Depression Inventory (BDI) - 4 minutes
Mood/Depression Assessment - 1 minute
Behavioural Inhibition and Behavioural Activation Scale (BIS/BAS) - 1 minute
Fear of Pain Questionnaire (FPQ) - 1 minute
Positive and Negative Affective Schedule (PANAS) - 2 minutes
Tridimensional Personality Questionnaire (TPQ) - 4 minutes
Quality of Life-R - 1 minute
Pittsburgh Sleep Quality Index (PSQI) (short version) - 1 minute
Insomnia Severity Index - 1 minute
Last night sleep questions - 1 minute
Adverse Childhood Experiences International Questionnaire (ACE-IQ) 1 minute
Early memory pain - 2 minutes
Adapted Credibility/Expectancy - 1 minute
Chronic Pain Coping Scale - 2 minutes

Pain Questionnaires:
• PEG - 2 minutes
• Fear of Pain Questionnaire (FPQ) - 2minutes
• Pain Catastrophizing Scale (PCS) - 3 minutes
• Pain Detect Questionnaire (PDQ) - 2minutes
• Functional Pain Scale (1 min)

PROMIS (Patient-Reported Outcomes Measurement Information System) - Short Forms
• Pain intensity - 1 minute
• Pain interference - 1 minute
• Pain behavior - 1 minute
• Prescription pain medication misuse - 1 minute
• Sleep disturbance - 1 minute
• Depression - 1 minute
• Anxiety - 1 minute

4 * Are any of the questions likely to cause discomfort in participants or cause harm if their confidentiality were breached? (i.e., Illegal activities)

e ves Q No

5 * Do any questions elicit information related to the potential for harm to self or others?

e ves Q No

5.1 If Yes, what procedures are in place to assure safety?

The BDI II has one question (#9) that asks the participant to rate their feelings of suicidal thoughts or wishes. We will review each participant's BDI form after completion to assess whether the participant displays the potential for harm to self. Any participant who scores a 2 or 3 on that item will be referred to their provider for follow-up. Also, participants who have a total score of 29 or above on any BDI administration will be referred to their provider for follow-up. The MASQ - item 61 asks about "Thought about death or suicide". In case of positive answer, participants will be referred to their provider for follow-up. If a psychiatric emergency arises because of a verbalization of suicidal ideations or thoughts, research personal will call 911 to ensure that the participant will safely arrive at a hospital for medical evaluation.
As we are not enrolling children, we believe that the results of this study may not meet any reporting requirements. However, in the event of distress due to a response of neglect and abuse on the EPM and ACE-IQ questionnaires , participants will be referred to psychiatry or social work as inpatients . If participants wish to fill out the optional questionnaires, they will be asked to do so by their first follow-up visit so that they may be receive a prompt referral in case of this kind of a response.

ID: VIEW4E09460F5EC00
Name: v2_Surveys/Questionnaires

View: v2_Sample Collection/Analysis

Sample Collection/ Analysis

You indicated on the "Type of Research" page that your study involves a sample (specimen) collection and/or analysis.

* What type of samples will be involved in this study? (Check all that apply)

m **Prospective (will be collected)**

0 Existing (previously collected at the time of initial IRB submission)

2 * Will genetic analysis/testing be done on any of the samples?

e **ves** Q No

J * Will this study involve banking of samples (storing for future research use)?

e **ves** Q No

4 * What is the purpose of the sample collection and/or analysis?

Saliva samples and blood samples will be collected for future study use. There will be no genetic analyses conducted for this study; however, genetic analyses may be conducted for future studies. In the consent form, it is written that although no genetic analyses will be conducted for this particular study, analyses may be conducted for future study. Participants will consent to allowing for the banking of their saliva and blood samples. In past and current research protocols, the PI has collected saliva and blood samples from participants in order to continuously collect data for a potential future research study on exploring the genetics associated with placebo analgesia and development of chronic pain. Both saliva and blood collection are optional.

5 * Is there the possibility that cell lines will be developed with any of the samples?

Q Yes e **No**

6 * Will the samples be released to anyone not listed as an investigator on the protocol?

Q Yes e **No**

6.1 If Yes, give name(s) and affiliation(s):

7 * Will the sample material be sold or given to any third parties?

Q Yes e **No**

1.1 If Yes, give name(s) and address(es):

ID: VIEW4E0E1A4B80000
Name: v2_Sample Collection/Analysis

View: v2_Prospective Samples

Prospective Samples

You indicated that the study involves collection of prospective samples (specimens).

* What type of sample will be collected? (Check all that apply)

m **Blood**

D Bone Marrow Aspirate/Biopsy

D Cerebrospinal Fluid

m **Saliva**

D Skin

D Sputum

D Stool

D Tissue

D Tumor

D Urine

0 Other

1.1 If Other, specify:

2 For blood draws, specify the amount drawn, in teaspoons, at each visit and across the course of the subject's entire participation time:

Optional blood samples will be drawn for assessment of the correlation between circulating gene expression patterns and psychological and physiological phenotypes. Additional blood will be drawn and banked for future studies analyzing the DNA, proteomics, microRNA, and cytokine expression. Blood samples will be collected, following blood borne pathogens guidelines, using the following tubes:

a. Tempus tube for blood RNA extraction (3ml)
b. Purple for PBMC (peripheral blood mononuclear cells) separation (500 ul)
d. Yellow top (SST) for serum protein extraction (5.0ml capacity)
e. Light blue (Sodium citrate) for cytokine extraction - 2.7 ml capacity

Optional blood samples will be drawn during Phase 1 (the hospitalization window) and at 6 months). Patients will be compensated $25 for each visit where they choose to give blood and/or saliva samples.

J * What type of samples will be collected? (Check all that apply)

0 Leftover samples that were obtained for clinical purposes (no additional research procedures required)

m **Samples obtained specifically for research purposes-additional taken during a clinical procedure**

0 Commercial (for profit) samples

0 Samples obtained specifically for research purposes-obtained via a separate collection procedure done solely for the purposes of the study

0 Other

J.1 If Other, specify:

4 * How are these samples labeled? For example, do they contain name, initials, dates, Social Security number, medical record number, or other unique code?

Each sample must contain the following minimum identifying information: 1. Study Number; 2. Subject Number; and 3. Date/time.

5 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?

Q Yes. **No**

6 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?

Q Yes. **No**

7 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.);

If participant withdraws, their saliva and blood samples will be destroyed. However, any information (from future studies) gained from the sample that has been collected up until that point will be retained. Any participant can ask to have their samples destroyed at any time. This procedure will be clearly outlined in the informed consent process.

a * Will the samples be destroyed after the study is over?

O Yes. **No**

s.1 If No, describe how the samples will be stored, where they will be stored, and for how long .

Saliva samples for DNA extraction will be stored at room temperature temporarily at STC and transferred for storage at -20 degrees Celsius at the School of Nursin 7th floor. Blood samples will be transported in ice or dry ice following bloodborn pathogens requirements from the STC to the SON 7th floor for storage at -80 degrees Celsius.

There is no limit to the length of time we will store participant samples and information. Since the sample is collected for future research use, there is no current limit to how the sample will be used. However, participants can ask to have their samples destroyed at any time and no further research will be conducted on their sample.

ID: VIEW4E0E257060COO
Name: v2_Prospective Samples

View: v2_Genetics Research

Genetics Research

You indicated that genetic analysis/testing is being done on the samples.

* How would you classify your genetic study? (choose all that apply)

0 Gene Transfer

0 Pedigree Study (to discover the pattern of inheritance of a disease and to catalog the range of symptoms)

0 Positional cloning (to localize and identify specific genes)

0 DNA diagnostic study (to develop techniques for determining the presence of specific DNA mutations or polymorphisms)

m **Other**

1.1 If Other, specify:
We will ask participants for an optional saliva and/or blood sample, which will be stored and potentially used for a future genetic study.

2 * Discuss the potential for psychological, social, and/or physical harm that could result from participation in this research. In your discussion, consider the following aspects: risks to privacy, confidentiality, insurablity, employability, immigration status, paternity status, educational opportunities, or social stigma.
There should be no psychological, social, nor physical harm resulting from consenting to the optional saliva and/or blood sample. Samples will be de-identified (only labelled with study ID, protocol ID, and date/time). Should any unanticipated issues occur in the future, we will submit a RNI and follow appropriate procedure as determined by the IRB.

3 * Will subjects receive any information resulting from the genetic analysis?

Q Yes. **No**

3.1 If Yes, describe the information that subjects will receive:
Please note: genetic analysis results should only be shared if the testing will be performed in a CLIA certified lab.

4 * Will participants be offered any type of genetic or educational counseling?

O Yes. **No**

4.1 If Yes, who will provide the education or counseling?

4.2 Under what conditions will education or counseling be provided?

5 * Is there the possibility that a family's pedigree will be presented or published?

O Yes. **No**

5.1 If Yes, describe how you will protect family members' confidentiality:

ID: VIEW4E0E7C50FBCOO
Name: v2_GeneticsResearch

View: v2_Sample Banking

Sample Banking

You indicated that the study involves banking of samples (storing for future research use).

* Where will the sample(s) be banked? (If this study involves the VA, please state the name of the registry/repository and the CICERO protocol number is was approved under.)
Saliva samples for DNA extraction will be stored at -20 degrees Celsius at the School of Nursing, floor 7.

2 * Does the banking institution have an approved policy for the distribution of samples?

Q Yes. **No**

3 How long will the sample(s) be kept?
There is no limit to the length of time we will store participant samples and information. Since the sample is collected for future research use, there is no current limit to how the sample will be used. However, participants can ask to have their samples destroyed at any time and no further research will be conducted on their sample.

4 * Will sample(s) be made available to the research subject (or his/her medical doctor) for other testing?

Q Yes. **No**

5 * If a participant withdraws from the study, will that participant have the option to get the remaining portion of their sample(s) back?

Q Yes. **No**

6 * If the participant withdraws, explain how their sample(s) will be handled (For example, will sample(s) be destroyed, anonymized, etc.):

If participant withdraws, their saliva sample will be destroyed.

7 * If the participant withdraws, explain how the data obtained from their sample(s) will be handled (e.g., will it be deleted?) ***(Please note that data for FDA regulated research cannot be deleted):***

However, any information (from future studies) gained from the sample that has been collected up until that point will be retained. Any participant can ask to have their sample destroyed at any time. This procedure will be clearly outlined in the informed consent process. Future studies may or may not be FDA regulated.

ID: VIEW4E0E7E8285800
Name: v2_Sample Banking

View: v2_Data Collection / Record Review

Data Collection/Record Review

You indicated on the "Type of Research" page that your study involves data collection or record review (i.e., chart review, not self-report).

* What type of data will be collected/analyzed in this study? (Check all that apply)

0 Retrospective/Secondary Analysis (data has already been collected at the time of initial IRB submission)

Iii **Prospective (data is not yet in existence and/or collected)**

2 * Will this study involve adding data to a registry or database for future use?

Q Yes. **No**

3 * Will the data be released to anyone not listed as an investigator on the protocol?

Q Yes. **No**

3.1 If Yes, give name(s) & affiliation(s):

10: VIEW4E0E25A8CA400
Name: v2_Data Collection I Record Review

View: v2_Prospective Data

Prospective Data

You indicated that the study involves the collection of prospective data.

* Where is the data being collected from? (Check all that apply)

Iii **Medical records**

0 Medical images

0 Commercial (for profit) entity

0 Publicly available records

0 Schools

Iii **Other**

1.1 If Other, please specify:

Information you will be taking from the medical record (EPIC) including medical history, treatments, demographics, pain assessment and vitals that will be stored in HIPAA compliant REDCap/MetricWire project.

2 * What data fields will you have access to/collect for the study? For example, name, initials, date of birth, Social Security number, income, demographic information, family units, housing, etc.

Name, initials, date of birth, phone number, and email address will be collected to enable logistics for Phase II (follow-up).

You can also upload a copy of the data fields/variables to be collected for the study:

Name	Created	Modified Date

Name	Created	Modified Date

There are no items to display

ID: VIEW4E0E25B643800
Name: v2_Prospective Data

View: v2_Clinical Trial Registration

Clinical Trial Registration

You indicated on the "Type of Research" page that your study is a clinical trial.

* Does the UM Clinical Trials Registry policy require registration of this trial?
e **ves** Q No

2 * Has this trial been registered?
e **ves** Q No

ID: VIEW4E093BF078COO
Name: v2_C/inica/ Trial Registration

View: v2_Clinical Trial Registration Information

Clinical Trial Registration Information

You indicated that this clinical trial has been registered.

* Was this trial registered at www.clinicaltrials.gov ?
e **ves** Q No

2 If no, was this trial registered on a site other than clinicaltrials.gov?
Q Yes Q No

2.1 If Yes, specify the name of the other site:

2.2 Provide justification for registering this trial on this site:

3 * Registration Number
NCT03426137

ID: VIEW4E093BF1O0800
Name: v2_Cfinical Trial Registration Information

View: v2_Participant Selection

Participant Selection

* How many local potential participants (or specimens/charts) do you anticipate will be screened for this study? ***Screening includes determining potential participants' initial eligibility for and/or interest in a study.***
10000

2 * How many participants (or specimens, or charts) will be enrolled/used for this study? ***A local prospective participant is considered enrolled in the study when a UM-approved Informed Consent Document (not including separate screening consent forms) is signed.***

Local - the number being enrolled at this site:
371

Worldwide - the number being enrolled total at all sites (including local enrollment):
371

3 * Gender:
m Male
m Female

4 * Age(s):
0 0 to 27 days (newborn infants)
0 28 days to 12 months (Infant)

D 13 months to 23 months (Toddler)

D 2 to 5 years (Preschool)

D 6 to 11 years (Child)

D 12 to 17 (Adolescents)

m **18 years and older (Adult)**

D 89 years and older

5 * Race/Ethnicity:

m **All Races Included**

D American Indian or Alaskan Native

D Asian/Other Asian

D AsianNietnamese

D Black or African American

D Hispanic or Latino

D Mixed Race or Ethnicity

D Native Hawaiian or Pacific Islander

D White or Caucasian

6

• Language(s):

m **English**

D Chinese

D French

D Italian

D Japanese

D Korean

D Local Dialect

D Spanish

D Vietnamese

D Other

6.1 Specify Other:

7

* Are you excluding a specific population, sub-group, or class?

e **ves** Q No

7.1

If Yes, indicate your justification for excluding a specific population, sub-group, class, etc.:

Patients with comorbid conditions requiring medication that may interfere with pain perception (e.g. anti-psychotic drugs, opioids for cancer-related pain, etc.) will be excluded from the study, as will patients with severe drug seeking behavior and/or positive toxicological screening for drugs other than those prescribed upon admission to STC/UMMC. Pregnant and/or breastfeeding women, prisoners, and will be excluded from the study as they are members of protected populations. Furthermore, we will not enroll pregnant and breastfeeding women for a study in which they would potentially receive opioid medication, given the substantial and well documented risks associated with prescription opioid use during pregnancy. We have uploaded a review of these risks, which include poor fetal growth, preterm birth, birth defects, and neonatal abstinence syndrome under "Additional Documents" (Yazdy, Desai, and Brogly, 2015). Although it would be beneficial to investigate the effectiveness of a placebo for analgesia in pregnant and breastfeeding women in a future study, it is outside the scope of this proposed study as we are interested in comparative effectiveness of placebo in a model of acute pain (trauma).

Patients with an admission creatinine >1.4 or with a history of chronic or acute renal injury will be excluded from the study as these issues may compromise drug metabolism.

The Principle Investigator and Dr. Murthi will retain discretion over eligibility of patients with multiple injuries, with the guidelines that injuries should not interfere with accurate pain ratings and participation would not adversely affect their well-being or recovery.

ID: VIEW4E0E519C1O000
Name: v2_Parlicipant Selection

View: v2_Vulnerable Populations

Vulnerable Populations

• Will you be targeting ANY of the following Vulnerable Populations for enrollment? (Select all that apply)

Employees or Lab Personnel

0 Children (Minors)

0 Cognitively Impaired / Impaired Decision Making Capacity

0 Pregnant Women/Fetuses

0 Wards of the State

Students

0 Prisoners

0 Nonviable Neonates or Neonates of Uncertain Viability

0 Economically/Educationally Disadvantaged

0 None of the above

Only select populations which you will be targeting for enrollment. Do not include populations that may be enrolled incidentally. Enrollment of a vulnerable population is considered to be "targeted" if the study team will be aware that a subject is from a vulnerable group as a result of interaction with the subject or collection of specific information about the subject, and the research team does not wish to exclude them. "Incidental" enrollment is limited to situations where a study team is unaware that a subject is from a vulnerable group.

ID: VIEW4E0E519917800
Name: v2_Vulnerable Populations

View: v2_Vulnerable Populations - Employees or Lab Personnel

Vulnerable Populations - Employees or Lab Personnel

You indicated that employees or lab personnel are included in this study.

• Describe how you will ensure particiption in this research will not affect employment and prevent undue influence:
UM employees and lab personnel may be recruited. The participation will be voluntary without any obligation or requirement associated with the performance of regular job-related activities. Employment status will not be affected by electing to participate or by choosing not to participate.

ID: VIEW4EOE5192BABOO
Name: v2_Vulnerable Populations • Employees or Lab Personnel

View: v2_Vulnerable Populations - Students

Vulnerable Populations - Students

You indicated that students are included in **this study.**

• Describe the types of students that are included in this study:
Undergraduate and graduate students may be recruited. Students are encouraged to seek their mentor's approval. Academic status will not be affected by electing to participate or by choosing not to participate.

2 • Describe how you will prevent undue influence.
Care should be taken to eliminate or reduce the risk that undue influence by faculty or coercion that affects student participation in research. Students may feel compelled to participate, believing that failure to do so will negatively affect their grades and the attitude of the investigator and other students toward them. For this reason, the Pis will not include her students as subjects in the investigator's research. Although students often provide a ready source of potential participants , they are not always an appropriate or representative study sample, as compared to other subject pools. Attention should be given to whether they are being solicited because they are a convenient and accessible sample, rather than as a representative sample for the research inquiry. Therefore , we will also recruit from the general local population and the local universities.

ID: VIEW4E0E519F32000
Name: v2_Vulnerable Populations - Students

View: v2_Eligibility

Eligibility

• Do you have an existing Eligibility checklist(s) for this study?
e ves Q No

1.1 If Yes, upload here. If you need a template, you can download it by clicking **HERE.** The checklists you upload will also be available under the Documents tab of this application.

Name	Created	Modified Date
Eligibility Checklist - SSU	12/14/2018 4:46 PM	12/14/2018 4:46 PM
Eligibility Checklist - STC	12/14/2018 4:46 PM	12/14/2018 4:46 PM
Eligibility Checklist - STC Track Changes	10/23/2018 3:21 PM	12/14/2018 4:45 PM

1.2 If No, create an eligibility checklist below:

List inclusion criteria (List each Inclusion Criteria individually, using the ADD button):

Number	Criteria

There are no items to display

List exclusion criteria (List each Exclusion Criteria individually, using the ADD button):

Number	Criteria

There are no items to display

After entering the inclusion and exclusion criteria above, click the Save link. CICERO will automatically generate a printable Eligibility Checklist for you to use in your research. To review the checklist, click on the resulting link below. This checklist is also available under the Documents tab of this application.

Eligibility Checklist for HP-00078742_5 v12-14-2018-1544823994448(0.01)

ID: VIEW4E0E5185F9000
Name: v2_Eligibility

View: v2_Recruitment

Recruitment

* Describe plans for recruitment, including the identification of potential participants (or acquisition of charts/records/samples) and initial interactions with them: (If this study involves the VA please list all sites at which recruitment will take place.):
Patients meeting initial screening criteria at time of hospitalization will undergo further chart review.

For all eligible subjects, the research staff will consult with the clinical staff to determine if the patient is able to speak with the recruiter. No family member will be approached before they have been advised by the clinical staff as to the status of their family member's injuries.
Due to the severity of their injuries, some patients eligible for this study will not be able to provide consent initially. The patient will be approached at the earliest opportunity after he or she is identified as a potentially eligible participant. The study procedures will be explained, and the patient will have the opportunity to discuss the consent form and ask questions. The patient will be asked if he or she would be interested in participating in this research study. If so, a signature will be obtained on the consent form and a copy of this document will be given to the patient while the original copy will be maintained in the research records. Patients will also asked to answer a few questions related to the study and the "Informed Consent Process Checklist" will be completed as an evaluation of the patient's ability to understand and provide verbal and written informed consent.

2 * Describe measures that will be implemented to avoid participant coercion or undue influence (if not applicable to the study, enter **"N/A"**):
Patients will be compensated $25 for each optional blood sample they choose to give. They will be asked to give an optional blood sample during hospitalization and 6 month follow-up visits. They will be compensated in the form of a check, gift card, or cash that will be given in person, electronically, over the phone, or mailed to the mailing address they provide. In addition, we will provide them with a parking voucher to assist with transportation costs.

In order to compensate patients, we will ask them for their social security number or visa number if they do not have a social security number. If a patient decides to withdraw your data at any time during or at the end of the procedure, they will still be paid. They can expect to receive the check, gift card, or cash within approximately 4-6 weeks. In case the compensation is provided electronically, over the phone, or by mail, they will be asked to confirm that you received ii.

Coercion will be avoided by emphasizing that the blood samples for which we provide compensation are completely optional and will not affect their participation nor their treatment.

J * Who will recruit participants (or acquire charts/records/samples) for this study? (Check all that apply)

m **PI**

m **Study Staff**

0 Third Party

J.1 If you are using a third party, specify Third Party Recruiters:

4 Upload any recruitment tools such as screening/telephone scripts and introductory letters (do not upload advertisements here):

Name	Created	Modified Date

There are no items to display

ID: VIEW4EOBCAAOA6COO
Name: v2_Recruitment

View: v2_Advertising

Advertising

• Will you be using advertisements to recruit potential participants?

Q Yes. **No**

ID: VIEW4E0BCCF811000
Name: v2_Adverlising

View: v2_Research Related Risks

Research Related Risks

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer box below.

• Individually list each research-related risk, using a separate line for each. Next to each risk, delineate the likelihood/seriousness of the risk, and the provisions for minimizing the risk:

Risks associated with data confidentiality: There is a minimal risk for a breach of confidentially of data. However, participant identifying numbers (PIO#) will be used instead of personally identifiable information on all paper and electronic documents. All documents will be stored in a locked cabinet in the Pis office and/or research personnel office. Electronic data will be password protected and accessible only to designated research personnel. Participant confidentiality is strictly held in trust by the investigators, study staff, and the sponsor(s) and our agents. This confidentiality is extended to cover testing of biological samples and genetic tests. This eventuality is unlikely to occur because adequate mentorship , oversight, and training will be provided to all study staff.
Risks associated with oxycodone treatment: There is a risk that treatment with oxycodone could trigger abuse in a manner similar to other opioids. There is a potential for overdose and related side effects (e.g. respiratory depression, head injury, and hypotensive responses). However, in order to minimize this risk, study staff (e.g. nurses, clinicians) and members of the research team will monitor participants throughout hospitalization and during the follow-up phase for symptoms of these potential complications. If an emergency arises because of oxycodone abuse or overdose during the hospitalization, staff clinicians will contact immediately APMS to ensure that the participant will safely monitored. If an emergency arises because of oxycodone abuse or overdose after the hospitalization, patients will be informed to call immediately 911.

Risks associated with psychological questionnaires (optional): There is a possibility that a participant could become emotionally distressed or fatigued while completing questionnaires and other parts of the study. Participants will be told that they are not required to answer any questions that make them feel emotionally distressed. If a participant reports any discomfort, the PI and/or sub-investigator will be notified and a psychological, psychiatric, or appropriate referral will be made if needed. If a psychiatric emergency arises because of a verbalization of suicidal ideations or thoughts, research personnel will contact the patient advising to call 911 to ensure that the participant will safely arrive at a hospital for medical evaluation. In order to minimize fatigue, participants will be offered breaks throughout the study procedure and participants can discontinue their participation at any time and are not required to provide a reason. All potential risks will be clearly delineated and verbalized to the participant during the informed consent form procedure. We have used this set of questionnaires in more than 400 healthy participants in other studies and have never observed distress and / or uncomfortable reactions.

ID: VIEW4E1852509F0OO
Name: v2_Research Related Risks

View: v2_Potential Benefits and Alternatives

Potential Benefits and Alternatives

If you uploaded a separate research protocol document in the 'Research Protocol' page, cite the applicable section and page numbers from that document in the answer boxes below.

• Describe the potential direct benefit(s) to participants:

One potential benefit for participating is that participants may need less opioid after placebos are introduced and still experience the same analgesic effect if they would have taken a greater dose. The findings of this study could improve knowledge about how expectancies can modulate pain, which is critical for minimizing the use of opioid treatments for those with acute pain.

2 • Describe the importance of the knowledge expected to result from the study :

The results of this study will illuminate how opioids can be tapered and can lead to success in opioid dose reduction for those who are prescribed opioids to treat acute pain in a clinical population with trauma.

3 • Describe how the potential risks to participants are reasonable in relationship to the potential benefits:

The long term benefits of this research are to develop improve therapies for treating pain. The risks to the participants in this study are less than the benefit therefore there is a net advantage in performing this research.

4 • Describe the alternatives to participation in this study. If there are no alternatives, state that participation is voluntary and the alternative is not to participate. For intervention studies, describe appropriate alternative clinical procedures or courses of treatment available to subjects .

The participation is voluntary and the alternative is not to participate. Patients within the elective spinal surgery population who choose patient controlled analgesia will have the option to participate only in the optional samples and followup.

ID: VIEW4E1B525180400
Name: v2_Potential Benefits and Alternatives

View: v2_Withdrawal of Participants

Withdrawal of Participants

If the questions below are not applicable to the research (i.e., chart review), enter "N/ A".

• Describe anticipated circumstances under which subjects will be withdrawn from the research without their agreement:

There may be circumstances under which the participant may need to withdraw from the research without agreeing to it. Such cases include:
a. Participants who do not follow instructions given by team members.
b. Participants who are not able to adhere to the protocol.

2 * Describe procedures for orderly termination:
Participants will be informed upon questioning that they were removed from the study and if they have any questions they can follow-up with Ors Luana Colloca and Sarah Murthi to discuss the matter in further detail. Participants will be told why they were withdrawn from the study. The termination of the study will occur as the end of the investigation is reached and data analysis is complete.

3 * Describe procedures that will be followed when subjects withdraw from the research, including partial withdrawal from procedures with continued data collection:
If partial withdrawal occurs, the PI will make a decision about whether already analyzed data can still be used or whether to remove the data from further analysis. All data collected up until the point and used for analysis before their withdrawal may be still used in the aggregate, this is also stated in the ICD so participants are aware of how data may be still used that was collected prior to withdrawal. After participants withdrawal, no more data will be collected from the participant.

ID: VIEW4E1B52531FBOO
Name: v2_Withdrawal of Participants

View: v2_Privacy of Participants

Privacy of Participants

If the study does not involve interaction with participants, answer "N/ A" to the questions below.

* Describe how you will ensure the privacy of potential participants throughout the study ***(privacy refers to persons and their interest in controlling access to themselves):***
To ensure participant privacy, participants will be able to choose a time that is suitable for them to discuss the study over the telephone or in person. While the participants are at the STC/UMMC facilities, study personnel will make sure others do not communicate with participants about research study details.

2 * Describe the location where potential participants will receive research information and detail the specific actions the study team will take to ensure adequate privacy areas:
All study procedures will occur in a locked room where participants and research study personnel are the only individuals in that room at that time. Further, no one who may be on the same area will have knowledge of why research study personnel and participants are meeting unless they are also a part of the protocol.

3 * Describe potential environmental stressors that may be associated with the research:
There are no known potential environmental stressors. All study procedures will take place in rooms that are situated in as quiet as possible settings. If there were to be any unplanned environmental stressors that arise, the research personnel will limit or eliminate any environmental stressors that could affect the participants.

4 * Will this study have a site based in the European Union?
0 Yes O No

5 * Will the study have planned recruitment or data collection from participants while they are located in the European Union?
0 Yes O No

Access link below for information about the EU General Data Protection Regulations to assist in answering these questions.
https://www.umaryland.edu/oac/general-data-protection-regulation /

ID: VIEW4E18525887COO
Name: v2_Privacy of Participants

View: v2_Confidentiality of Data

Confidentiality of Data

* Will stored research data contain identifiers or be able to be linked to and identify individual participants (either directly or through a code/research ID)?

- **Yes**

0 No, the data will be stored de-identified/anonymous (stripped of all identifiers, no way to identify individual participants)

2 * Where will research data be kept (address electronic and paper data as applicable)? (If this is a VA study please list specific sites that data will be kept.)
All paper data collected by research team members will be secured in the Pis areas in locked file cabinets and in a locked cabinet located in the clinical studies suite at the School of Nursing, Floor 7. All electronic data will be kept on a password protected UMB computer. All data files will be password protected to ensure confidentiality. Some or all data may be stored on REDCap/MetricWire, which are secured HIPAA compliant software system managed by the SOM. The project files linked to this project on REDCap /MetricWire will only be shared with study personal and most research study personal users will only have access to de-identified data. Some paper data may need to be temporarily stored in locked, secure filing cabinets within the collaborator's offices at the STC and UMMC. The research coordinators will ensure that any data stored in this fashion will be secure, promptly transferred (within one week) to the SON for permanent storage, and accounted for at all times during storage and transfer.

3 * How will such data be secured?
All electronic data is secured by passwords on a UM appointed computers. Computers must be logged into and files with data will be password protected .
REDCap /MetricWire project privilege will only be given to designated research personal. The VPN for REDCap/MetricWire ensure security of REDCap/MetricWire project data collected at UM.

All paper data will be stored in locked cabinets in locked offices. Only the PI and designated research personal will have a key to these locked cabinets.

4 • Who will have access to research data?
The PI, the Research Coordinator and other research personnel designated by the PI will have access. All access to data will be terminated when a staff member leaves employment or is no longer a member of the research team.

5 • Will study data or test results be recorded in the participant's medical records?
Q Yes. **No**

6 • Will any data be destroyed? ***(Please note that data for FDA regulated research and VA research cannot be deleted)***
Q Yes. **No**

6.1 If Yes, what data (e.g., all data, some recordings, interview notes), when and how?

7 Do you plan to obtain a Certificate of Confidentiality?
Q Yes. **No**

7.1 If Yes, upload your Certificate of Confidentia lity . If you have not yet obtained the Certificate, please note that once it is obtained, you will need to submit an amendment to attach the document, make any needed changes to the submission and make needed changes to the Informed Consent Document .

Name	Created	Modified Date

There are no items to display

a • Discuss any other potential confidentiality issues related to this study :
There is always a chance for a breach of data confidentiality, although the small likelihood of this occurring will be further reduced by ensuring that all data collected will be secured in a locked cabinet and room, and/or password protected on a UMSON computer. Moreover, all documentation will only contain codes and no personally identifiable information when possible.

ID: VIEW4E1B5265E0400
Name: v2_ConfidentialityofData

View: v2_Monitoring Plan Selection

Monitoring Plan Selection

• Type of data safety monitoring plan for the study:
Q Will use/defer to the external sponsor's Data Safety Monitoring Plan
Q Data Safety Monitoring by a Committee
• **Data Safety Monitoring by an Individual**
Q There is no data safety monitoring plan in place

ID: VIEW4E1B00E30D400
Name: v2_MonitoringPlan Selection

View: v2_Monitoring Plan - Individual

Monitoring Plan - Individual

You indicated that the monitoring will be done by an Individual.

• Identify the individual who will be performing the safety monitoring:
Luana Colloca

2 • Describe this individual's role in relation to the protocol:
Dr. Colloca is the study PI

3 • What data will be reviewed?
0 Adverse Events
m **Enrollment Numbers**

- m **Patient Charts/Clinical Summaries**
- D Laboratory Tests
- D Medical Compliance
- D Procedure Reports
- m **Raw Data**
- m **Outcomes (Primary, Secondary)**
- m **Preliminary Analyses**
- D Other

3.1 If Other, specify:

4 • What will be the frequency of the review?

- **Annually**
- Q Bi-Annually
- Q Other

4.1 If Other, specify:

5 • Safety monitoring results will be reported to:

- m **IRB**
- D GCRC
- 0 Sponsor
- 0 Other

5.1 If Other, specify:

ID: V/EW4E18026A2A400
Name: v2_Monitoring Plan - Individual

View: v2_Research Related Costs

Research-Related Costs

• Is the study's financial supporter (e.g., commercial sponsor, federal or state grant or contract, private foundation, physician-sponsor) covering any research-related costs?

- Q No
- **Yes**

1.1 If Yes, check all that apply:

- m **Research-Related Services (personnel costs, tests, supplies, exams, x-rays, or consultations required in the study)**
- 0 Investigational or Study Device
- 0 Investigational or Study Drug
- 0 Investigational Procedure(s)

1.2 If No, who is responsible for payment?

2 • Who is responsible for the uncovered research-related costs?

- 0 Participant
- 0 Sponsor
- D UM

m **Other**

0 There will be no uncovered research-related costs

2.1 If Other, specify:
Luana Colloca and Sarah Murthi will cover all research-related costs.

3 If the participant is responsible for any research-related costs, identify and estimate the dollar amount:

ID: VIEW4E18509641800
Name: v2_Research Related Costs

View: v2_Compensation for Research-Related Injury

Compensation for Research-Related Injury

* Is this study under a master agreement that includes a provision requiring the sponsor to provide compensation to participants for research-related injury?

Q Yes. **No**

1.1 If Yes, please provide the date and title of the agreement and upload the portion of the contract language relevant to compensation for research-related injury:

Name	Created	Modified Date

There are no items to display

1.2 If No (the study is not under a master agreement), is there proposed contract language concerning payment to participants for treatment in the event of a research-related injury?

Q Yes. **No**

1.2.1 If Yes, indicate the status of the contract review/approval with the ORD and upload the proposed language relevant to compensation for research-related injury:

1.2.2

Name	Created	Modified Date

There are no items to display

10: VIEW4E18629EEC0OO
Name: v2_Compensation for Research-Related Injury

View: v2_Payment to Participants

Payment/Reimbursement to Participants

• Will participants receive payment (money, gift certificates, coupons, etc.) or reimbursement for their participation in this research?

e **ves** Q No

ID: VIEW4E1C52A507800
Name: v2_PaymenttoParticipants

View: v2_Payment Detail

Payment/Reimbursement Detail

You indicated that participants will receive payment (money, gift certificates, coupons, etc.) or reimbursement for their participation in this research.

• Payment/reimbursement to participants will be for: (check all that apply)

m **Travel**

m Parking

D Meals

D Lodging

m Time and effort

D Other

1.1 If Other, specify:

2 • What is the total dollar value of the payments/reimbursements over the duration of the study? ***Total payment(s) for participation in research of $600 or more is required to be reported on an IRS Form 1099.***
59

3 • Describe the timing and distribution plan for the payment/reimbursement (schedule, means, etc.)?
Parking vouchers will be purchased ahead of time and given to participants if they need to return to UMMC during Phase II. We have described the timing schedule, means, and reason for payment as follows in the consent form:

"• During hospitalization and at 6 month follow-up visits , you will be asked for an optional blood sample that you choose to give or not. In order to give a blood sample during Phase II (the follow-up period), you will be asked to schedule a time to come in person.
• For up to 2 of the blood samples, you will be compensated in the form of a check, gift card, or cash that will be given in person, electronically, over the phone, or mailed to the mailing address you provide. In addition, we will provide you with a parking vouchers for each visit..
• The blood samples we provide compensation for are completely optional and will not have any effect on your participation and treatment. "

4 • Method(s) of payment/reimbursement to be Used :
a **Cash**
a **Check**
0 Money Order
a **Gift Certificate/Gift Card**
a **Other**

4.1 If Other, specify:
Parking Vouchers and either checks, gift cards, or cash.

ID: VIEW4E1C54A6ACCOO
Name: v2_Payment Detail

View: v2_HIPAA

HIPAA (Health Insurance Portability and Accountability Act)

• HI PAA applies to the University of Maryland School of Medicine, the University of Maryland School of Dentistry and the VA. Are you affiliated with, or will be accessing data from, any of these places? e **Yes** O No

2 If Yes, will the study view, access, share, collect, use, or analyze health information that is individually identifiable under HIPAA? • **Yes** Q No

10: VIEW4E180A2114400
Name: v2_HIPAA

View: v2_Protected Health Information

Protected Health Information (PHI)

You indicated that HIPAA applies and the study will view, access, share, collect, use, or analyze health information that is individually identifiable.

• Which PHI elements will be used or disclosed in this study? (Check all that apply)
a Name
a **Address (if more specific than Zip Code)**
a **Dates**
D Ages over age 89
a **Telephone numbers**
D Fax numbers
a **Email addresses**
D Social Security numbers
a **Medical record numbers**
D Health plan beneficiary numbers
D Account numbers

D Certificate/license numbers

D Vehicle identifiers and serial numbers, including license plate numbers

D Device identifiers and serial numbers

D Web universal resource locators (URLs)

D Internet protocol (IP) address numbers

D Biometric identifiers, including fingerprints and voiceprints

D Full-face photographic images and any comparable images

D Any other unique identifying number, characteristic, or code, unless otherwise permitted by the Privacy Rule for re-identification

D None

2 • Why is the PHI necessary for this research?
If SSNs are going to be used, describe the specific use and type of SSN to be used (real, scrambled, last 4 digits),
This research could not be logistically conducted without access to and use of participant's PHI. We need access to PHI in order to contact participants to confirm their participation schedule and in order to compensate them.

3 • What is the source(s) of the PHI?
Patients will provide this information to the study coordinator in person or remotely via hardcopy or HIPAA compliant REDCap/Metricwire links. Alternatively, participants may indicate that we may access their medical record to obtain this and only this PHI.

4 • Provide written assurance that Protected Health Information will not be reused. (Note: this refers to re-use on another study or for a purpose which has not been approved, not to the re-use of screening data during the current study).
PHI will not be re-used for another study for a purpose that has not been approved. Participants may be contacted with the contact information (email address or phone number) they provide for this study if they indicate that they wish to be contacted for future studies that they may be eligible to participate in.

5 • How will permission to allow the use/disclosure of the individual's protected health information (PHI) be obtained? (Choose all that apply:)

m **Obtain written authorization** ***(upload authorization form at the end of the application under "Consent and HIPAA Authorization Forms")***

m **Requesting waiver/alteration of authorization (includes waiver of authorization for recruitment only)**

0 Qualifies as a limited data set (LOS)

5.1 If you are using a limited data set (LOS), please attach the Data Use Agreement (DUA):

Name	Created	Modified Date

There are no items to display

ID: VIEW4E1B0A24AA400
Name: v2_Protected Health Information

View: v2_Waiver/Alteration of Authorization

Waiver/Alteration of Authorization

You indicated that a waiver/alteration of authorization is requested.

• Provide rationale for how the research presents no more than minimal risk to the 1:1rivacy of individuals:
All study procedures will occur in a private and secure setting. Moreover, research personal will not inform anyone who is not a part of the research team why the two parties (research staff and participants) are meeting.

2 • Describe the plan to ensure the protection of PHI collected during this study from improper use and disclosure:
Data will be entered directly into REDCap/Qualtrics/MetricWire databases using participant study ID. This information will not be reused or disclosed to any other person or entity, except as required by law. Therefore the risk of disclosure of any PHI with these individuals, outside the team members of this investigation, is extremely All research data when possible will be coded and stripped of identifiable information, and will be stored separately from documents that require participant identifiable information. The study ID will be linked only on paper, and this will be stored in a locked office and then in a locked room. Computer data will be identified only using the study ID, and for additional security will be kept on a password protected computer in a locked office and on the REDCap/Qualtrics/MetricWire databases. All data will be locked either by a password and/or in a locked cabinet and office and no one will have access to this data unless they are designated by the PI.

3 • Describe the plan to destroy the PHI collected during this study at the earliest opportunity consistent with the conduct of the research. If there is a need to retain PHI, provide a justification:
We will maintain human research records, including signed and dated consent documents for at least five years after completion of the research. Signed and dated HIPAA authorizations and screening documents will be maintained for at least five years after completion of the research. Afterwards, we will destroy these documents in line with any UMB policies.

4 • Why could the research not practicably be done without access to and use of this PHI?
This study will recruit patient participants solely for the fact that they are patients who experience pain. It is important to have access to certain medical information to ensure patient safety (for example, safety in taking the prescribed dose) and to collect data that is valid for this study's aims.

5 * Why could the research not practicably be done without the waiver or alteration?
We need to be able to determine which patients are eligible before approaching them for consent and enrollment in the study. The only way to determine eligibility is to view their admitting diagnosis and medical record number to identify the patient. It would not be practical to conduct this study without first determining their potential eligibility. Participants will be recruited for the study by reviewing their medical records once admitted to the hospital and interaction with treating clinical staff. Access is required to review medical records prior to enrollment to determine their potential eligibility.

6 * Will the subjects' PHI be disclosed to (or shared with) any individuals or entities outside of UM?
O Yes. **No**

6.1 If Yes, describe the individuals or entities outside of UM to whom PHI will be disclosed.

ID: VIEW4E180A2896400
Name: v2_Waiver/Alteration of Authorization

View: v2_Informed Consent Process

Informed Consent Process

If the study does not involve interaction with participants or a waiver of consent is being requested , answer "N/ A" to the questions below.

* Indicate the type(s) of consent that will be involved in this study: (check all that apply)
0 Not applicable (study may qualify as exempt)
0 Request to Waive ConsenUParental Permission (Consent is not being obtained)
0 Request to Alter Consent (Some Elements of Consent Waived)
0 Request to Waive Documentation of Consent (Verbal/Oral Consent)
a **Written Consent Form**
0 Electronic Consent

2 * Describe the Informed Consent process in detail:
Before participating in this research study, eligible participants will be required to read and sign an informed consent form, and then correctly answer questions presented by trained research personnel about critical study details. Participants will be asked what is expected of them by participating, if they fulfill any of the exclusion criteria, if they are fully aware that participation is voluntary and if they have any questions about the study and procedure. The investigatory will confirm the participant's understanding by using the "Informed Consent Checklist" under "Additional documents." Participants will be able to read the consent form in a quiet and locked room with no distractions and will be provided with a copy of their signed forms and the PI's contact information to take with them.

3 Confirm that the consent process will explain the following:

- The activities involve research.
- The procedures to be performed.
- That participation is voluntary.
- The name and contact information for the investigator.

* • **Yes** O No

4 * Describe who will obtain Informed Consent:
Luana Colloca (PI) or other trained research personnel affiliated with the protocol. All research personnel will be adequately trained to administer the informed consent form, and to answer and ask questions to test the participant's knowledge.

5 * If obtaining consent from a legally authorized representative (LAR), describe how you will confirm that the individual is the LAR and can provide legally effective informed consent. *(Answer "NIA" if not obtaining consent from LARs)*
N/A

6 * Describe the setting for consent:
The consent procedure will occur in a quiet and locked room with no distractions. Participants can take as much time as they would like to read over the form and to ask questions before agreeing to participate in the study.

1 * Describe the provisions for assessing participant understanding:
After a participant agrees to participate, they will be asked verbally the following questions to test their knowledge about the study:
• 1) What is expected of you when participating in this study? Please reflect on the procedure.
• 2) Do you fulfill any of the exclusion criteria listed on this form?
• 3) Are you fully aware that participation is entirely voluntary?
• 4) Do you have any questions about the study purpose and procedure?

In addition, the participant will be asked to state the following pieces of information, and a record of their ability to do so will be kept on the Informed Consent Checklist (see "Additional documents"):

The purpose of the study: YES NO

One potential risk of study participation: YES NO

How treatments are assigned during the study: YES NO

The requirements to participate in the study (the study procedures): YES NO

What to do if experiencing concerns that are not being properly addressed: YES NO

What to do if they decide that they no longer wish to participate in the study: YES NO

a • Describe the consideration for ongoing consent :

Ongoing consent will be assessed verbally at discharge and at each follow-up point (approximately 2 weeks and 1, 3, and 6 months) either in person, over the phone, via a phone application, or via REDCap/Qualtrics/MetricWire.

ID: VIEW4E1C661D0ACOO
Name: v2_/nformed Consent Process

View: v2_Consent Forms - Draft

Consent and HIPAA Authorization Forms - Draft

Upload all of your Consent Forms for approval. Use only Microsoft Word.

Name	Created	Modified Date
ICF AMOS SSU NEW	1/22/2019 2:44 PM	3/6/2019 11:58 AM
ICF AMOS STC Clean	12/14/2018 5:24 PM	3/6/2019 11:58 AM
ICF AMOS STC Track Changes	12/14/2018 5:24 PM	12/14/2018 5:24 PM

IMPORTANT NOTE: the above list of consent forms (if any) are DRAFT versions. Under no circumstances should copies of these be distributed to patients/study subjects. If/when this research submission is approved by the IRB, approved consent forms will be available for download and use from the "Documents" tab of the Submission's workspace (click Exit and then look for the Documents tab - approved submissions only)

1A Archived Consent Forms:

Name	Created	Modified Date
ICF AMOS SSU NEW	12/14 /2018 5:24 PM	12/14/2018 6:28 PM
ICF AMD4 Track Changes	10/23/2018 1:25 PM	10/23/2018 3:17 PM
ICF AMD4 Clean	10/23/2018 1:25 PM	10/23/2018 3:17 PM
ICF UPDATED clean	4/10/2018 8:21 PM	7/31/2018 10:09 AM
ICF UPDATED with Track Changes	12/15/2017 9:07 PM	7/31/2018 10:09 AM

2 Upload any HIPAA authorization forms here:

HIPAA UPDATED	12/15/2017 9:08 PM	3/7/2018 7:44 PM

Please refer to HRPO's website for specific instructions for preparing informed consent documents and to access current templates: http://hrpo.umaryland.edu/researchers/consents.html

ID: VIEW4E1C7712O3000
Name: v2_Consent Forms- Draft

View: v2_Organization Review Requirements (other than IRB)

Organization Review Requirements (other than IRB)

Answer the following questions to determine additional organizational review requirements:

Department/Division Review - All research submissions are required to undergo department/division/institutional review prior to IRB review. The following entity is listed as the required department/division/institutional review:

SON Pain & ***Trans Symptom Sci***

If this information is incorrect, please notify the HRPO office.

2

RSC Review Criteria - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Radiation Safety Committee may be required.

* 2.1 Does the research involve the use of ionizing radiation? Q Yes. **No**

2.2 Does the research involve the sampling of radioactive human materials for subsequent use or analysis in a laboratory?

3 **IBC Review Criteria** - select 'Yes' if the answer is 'Yes' for any of the following questions. Review by the Institutional Biosafety Committee may be required.

* 3.1 Does the research involve human gene transfer? e **Yes** O No
-OR-
Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials .

3.2 Does the research involve the exposure of human subjects to pathogenic microorganisms, or the exposure of research staff to human subjects or samples known or reasonably expected to carry infectious disease(s)?

3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

4 **Cancer Center Criteria** - Answer the following to determine if review by the Cancer Center (Hematology-Oncology) may be required.

• Does the protocol involve in any way studies related to the prevention, treatment, diagnosis, or imaging of neoplastic diseases? O Yes e **No**

5

General Clinical Research Center Review Criteria - the GCRC offers free and/or cost shared resources for patient-oriented research. Click Here for more information .

Answer the following to determine if review by the GCRC may be required .

* Will the General Clinical Research Center (GCRC) facility or resources be used to conduct this activity? Q Yes. **No**

6

VA Review Criteria - Answer the following questions to determine if review by the VAMHCS R&D Committee may be required.

• 6.1 - Will the research be conducted by VA Investigators including Pis, Co-Pis, and Site Investigators on VA time (serving on compensated, WOE, or IPA appointments)? O Yes e No

* 6.2 - Will the research utilize VA resources (e.g., equipment, funds, medical records, databases, tissues, etc.)? 0 Yes e **No**

* 6.3 - Will the research be conducted on VA property, including space leased to and used by VA? 0 Yes e No

PLEASE NOTE that the research may be funded by VA, by other sponsors, or may be unfunded.

ID: VIEW4E1AF91AB2400
Name: v2_0rganizationReview Requirements (other than /RB)

View: v2_1n stitutional Biosafety Committee Review Required

Institutional Biosafety Committee Review Required

NOTE: based on your answers to questions on a previous page (see below) review by the Institutional Biosafety Committee (IBC) is required. This will involve extra steps on your (study team) part. Clicking the Continue button will result in the system creating a blank IBC Submission form for you. You will be required to fill out and submit this IBC form before you will be able to submit the Protocol form. The IBC Submission workspace and form can be reached by clicking the appropriate

button on the left hand side of the Protocol submission's workspace (web page) after exiting the Protocol form .

2 **Question** - answered on IBC RSC review requirements page:

3.1 Does the research involve human gene transfer? - OR - Does the research specifically apply to human studies in which induction or enhancement of an immune response to a vector-encoded microbial immunogen is the major goal, and such an immune response has been demonstrated in model systems, and the persistence of the vector-encoded immunogen is not expected? This type of research is often referred to as recombinant vaccine trials.

3.2 Does the research involve : a) the exposure of human subjects to pathogenic microorganisms, orb) thepotentia l exposure of UMB research staff to infectious materials through the sampling or processing of materials from patients with known infectious disease or from environmental surfaces?

3.3 Does the research involve the sampling of materials from persons with no known infectious disease and where the only risk to study staff is occupational exposure to bloodborne pathogens as defined by the OSHA Bloodborne Pathogen Standard?

Yes

If the answer to this question is wrong, an IBC submission is not required, use the Jump To menu or your browser's<

3 **Confirm** - you have read the above information and understand that in addition to the IRB Protocol form, you will fill out and submit the IBC Submission form

e ves Q No

ID: VIEW4E1AF91ED4COO
Name: v2_/nstitutional Biosafety Committee Review Required

View: v2_Summary of Required Reviews (other than IRB)

Summary of Required Reviews (other than IRB)

Additional Committee Reviews - Based on your responses to the previous questions, you have identified the following additional reviews. To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's webpage.

Name of Related Submission		
IBC: Relieving Acute Pain (RAP) Study (HP-00078742_4)	Workspace	SmartForm

2 **Required Department and Specialty Reviews** - Based on the PI's organization (department, division, etc.) affiliation and answers to previous questions (use of Cancer Center, etc.), the organizations listed below are required to review this application. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	Review Status
SON Pain & Trans Symptom Sci	Complete
SOM Program in Trauma	Complete

ID: VIEW4E1C8D9AE4000
Name: v2_Summary of Required Reviews (other than /RB)

Vie w: v2_Additional Documents

Additional Documents

Upload all additional documents here:

Name	Created	Modified Date
Figure 2 - Administration Schedule - updated	4/10/2018 3:41 PM	12/14/2018 6:30 PM
Script for Consenting	12/14/2018 5:27 PM	12/14/2018 5:27 PM
Opioid Brochure	12/14/2018 5:26 PM	12/14/2018 5:26 PM
CRF AMD5 Clean	6/19/2018 5:16 PM	12/14/2018 5:26 PM
CRF AMD5 Track Changes	8/1/2018 10:00 AM	12/14/2018 5:25 PM
Glascow Coma Scale	10/22/2018 8:03 PM	10/22/2018 8:03 PM
Yang Wang Compiled Trainings	8/21/2018 11:47 AM	8/21/2018 11:47 AM
IC_Evaluation	6/19/2018 5:17 PM	6/19/2018 5:17 PM
Informed Consent Checklist Revised.docx	4/12/2018 2:45 PM	6/18/2018 4:26 PM
Yazdy Desai Brogly 2015 Prescription Opioids in Pregnancy and Birth	4/11/2018 1:16 AM	4/11/2018 1:16 AM
Zelcer et al (2005) Selective potentiation of opioid analgesia by nsaids	4/11/2018 1:04 AM	4/11/2018 1:04 AM
Vanegas, Vazquez, and Tortorici (2010) NSAIDs, Opioids, Cannabinoids and the Control of Pain	4/11/2018 1:04 AM	4/11/2018 1:04 AM
Cochrane Review of NSAID Opioid Interactions	4/11/2018 1:03 AM	4/11/2018 1:03 AM
Figure 3 - Randomized Consent Desgin Zelen NEJM 1979	4/10/2018 9:23 PM	4/10/2018 9:23 PM
EPIC Pain Recording Tool	3/7/2018 5:13 PM	3/7/2018 5:13 PM
Robert (Scott) Murray Certificates	2/7/2018 12:37 PM	2/7/2018 12:37 PM
Jeffrey Gonzales Certificates	2/7/2018 12:36 PM	2/7/2018 12:36 PM
NCT ID opioids	1/11/2018 11:21 AM	1/11/2018 11:21 AM
Figure 1 - Power calculation	12/16/2017 8:00 PM	12/16/2017 8:01 PM
Guidelines For NSAID use	12/15/2017 9:09 PM	12/15/2017 9:09 PM

10: VIEW4E0962513AOOO
Name: v2_Additional Documents

View: v2_Final Page of Application

Final Page of Application

You have reached the final page of this application. It is recommended that you click on the "Hide/Show Errors" link on the upper or lower breadcrumb row of this

page . The "Hide/Show Errors" will do a search of your application, and highlight areas that are required or need to be completed prior to submitting.

By submitting this application, you are electronically routing the protocol for departmental scientific review and all other necessary reviews. According to information you have provided, this application will be routed to the following Departments for review prior to being forwarded to the IRB for review. These reviews are conducted online and no additional forms or steps by the study team are required.

Name of Organization	Review Status
SON Pain & Trans Symptom Sci	Complete
SOM Program in Trauma	Complete

Required Safety Committee Reviews - In addition to the IRB, the following committees must review this submission. Each additional committee has a separate online form that the study team will be required to fill out. All committee applications (IRB plus those listed here) must be completed properly before the 'package' of applications can be submitted. The team may complete these additional forms in any order or at any time prior to submission of the IRB Application . To complete or view these additional committees' forms, click on the links below or exit this application and click on the appropriate button on left side of this submission's Workspace.

Name of Related Submission		
IBC: Relieving Acute Pain (RAP) Study (HP-00078742_4)	Workspace	SmartForm

You may check the progress of your application at any time by returning to the Workspace of this submission. A detailed history, including notes, dates, and times of events, is provided to you for this purpose.

If a reviewer returns the application to you, you must address their concerns and resubmit the protocol for review to all designated departments. After all departments have reviewed the application, it will automatically be sent to the IRB for review. Changes made to the submission after its approval must be submitted as modifications.

Investigator Attestation
By submitting this application, I, the Principal Investigator (PI), certify that the information provided in this application is complete and correct. Research will be conducted according to the submission as described, only by the approved principal investigator and study team members.

In addition, I agree to the responsibilities of a PI, including:

- Obtaining informed consent (if applicable) from all subjects as outlined in the submission.
- Reporting new information to the IRB per the requirements of the Investigator Manual.
- If Required, obtaining renewal of the protocol prior to the expiration of the approval period or halt all study activities upon study expiration.
- Accepting ultimate responsibility for the protection of the rights and welfare of human subjects, conduct of the study and the ethical performance of the project.
- Ensuring performance of all research activities by qualified personnel according to the IRB approved submission.
- Ensuring that research personnel have or will receive appropriate training.
- Ensuring no changes will be made in the research until approved by the IRB (except when necessary to eliminate apparent immediate hazards to subjects).

Click the "Finish" button and then click "Submit Application" in the submission Workspace.

ID: VIEW4E1B10C500000
Name: v2_Final Page of Application

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Madison Binder

2 Research Role:
Technician or Assistant

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

e ves Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Madison Binder, member of the STAR CORE research unit at Shock Trauma Center will work under the

supervision of Ors . Scarobo and Colloca to help recruit, consent eligible study participants and manage research related tasks (e.g. collection of saliva, quality management, and completion of checklists).

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Denise Whye

2 Research Role:
Technician or Assistant

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, *even* if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Denise Whye, member of the STAR CORE research unit at Shock Trauma Center will work under the supervision of Ors. Scarobo and Colloca to help recruit, consent eligible study participants and manage research related tasks (e.g. collection of saliva, quality management, and completion of checklists).

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Lauren Offer

2 Research Role:
Technician or Assistant

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, *even* if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
e **ves** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 • Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Lauren Offer, member of the STAR CORE research unit at Shock Trauma Center will work under the supervision of Ors. Scarobo and Colloca to help recruit, consent eligible study participants and manage research related tasks (e.g. collection of saliva, quality management, and completion of checklists).

View: IRB - Add a Team Member

Add a Team Member

• Select Team Member:
Brandon Cave

2 Research Role:
Research Team Member

3 • Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 • CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 • Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 • Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Brandon is an Anesthesiology Resident

View: IRB - Add a Team Member

Add a Team Member

• Select Team Member:
Rebecca Lopas

2 Research Role:
Technician or Assistant

3 • Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 • CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
e ves Q No

5 • Does this study team member have a potential conflict of interest, financial or otherwise , related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Rebecca Lopas, member of the STAR CORE research unit at Shock Trauma Center will work under the supervision of Ors. Scarobo and Colloca to help recruit, consent eligible study participants and manage research related tasks (e.g. collection of saliva, quality management, and completion of checklists).

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Deborah Stein

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Assist with study design and data interpretation

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Tlmileyin Adediran

2 Research Role:
Technician or Assistant

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
ileyin Adediran holds a MPH in epidemiology awarded by University of Maryland and a BA in Biology and Health Administration and Public Policy awarded by University of Maryland Baltimore County. Her primary research experience is in data collection and data analysis of secondary data. She has written protocols, codes for data analysis and presented findings at both local and national conferences. She will utilize this expertise within this protocol as a research assistant.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Mark Scarboro

2 Research Role:
Sub-Investigator

3 • Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
e **ves** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Mark Scarboro , Director of Research Operations and Compliance, STAR Center will provide his support with his team of research assistant.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Margaret Lauerman

2 Research Role:
Research Team Member

3 • Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 • CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Dr. Lauerman will be able to sign for prescriptions and will assist with APMS consults.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Samuel Phillips

2 Research Role:
Technician or Assistant

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
. **Yes** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Samuel Phillips is a junior majoring in biology at the University of Maryland College Park. He is assisting at Dr. Colloca's lab during the summer of 2018 to gain more experience and assist in research opportunities. He will primarily assist with recruitment, data collection and data entry.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Daniel E. Gelb

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will

automatically receive all emails:
Q Yes e No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes e No

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Daniel E Gelb. MD; Dr. Daniel E. Gelb is a professor of orthopedics and vice chairman of the Department of Orthopaedics. His areas of clinical interest include adult and pediatric spinal deformity, including scoliosis and kyphosis, spinal tumors and infections, spinal trauma, and a full range of degenerative spinal conditions.

View: IRB - Add a Team Member

Add a Team Member

• Select Team Member:
Sarah Murthi

2 Research Role:
Sub-Investigator

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
e ves Q No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
e ves Q No

5 • Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes e No

6 • Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Sarah Murthi is an Associate Professor of Surgery and Director of the Trauma and Critical Care Ultrasound Program at the
R Adams Cowley Shock Trauma Center. She has extensive experience within the UMMC system as she completed her post-residency fellowship with surgery critical care at UMMC. She currently leads the Maryland Blended Reality Center which capitalizes on the growth of virtual and augmented reality and develops innovative new uses, combining the advanced computing, visual capture and display resources at UMCP with the clinical data, biomedical and patient care at UMB.

View: IRB - Add a Team Member

Add a Team Member

• Select Team Member:
Kaitlyn Welk

2 Research Role:
Technician or Assistant

3 • Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all

emails regarding this protocol, even if the answer to #4 below is No.

Q Yes e **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

e **ves** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

Q Yes e **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:

Kaitlyn Welk, member of the STAR CORE research unit at Shock Trauma Center will work under the supervision of Ors. Scarobo and Colloca to help recruit, consent eligible study participants and manage research related tasks (e.g. collection of saliva, quality management, and completion of checklists).

View: IRB - Add a Team Member

Add a Team Member

• Select Team Member:

Yvette Fouche

2 Research Role:

Sub-Investigator

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

Q Yes e **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

e **ves** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

Q Yes e **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:

Dr. Fouche , as Division Head of Anesthesiology for the Program In Trauma, will assist with study design, procedures, and APMS consults.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:

Chika Okusogu

2 Research Role:

Research Team Member

J * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
e **ves** Q No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
e **ves** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes e **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Chika Okusogu is a MPower Scholar and Nurse student who will assign with the study operational activities.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Linda Phillips

2 Research Role:
Technician or Assistant

J * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes e **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
e **ves** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes e **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Linda Phillips , member of the STAR CORE research unit at Shock Trauma Center will work under the supervision of Ors. Scarobo and Colloca to help recruit, consent eligible study participants and manage research related tasks (e.g. collection of saliva, quality management, and completion of checklists).

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Mohammad Usmani

2 Research Role:
Study Coordinator

J * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:

M. Farooq Usmani, MS; is research coordinator for spine orthopedics division. Farooq is a 4th year medical student who decided to enhance his application for residency by perfoming a year of clinical research. He will assist in protocol development, patient screening and recruitment, among other duties assigned.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Caroline Stanley

2 Research Role:
Technician or Assistant

J * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

. **Yes** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:

Caroline Stanley, member of the STAR CORE research unit at Shock Trauma Center will work under the supervision of Ors . Scarobo and Colloca to help recruit, consent eligible study participants and manage research related tasks (e.g. collection of saliva, quality management, and completion of checklists).

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Robert Murray

2 Research Role:
Research Team Member

J * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
As an undergraduate student, Scott attended Towson University and UMBC while obtaining degrees in Chemistry, Biochemistry, and Molecular Biology. With a passion for medicine and research, he decided to apply for a position at Shock Trauma as a Clinical Research Assistant in September of 2014. Over the past three years, he has grown to truly love research and all that it hopes to accomplish for our presenUfuture patients.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Steven Butkus

2 Research Role:
Technician or Assistant

J * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Steven Butkus will assist with any technological aspects of this study included but not limited to MetricWire and programming scripts for data collection and analyses.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Rachel Paganelli

2 Research Role:
Technician or Assistant

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, *even* if the answer to #4 below is No.

Q Ves e **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

e **ves** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

Q Ves e **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Rachel Paganelli, member of the STAR CORE research unit at Shock Trauma Center will work under the supervision of Ors. Scarobo and Colloca to help recruit, consent eligible study participants and manage research related tasks (e.g. collection of saliva, quality management, and completion of checklists).

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Ilana Grabenstein

2 Research Role:
Technician or Assistant

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, *even* if the answer to #4 below is No.

Q Ves e **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

e **ves** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

Q Ves e **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Ilana Grabenstein, member of the STAR CORE research unit at Shock Trauma Center will work under the supervision of Ors. Scarobo and Colloca to help recruit, consent eligible study participants and manage research related tasks (e.g. collection of saliva, quality management, and completion of checklists).

View: IRB - Add a Team Member

Add a Team Member

• Select Team Member:
Yang Wang

2 Research Role:
Research Team Member

3 • Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, *even* if the answer to #4 below is No.
Q Yes. **No**

4 • CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 • Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 • Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Yang received her BA in English from China University of Political Science and Law, Beijng, China and both a Master's of Psychology and PhD in Psychology from Southwest University, Chongqing, China. Her research interests include exploring the influences of expectations on pain perceptions within healthy and clinical participants, and she will utilize her expertise in data analysis and clinical research to assust in this protocol.

View: IRB - Add a Team Member

Add a Team Member

• Select Team Member:
Leslie Sult

2 Research Role:
Technician or Assistant

3 • Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, *even* if the answer to #4 below is No.
Q Yes. **No**

4 • CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails :
e **ves** Q No

5 • Does this study team member have a potential conflict of interest, financial or otherwise , related to this research?
Q Yes. **No**

6 • Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Leslie Sult, member of the STAR CORE research unit at Shock Trauma Center will work under the supervision of Ors. Scarobo and Colloca to help recruit, consent eligible study participants and manage research related tasks (e.g. collection of saliva, quality management, and completion of checklists).

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Eugene Koh

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Eugene Y. Koh, MD, PhD; Dr. Koh serves as the dedicated spine surgeon and the Chief of Orthopaedics for the Baltimore VA Medical Center. He received a dual degree of MD-PhD from the Harvard School of Medicine and the Massachusetts Institute of Technology. Dr. Koh's specific area of interest and clinical expertise , include disorders of the cervical and lumbar spine, minimally invasive spinal techniques, and reconstruction of the traumatically injured spine.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Jael Camacho

2 Research Role:
Study Coordinator

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Jael E Camacho, MD; is research coordinator for spine orthopedics division. Jael graduated medical school in 2018 and decided to expand is medical education by completing a year of clinical research. He will assist in protocol development, patient screening and recruitment, among other duties assigned.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Kristina Park

2 Research Role:
Technician or Assistant

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Kristina Park is currently a student at UMSON, Master of Science in Nursing: Clinical Nurse Leader, and will assist with data collection, entry and analyses. She has completed the required HRPO training and will work under the supervision of the PI.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
patricia casper

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

Q Yes. No

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Patricia Casper, CRNP, will be able to sign for prescriptions and will assist with APMS consults.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Jackson Barr

2 Research Role:
Research Team Member

3 • Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. No

4 • CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes . No

5 • Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. No

6 • Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Jackson Barr, member of the STAR CORE research unit at Shock Trauma Center will work under the supervision of Ors. Scarobo and Colloca to help recruit, consent eligible study participants and manage research related tasks (e.g. collection of saliva, quality management, and completion of checklists).

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Steven C. Ludwig

2 Research Role:
Sub-Investigator

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

Q Yes e **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:

Steven C Ludwig, MD; is a professor of orthopedics and Chief of the Spine Orthopedics Division. Dr. Ludwig 's areas of interest are adult reconstructive spine surgery, degenerative diseases of the cervical and lumbar spine, disc herniation and replacement, spinal stenosis, spinal tumors and infections, sports-related spine injuries, and traumatic injuries to the cervical spine.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:

Se Eun Lee

2 Research Role:

Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

e **ves** Q No

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:

e **ves** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?

Q Yes e **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture , and society:

Se Eun Lee is a registered nurse who will help with all the phases of this research. She will be working under the supervision of the PI.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:

Robert Goodfellow

2 Research Role:

Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.

Q Yes e **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will

automatically receive all emails:
e ves Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Robert Goodfellow, nurse practitioner with the Department of Anesthesiology at Shock Trauma Center, will help coordinate the clinical and research aspects of this protocol, interpret the results, monitor patients as part of the APMS and write the publications from this study. He completed the CITI and HIPAA training.

View: IRB - Add a Team Member

Add a Team Member

• Select Team Member:
Kelley Banagan

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including: editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 • Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 • Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Kelley E Banagan, MD; is an assistant professor of orthopaedics at the University of Maryland School of Medicine. Dr. Banagan specializes in adult and pediatric spine patients and treats cervical thoracic and lumbar spine conditions, as well as spine infections.

View: IRB - Add a Team Member

Add a Team Member

• Select Team Member:
Soojin Yim

2 Research Role:
Technician or Assistant

3 • Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
Q Yes. **No**

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Soojin Yim is a Master's student in the School of Nursing. She will assist with data collection and entry.

View: IRB - Add a Team Member

Add a Team Member

* Select Team Member:
Seeta Kallam

2 Research Role:
Research Team Member

3 * Edit Rights - Should this person be allowed full edit rights to the submission, including : editing the online forms and the ability to execute activities? Note - a person with edit rights will automatically be added to the CC list and will receive all emails regarding this protocol, even if the answer to #4 below is No.
Q Yes. **No**

4 * CC on Email Correspondence - Should this person be copied on all emails sent by the HRPO office to the PI/POC? Study team members with edit rights will automatically receive all emails:
. **Yes** Q No

5 * Does this study team member have a potential conflict of interest, financial or otherwise, related to this research?
Q Yes. **No**

6 * Briefly describe experience conducting research and knowledge of the local study sites, culture, and society:
Assist with IRB and regulatory requirements

UNIVERSITY of MARYLAND
THE FOUNDING CAMPUS

RESEARCH CONSENT FORM

- Shock Trauma Center

Protocol Title: Relieving Acute Pain: A Pilot Study
Study No.: HP-00078742

Principal Investigator:
Luana Colloca MD, PhD

Sponsor:
MPowering the State of Maryland

Sub-Investigator:
Sarah Murthi MD

- This is a research study. Participation is voluntary. Feel free to ask questions at any time.

PURPOSE OF STUDY

- The aim of this study is to determine the usefulness of a new method of providing opioids. This new method should reduce overall opioid intake and decrease physiological or psychological dependence on the opioid. It aims to be equally effective in relieving pain and preventing pain from interfering with daily life.
- Opioids are an important part of managing acute pain. However, they carry a risk of harming patients, particularly if prescribed in larger doses over a longer period of time. **The opioid epidemic is a public health crisis causing 16 deaths per day in the USA.** Most of these deaths are patients who have misused or abused prescription painkillers
- You are being asked to participate in this study because you have physical trauma and your doctors are monitoring your pain relief.
- This study plans to enroll a total of 159 patients from the Shock Trauma Center and evaluate three distinct pain reduction strategies.

PROCEDURES

Phase I

- If you agree to be part of the study, you will be assigned to one of the three therapeutic treatment arms. Each arm will receive standard therapeutic doses of Ketorolac, a type of non-steroid pain reliever. Oxycodone and Dose-extending Placebos will be used as additional means of pain relief. Dose-extending placebos are treatments given to mimic the effect of oxycodone. Giving both medications will allow your body to respond to the dose-extending placebos as if they were oxycodone. You will receive a strong, effective rescue therapy whenever needed.
- Based on which treatment arm you are assigned to, you may receive dose-extending placebos at some point during the hospitalization. Oxycodone and Placebo doses will be alternated. For example, you might receive two doses of oxycodone followed by a dose of placebo. As explained above, this administration of both medications will condition your body to respond to the placebo as if it were oxycodone. The placebo doses will

likely continue to relieve any pain you are feeling from your injury, and if you ever feel your pain is unbearable you can inform the clinician who will provide appropriate care.

- The study will last for three days of your hospitalization..
- While in the study, your pain will be managed by the Acute Pain Management Service, which has expertise in the care of post-operative pain.
- The types of medicine you receive when you go home will not be affected by enrollment in this study or your study group assignment.
- Your rescue pain medication is the treatment you receive if you have severe pain after taking the study medications. It will not be affected by enrollment in this study.
- After you are discharged, you will have one in person visit with a study team member. This visit will be timed with your follow-up with your doctor at about two weeks. If you do not schedule one, you may be contacted by phone or email to do so.

Saliva (~3 minutes)

- During your time in the hospital or after you are discharged, the research team will collect a saliva sample. You will spit 2-3 tablespoons of saliva into a plastic tube to be used for DNA lab tests. These samples will not be used to see if you have any conditions or diseases. No one will be able to identify you from your sample to protect your identity. The samples will be coded. Only, Dr. Luana Colloca, the Principal Investigator, has access to the coded list. Please initial one of the options below:

  _____ **I** consent to giving a saliva sample

  __ __ __ __ __ __ __ I do not consent to giving a saliva sample

Blood (~5 minutes)

- During the time you are in the hospital and at 6 month follow-up point after you are discharged, you will be asked for an optional blood sample. Blood samples will be drawn and banked for future studies analyzing proteomics, microRNA, and cytokine expression. These samples will not be used to see if you have any conditions or diseases. No one will be able to identify you from your sample to protect your identity. The samples will be coded. Only, Dr. Luana Colloca, the Principal Investigator, will have access to the coded list. Please initial one of the options below:

  _____ **I** consent to giving a blood sample

  _____ **I** do not consent to giving a blood sample

Storage

- Your saliva and blood samples will be stored in locked refrigerators and freezers. Your samples will not be used to grow new cells. Any information gained from these samples will not be provided to you. There is no limit for the amount of time we may store your saliva samples. Your responses to the psychological questionnaires will be stored in secure and private online tools that are called REDCap and MetricWire. We may continue to use it for research purposes until request to withdraw from this study in writing or the research study ends. You can ask for the saliva and blood samples to be destroyed at any time. If you decide to withdraw, no further information from these samples will be collected. However, already collected information may be retained.
- When researchers share information with other researchers it assists with conducting more powerful research studies. Researchers share information by putting it into a scientific Database, where it is stored along with information from other studies. Although no genetic analyses will be conducted for this study, analyses may be conducted for future research. Your personal information such as your address or social security number will never be placed into a scientific database. In order to conduct analyses on the information from your sample in the future, your information may be shared with researchers from the University of Maryland, other universities, the government, and drug- or health-related companies. The information from your samples may be shared with those not from the United States. The investigator will abide by the federal privacy rules that are in place to safeguard your privacy and confidentiality. Your name and personally identifiable information will never be shared, except as required by law. The research investigator of this study will work to ensure the protection of your confidentiality and privacy.
  You may choose to not have your saliva sample stored. You can also contact the principal investigator at any time to have it destroyed. Please initial one of the options below:

  _____I consent to indefinite storage of saliva and blood samples for future studies

  _____I do not consent to indefinite storage of saliva and blood samples for future studies

Phase II: Follow Up

- After you are discharged, you will have one mandatory in person visit with a study team member. This visit will be timed with your follow-up with your doctor at about two weeks. If you do not schedule one, you may be contacted by calls, letters, emails, or text messages to do so.
- After the two-week follow-up, you will also be contacted by the research team at one month, three months, and 6 months after discharge. The research team may reach out to you through calls, letters, emails, or text messages. The research team will ask you about your pain, how much your pain interferes with daily life activities, and your use of pain medication. You will also be given the option to come in person to give blood samples, for which you will receive compensation described below.

Psychological/Emotional Questionnaires (~1 hour)

- You will be asked to complete a series of questionnaires that measure personality factors, depression, anxiety, and medical history. The research staff will assist you if you have any questions about these questionnaires. Each questionnaires will take roughly 1-4 minutes on average to complete individually. We will carefully review your scores. If you score positively for being at risk for depression or self-harm, we will inform you of this. We will refer you to see your primary care medical provider if you are concerned about depression. Please initial one of the options below:

  _____I consent to complete a set of surveys

  __ __ __ __ __ __ __ I do not consent to complete a set of surveys

- You will be contacted at two weeks, month one, three, and six after you are discharged. We may ask to come in person, or we may send you the required data collection tools via mail, email, calls and texts. Please initial one of the options below:

  _____I consent to be re-contacted for the follow-up phase

  _____I do not consent to be re-contacted for the follow-up phase

Treatment allocation

- As a result of being in a clinical trial, you will not know which treatment you will receive. At some point during the study, you may receive dose-extending placebos. Dose-extending placebos are treatments given to mimic the effect of oxycodone. Giving both medications will allow your body to respond to the dose-extending placebos as if they were oxycodone. When Phase I of the study is finished, you can contact us if you wish to know which treatment you had received. We will answer any questions that you have.

WHAT ARE MY RESPONSIBILITIES IF I TAKE PART IN THIS RESEARCH?

- Your role in the study is to adhere to the protocol and inform the doctors and research team of any relevant changes in your pain sensation.
- Since this study involves a drug (Oxycodone and Ketorolac), you will not be allowed to enroll in any other investigational drug-related study while participating. You will, however, be allowed to enroll in other observational studies. You will be responsible for contacting the study team if you would like to enroll in any additional studies.

POTENTIAL RISKS/DISCOMFORTS:

- There is a low risk from each of the three pain strategies under investigation.
- There is a risk that treatment with oxycodone could trigger abuse in a manner similar to other opioids. There is a potential for overdose and related side effects (e.g. respiratory depression, head injury, and hypotensive responses). However, in order to minimize this

risk, study staff (e.g. nurses, clinicians) and members of the research team will monitor you throughout hospitalization and during the follow-up phase for symptoms of these potential complications. If an emergency arises because of oxycodone abuse or overdose during the hospitalization, staff clinicians will contact immediately APMS to ensure that the participant will safely monitored. If an emergency arises because of oxycodone abuse or overdose after the hospitalization, patients will be informed to call immediately 911. There is a possibility you could become emotionally distressed or fatigued while completing questionnaires, which are optional. If you feel distressed, have thoughts of suicide, or are in any way concerned for your mental well-being, you can alert your clinician or a member of the research team, and you will be referred to a mental health professional for further care. In order to minimize these risks, you will be offered breaks throughout the study procedure and you can discontinue participation at any time.

- There is a small risk of loss or breach of confidentiality. This means that there is a risk that individuals could gain access to your personal information, like name and age.
- Loss of confidentiality will be minimized by storing data in a secure location, such as a locked office and locked cabinet. Electronic data will be password-protected.
- There is a small risk of breach of privacy. This means that there is a risk of being seen and/or identified during participation in the study by individuals not directly involved in the study.
- There is potential for physical pain. We will treat the pain, but you should expect that you will have some pain.
- There are no other anticipated physical, social, psychological, legal or economic risks.

POTENTIAL BENEFITS

- You may experience fewer side effects related to opioids than with usual care.
- Your participation may lower your risk for dependence and addiction with opioids.
- There is also a potential benefit to the field of pain medicine in that it may help to find much safer way to manage acute pain with fewer unintended consequences (e.g. long-term dangerous use of opioids with life threating events).

ALTERNATIVES TO PARTICIPATION

- This is a treatment study. Your alternative is to not take part. If you choose not to take part, your healthcare at University of Maryland Medical Center will not be affected in anyway.

COSTS TO PARTICIPANTS

- It will not cost you anything to take part in this study.

PAYMENT TO PARTICIPANTS

- For up to two of the blood samples, you will be compensated a total of $50 ($25 per sample) in the form of a check, gift card, or cash that will be given in person,

electronically, over the phone, or mailed to the mailing address you provide. In addition, we will provide you with parking vouchers for each visit.

- The blood samples we provide compensation for are completely optional and will not have any effect on your participation and treatment.

CONFIDENTIALITY AND ACCESS TO RECORDS

- Your privacy will be maintained by the study team.
- We will utilize a password-protected spreadsheet that is only accessible by the PI and co-investigator. Names will not be used. Medical record numbers will be used temporarily while collecting data. Patients will then be assigned an identifier made up of numbers and letters. The data files will be kept on a secured workstation on the premises of the medical center.
- As part of this study we will review your medical records for research purposes. We will look at clinical information such as medical history, treatments, demographics, pain assessment and vitals.
- The study records can be reviewed by the Institutional Review Board.
- Efforts will be made to limit sharing of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete secrecy. Organizations that may inspect and copy your information include the IRB and other representatives of this organization.
- The data from the study may be published. You will not be identified by name. People designated from the institutions where the study is being conducted will be allowed to inspect sections of your medical and research records related to the study. Everyone using study information will work to keep your personal information confidential. Your personal information will not be given out unless required by law.

RIGHT TO WITHDRAW

- Your participation in this study is voluntary. You do not have to take part in this research. You are free to withdraw your consent at any time. Refusal to take part or to stop taking part in the study will involve no penalty or loss of benefits to which you are otherwise entitled. If you decide to stop taking part, if you have questions, concerns, or complaints, or if you need to report a medical injury related to the research, please contact the contact the principle investigator Dr. Luana Colloca (Phone: 410-706-8244) or sub-investigator Dr. Sarah Murthi (Phone:410-328-1205).
- There are no adverse consequences (physical, social, economic, legal, or psychological) of a participant's decision to withdraw from the research.
- You will be told of any significant new findings that develop during the study, which may affect your willingness to participate in the study.

CAN I BE REMOVED FROM THE RESEARCH?

- The person in charge of the research study or the sponsor can remove you from the research study without your approval. Possible reasons for removal include inability to collect data or inability complete the study. The sponsor can also end the research study early. The study doctor would tell you about this, and you would have the chance to ask questions if this were to happen.

UNIVERSITY STATEMENT CONCERNING RESEARCH RISKS

The University of Maryland, Baltimore (UMB) is committed to providing participants in its research the rights due them under State and federal law. You give up none of your legal rights by signing this consent form or by participating in the research project. This research has been reviewed and approved by the Institutional Review Board (IRB). Please call the Institutional Review Board (IRB) if you have questions about your rights as a research subject.

Participating in research may result in an injury, as explained above. If you suffer an injury directly related to your participation in this project, UMB and/or one of its affiliated institutions or health care groups will help you obtain medical treatment for the specific injury and provide referrals to other health care facilities, as appropriate. UMB and/or its affiliated institutions or health care groups will not provide you with financial compensation or reimbursement for the cost of care provided to treat a research-related injury or for other expenses arising from a research-related injury. The institution or group providing medical treatment will charge your insurance carrier, you, or any other party responsible for your treatment costs. If you incur uninsured medical costs, they are your responsibility. The study staff can give you more information about this if you have a study injury.

By signing this Consent Form, you are not giving up any legal rights. If this research project is conducted in a negligent manner and you are injured as a direct result, you may be able to recover the costs of care and other damages from the individuals or organizations responsible for your injury.

If you have questions, concerns, complaints, or believe you have been harmed through participation in this research study as a result of researcher negligence, you can contact members of the IRB or the Human Research Protections Office (HRPO) to ask questions, discuss problems or concerns, obtain information, or offer input about your rights as a research participant. The contact information for the IRB and the HRPO is:

University of Maryland Baltimore
Human Research Protections Office
620 W. Lexington Street, Second Floor
Baltimore, MD 21201
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Signing this consent form indicates that you have read this consent form (or have had it read to you), that your questions have been answered to your satisfaction, and that you voluntarily agree to participate in this research study. You will receive a copy of this signed consent form. If you agree to participate in this study, please sign your name below.

Participant's Signature	Signature of Investigator or Designee Obtaining Consent
Date: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _	Date: _ _ _ _ _ _ _ _ _ _ _ _ _ _ _ _