Effect of Ultra-low Dose Naloxone on Remifentanil-Induced Hyperalgesia

NCT Number: NCT03066739
Document Date: December 1, 2025
Organization: University of California, Irvine – Department of Anesthesiology

Study Protocol and Statistical Analysis Plan

PROTOCOLS

Shima Khanahmadi

#20141345 - Effect of Ultra-low Dose Naloxone on Remifentanil-Induced Hyperalgesia

Protocol Information

Submission Type	Review Type	Status	Time in Current Status
Close Request	**Expedited**	**Closed**	**Since June 3 – 6 months**

Submission Number	Initial Approval Date	Initial Review Type
16	**Apr 08, 2021**	**Expedited**

Feedback

Close Comment

Closed.

Protocol Close Request Form

Protocol Type

Are you requesting to close a IRB, sIRB, or hSCRO protocol?

IRB (UCI is the IRB of Record)

IRB Closing Instructions

- **An IRB protocol may be closed once subject accrual has ended, research interventions and data collection are complete, and analyses of subject identifiable data have concluded.**
- **The official retention period for UCI's IRB records begins on the date a closing report is submitted by the Lead Researcher (LR).**

For more information, visit:

- **Protocol Closure**
- **Lead Researcher's IRB Recordkeeping Responsibilities**

Closure Status

Closing criteria:

- **All subject specimens, records, data have been obtained (i.e., no further collection is required).**
- **No further contact with subjects is necessary (i.e., all interactions or interventions are complete).**
- **Analysis of subject identifiable data, records, and specimens are complete (i.e., use or access to subject identifiable data and review of source documents by study sponsors is no longer necessary).**

Please mark the option that represents the closing status of subject enrollments:

Subject enrollment and research procedures are complete. This study meets the above criteria and can be closed.

Have there been any problems that required prompt reporting

to the UCI IRB?

Yes, the problem(s) was previously reported to the IRB

Have there been any complaints from UCI participants or others that required reporting to the UCI IRB?

No

Provide a brief summary of the project's results (preliminary or final):

Due to low enrollment, the study was closed after enrolling 8 participants out of the planned 105. Although data collection is complete, data analysis has not yet been conducted. We plan to complete the analysis and submit the results to ClinicalTrials.gov by the reporting deadline of December 10, 2026.

Closure Attachments (Optional)

Submit any supporting documents for the closure in the Attachments section below.

Lead Researcher Certification

Upon submission of this final closing application, I hereby certify my intent to close the study and I affirm that all the information contained herein is true and accurate to the best of my knowledge. If additional significant information about the safety or welfare of study participants should become available after study closure, I will forward it to the IRB promptly for review and inclusion in the protocol record.

As Lead Researcher, I affirm the above statement

End of form. Please review responses for accuracy and

End of form. Please review responses for accuracy and completeness.

Project Details

Specify the study title (this title should not exceed more than 100 words):
Effect of Ultra-low Dose Naloxone on Remifentanil-Induced Hyperalgesia

Lead Researcher/Investigator:
Ariana M Nelson

Enter the Lead Unit:

IR-7450 - ANESTHESIOLOGY & PERIOPERATIVE CARE (Lead Unit)

Project Screener

Submit a Human Subject Protocol for UCI Institutional Review Board (IRB) Review

Will this protocol be reviewed under a sIRB process?
No, there is no reliance involved. UCI serves as the IRB of record

Are the research procedures limited to the use/analysis of identifiable private information and/or identifiable biospecimens (no subject contact)?
No

Select the required level of review for this protocol:
Greater than Minimal Risk (Full Committee)

Check all sites where UCI investigator(s) will conduct research activities (e.g., recruitment,

informed consent, and research procedures including accessing identifiable, private information about participants):

UCI Facilities or Sites (e.g. school, hospital or clinics, etc.)

Provide a non-technical summary of the project that can be understood by IRB/hSCRO members with varied research backgrounds, including non-scientists and community members (this summary should not exceed more than 250 words):

Opioids are known to produce excellent intraoperative and postoperative pain relief. However, their effects can be limited by unwanted side effects such as nausea, constipation, itchiness, sedation, and respiratory depression. Additionally, their use perioperatively has been shown to result in the development of tolerance and hyperalgesia. Opioid-induced hyperalgesia (OIH) is a paradoxical increase in pain sensitivity following opioid exposure. OIH has been noted with many different opioids, but the most clinically well-documented hyperalgesic effect is with remifentanil. Studies have attempted to reduce the development of tolerance and hyperalgesia through various agents. Their role in pain management is thought to decrease reported pain, increase the time to the patient's first request for pain medication, and lower the cumulative dose of pain medications over the first 48 hours postoperatively. Recent research by Dr. Catherine Cahill have shown the mechanism for OIH in rats is due to an alteration in opioid receptor signaling and activation and hypertrophy of spinal glial cells (gliosis), and that this response can be attenuated by ultra-low dose opioid antagonists. However, there are no prospective, randomized clinical studies that have evaluated the effects ultra-low dose opioid antagonist naloxone on preventing OIH. The purpose of this study is to evaluate whether using ultra-low dose naloxone, an opioid antagonist, has the potential to block remifentanil-induced hyperalgesia and tolerance following surgery. There are 3 study groups: (1) low dose remifentanil infusion (LO, titrated from 0 to 0.2 mcg for an estimated average of 0.1 micrograms/kg/min), (2) high dose remifentanil infusion combined with placebo (HI, titrated from 0.3 to 0.5 mcg for an estimated average of 0.4 micrograms/kg/min), or (3) high dose remifentanil infusion combined with

ultra-low dose naloxone (HN, titrated from 0.3 to 0.5 mcg for an average of 0.4 micrograms/kg/min remifentanil with 0.004 micrograms/kg/min naloxone). The hypothesis of the study is that occurrence of remifentanil-induced hyperalgesia (low score in mechanical pain threshold) in the HN group will be lower than in the HI group. Adult patients (over 18 years old) undergoing similar surgeries will be selected via routine clinical care. Patients who consent to participate in the study will be administered naloxone or placebo alongside Remifentanil and data will be collected using self-reported and physiological measures.

Instructions

IRB Protocol Instructions

- **For research with a Master Protocol or with a detailed project proposal, specify this in the protocol and an abbreviated protocol will be generated.**
- **Submit all new and/or revised supporting documents in the Protocol Attachments section near the end of the protocol.**
- **The Lead Researcher (LR) is responsible for maintaining all supplemental documentation (as indicated in the form) in the research records. This documentation may be requested by Human Research Protections for quality assurance review.**

For regulatory or institutional guidance:

- **Visit Human Research Protections**
- **Contact the Human Research Protections staff**

For technical issues or questions:

- **Visit the Kuali Research Protocols (KRP) User Guide**
- **Contact Electronic Research Administration (ERA)**

Type of Research

The purpose, specific aims or objectives of the research is:
Biomedical

The research protocol is:
Investigator-Initiated

Does the investigator-initiated study have any industry support?
No

Does this study include a Master Protocol or detailed project proposal?
No

Is this study an extension of a UCI IRB approved study (e.g., resubmission of ongoing exempt research; Open Label Extension) or is it otherwise related to a UCI IRB approved study?
No

Does this research meet the definition of a clinical trial that requires adherence to Clinicaltrials.gov?
Yes

If currently available, provide the CT.gov registration NCT # (**Enter 8-digit sequence of numbers only**):
03066739

Specify the rationale for Clinicaltrials.gov registration:
Applicable Clinical Trial

STOP! All clinical trials must be conducted under the auspices of an Organized Lead Unit (OLU). Please update. Go to Project Details and choose the appropriate OLU for the trial.

Study Funding

Select the funding source(s) (**check all that apply**):

Department or campus funds (includes department support, unrestricted funds, start-up funds, personal funds, campus program awards, etc.)

Scientific/Scholarly Review

Is the research Sponsor-Initiated?

No

Is the research cancer-related?

No

The proposed research qualifies as greater than minimal risk, investigator-initiated biodmedical research. For greater than minimal risk biomedical research that is investigator initiated and has not been peer reviewed, Biostatistics, Epidemiology and Research design (BERD) review is required. The UCI IRB will review the research for scientific merit in conjunction with the expertise of the BERD) unit of the Institute for Clinical and Translational Science (ICTS). The UCI IRB staff will coordinate the review process.

Please click on the following link to arrange a consultation with one of the ICTS BERD Statisticians: ICTS BERD Statisticians - Consultations

Greater than Minimal Risk Non-Cancer, Investigator Initiated Biomedical Research - IRB / BERD Review Required

Data Safety Monitoring Plan

Does this protocol require a DSM plan?

Yes

Provide details of those individuals who will be responsible for the safety oversight of your protocol, including the relevant experience/expertise of each individual (for UCI investigator initiated studies conducted only at UCI, provide the names and titles as well):

The board will be comprised of the Department of Anesthesiology and Perioperative Care Research Council. The council is composed of

researchers, educators, and administration that oversee all aspects of research of the department. One of the duties of the council is to ensure the safety of all research being conducted with the department. The Members are the following: Dr.Scott Engwall, Chair of the Department of Anesthesiology & Perioperative Care; Dr. Cameron Ricks, Associate Clinical Professor and Director of the Medical Education Simulation Center; Dr. Kei Togashi, Associate Clinical Professor; and Dr. Sean Ostlund, Assistant Professor and Director of the Ostlund Research Lab.

Indicate how frequently accumulated protocol data will be reviewed and evaluated for participant safety, protocol conduct and progress, and, when appropriate, efficacy:

The committee meets in-person or via Zoom on a quarterly basis. They also communicate on a regular basis with research updates.

Describe the events that would trigger an unscheduled review. Also include stopping guidelines and un-blinding rules if applicable:

Events such as protocol deviations, adverse events and major changes to the approved study protocol would trigger an unscheduled review.

List who will be *locally* monitoring and collecting information on adverse events and/or unanticipated problems (e.g., UCI Lead Researcher, Research Coordinator, etc.). Include the name, title and experience of the individual(s) and further describe each individual's role in the oversight of subject/patient participating in the protocol:

Aside from the lead researcher, Paulette Mensah, who is a senior CRC and the Clinical Research Supervisor, will be locally monitoring and collecting information on adverse events and/or unanticipated problems.

Describe the plan for annual reporting of the participants' safety, and the protocol's conduct, progress, and efficacy, when appropriate:

The PI will submit a CPA to the IRB for annual reporting of study progress, participants' safety and enrollment status.

Potentially Hazardous Materials

If any of the following hazardous materials are involved in this research please check below:
N/A

Other UCI Committee Reviews

Check all ancillary committees that apply:
N/A

Study Team

Study Team:

- **List only study team members who are engaged in human subjects research below.**
    - **Administrative Contact (AC): Do not add ACs to the study team table. To add ACs, navigate to the Permissions tab on top-right-hand-side of form. All ACs must complete the requisite Human Research Protections CITI Training.**
- **Lead Researcher (LR): LRs must meet requirements specified on the Lead Researcher Eligibility page for study to be approved.**
    - **Select 'Oversight of Research' along with other applicable duties.**
    - **Select 'Full Access'.**
- **Faculty Sponsor (FS): FSs are required when the person serving the LR role is not qualified to serve as LR-- the FS must be eligible to be LR.**
    - **Select 'Oversight of Research' along with other applicable duties.**
    - **Select 'Full Access'.**
- **Co-Researcher (CR): CRs are faculty, staff, students and other academic appointees who the LR considers to be key personnel for conducting the research study. These individuals work closely with the LR to design, conduct, and/or report on the research.**
- **Research Personnel (RP): List RP as required per the Research Personnel Heat Map. For those RP who do not need to be listed on the protocol, they may be tracked by alternative methods, see below.**

- **IMPORTANT! Do NOT list non-UCI researchers below, in the Permissions tab at top or on the Study Team Tracking Log (or equivalent); instead, follow the Single IRB Reliance (sIRB) process.**

- **Collaborative Institutional Training Initiative (CITI) Human Research Protections Training Courses**
  - **Confirm CITI training is complete and current for all study team members.**
  - **Incomplete or expired CITI training will delay IRB approval.**
  - **For more information, visit HRP Training and Education.**

Researcher

Ariana M Nelson

Training

GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Refresher Course
06/04/21 - 06/03/24
Expired

Biomedical Investigators - Refresher Course
06/29/21 - 06/28/26

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

“Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

MD

Degree Other

Position/Title

Associate Professor

Department

IR-7450 - ANESTHESIOLOGY & PERIOPERATIVE CARE (Lead Unit)

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Lead Researcher

Permissions

Full Access

Duties

Oversight of Research
Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information

Describe additional research procedures below:

Data analysis & manuscript writing.

Specify relevant training and experience for the referenced duties/responsibilities:

Dr. Nelson is a board-certified anesthesiologist who specializes in interventional pain management, as well as in acute and chronic pain. Her clinical interests include back, joint, neck and nerve pain. She also is skilled in peripheral nerve and spinal cord stimulation. She is also a core faculty member for the Program in Medical Education for the Latino Community (PRIME-LC), a five-year, combined MD and master's training program for physicians committed to serving under-resourced Latino communities.

Researcher

Yu-Po Lee

Training

GCP for Clinical Investigations of Devices - Basic Course 08/09/22 - (no expiration)	Biomedical Investigators - Basic Course 09/03/20 - 09/02/25 **Expired**

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No

Degree

MD

Degree Other

Position/Title

Professor

Department

IR-7459 - ORTHOPEDIC SURGERY (Lead Unit)

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information
Access/Analyze Identifiable Biospecimens

Describe additional research procedures below:

Data analysis & manuscript writing

Specify relevant training and experience for the referenced duties/responsibilities:

Dr. Lee is a board-certified orthopaedic surgeon who specializes in spine surgery with a focus on adult degenerative conditions. He specializes in minimally invasive spine surgery to treat diseases such as disc herniation, spinal stenosis, scoliosis, tumors and trauma.

Researcher

Navid Alem

Training

GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Basic Course
01/13/15 - 01/12/18
Expired

Biomedical Investigators - Refresher Course
11/12/20 - 11/11/25
Expired

Research and HIPAA Privacy Protections
11/12/20 - 11/11/25
Expired

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Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

MD

Degree Other

Position/Title

Clinical Professor

Department

IR-7450 - ANESTHESIOLOGY & PERIOPERATIVE CARE (Lead Unit)

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information
Access/Analyze Identifiable Biospecimens

Describe additional research procedures below:

Data Analysis & Manuscript Writing

Specify relevant training and experience for the referenced duties/responsibilities:

Dr. Alem is a board-certified UCI Health anesthesiology who has advanced training in pain management and anesthesia. His research interests include perioperative and intraoperative techniques that can help prevent patients from developing chronic pain syndromes post-surgery.

Researcher

Brent Yeung

Training

GCP for Clinical Investigations of Devices - Refresher Course
10/10/20 - 10/10/23
Expired

GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Refresher Course
10/10/20 - 10/10/23
Expired

Biomedical Investigators - Basic Course
08/04/16 - 08/03/21
Expired

Biomedical Investigators - Refresher Course
10/01/21 - 09/30/26

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

MD

Degree Other

Position/Title

Clinical Professor

Department

IR-7450 - ANESTHESIOLOGY & PERIOPERATIVE CARE (Lead Unit)

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information
Access/Analyze Identifiable Biospecimens

Describe additional research procedures below:
Data Analysis & Manuscript Writing

Specify relevant training and experience for the referenced duties/responsibilities:
Dr. Yeung is a UCI Health anesthesiologist who specializes in the management and treatment of pain. His clinical interests include interventional procedures for chronic pain management and the use of cannabis for pain.

Researcher

Shalini S Shah

Training

GCP for Clinical Investigations of Devices - Refresher Course
09/02/17 - 09/02/20
Expired

GCP for Clinical Trials with Investigational Drugs and Biologics (ICH Focus) - Refresher Course
09/02/17 - 09/02/20
Expired

GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Basic Course
08/20/20 - 08/20/23
Expired

Biomedical Investigators - Refresher Course
03/14/19 - 03/12/24
Expired

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

MD

Degree Other

Position/Title

Vice Chair of Pain Management

Department

IR-7450 - ANESTHESIOLOGY & PERIOPERATIVE CARE (Lead Unit)

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information
Access/Analyze Identifiable Biospecimens

Describe additional research procedures below:

Data Analysis & Manuscript Writing

Specify relevant training and experience for the referenced duties/responsibilities:

Dr. Shah is a board-certified and fellowship-trained UCI Health physician who specializes in the management and treatment of adult and pediatric pain. She has extensive training in chronic pain disorders in children, specifically in oncologic pain, head and neck pain, abdominal pain, scoliosis and spasticity disorders.

Researcher

Rakhi Dayal

Training

Biomedical Investigators - Refresher Course 07/16/21 - 07/15/26	**Research and HIPAA Privacy Protections** 07/16/21 - 07/15/26

To promote the objectivity of the research, all researchers are required to disclose their related disclosable financial interests, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

MD

Degree Other

Position/Title

Clinical Professor

Department

IR-7450 - ANESTHESIOLOGY & PERIOPERATIVE CARE (Lead Unit)

Affiliation
UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information
Access/Analyze Identifiable Biospecimens

Describe additional research procedures below:
Data Analysis & Manuscript Writing

Specify relevant training and experience for the referenced duties/responsibilities:
Dr. Dayal is a board-certified UCI Health anesthesiologist who specializes in pain medicine. Her clinical interests include pain medicine, spine pain, neuropathic pain, cancer pain, complex regional pain syndrome and headaches.

Researcher

Joseph Brian Rinehart

Training

GCP for Clinical Investigations of Devices - Refresher Course
08/10/18 - 08/10/21
Expired

GCP for Clinical Trials with Investigational Drugs and Medical Devices (U.S. FDA focus) - Refresher Course
06/08/20 - 06/08/23
Expired

Biomedical Investigators - Basic Course
08/10/18 - 08/09/23
Expired

Biomedical Investigators - Refresher Course
08/10/23 - (no expiration)

Research and HIPAA Privacy Protections
08/10/23 - (no expiration)

To promote the objectivity of the research, all researchers are required to disclose their related disclosable financial interests, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

MD

Degree Other

Position/Title

Vice Chair of Research

Department

IR-7450 - ANESTHESIOLOGY & PERIOPERATIVE CARE (Lead Unit)

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information
Access/Analyze Identifiable Biospecimens

Describe additional research procedures below:

Data analysis, biostatistics, and manuscript writing.

Specify relevant training and experience for the referenced duties/responsibilities:

Dr. Rinehart is a board-certified UCI Health anesthesiologist and vice chair of research for the department of anesthesiology. He leads the department in peer-reviewed journal submissions, has grant funded, industry, and federally funded studies. He also serves on multiple IRB review committees.

Researcher

Nitin Narain Bhatia

Training

GCP for Clinical Trials with Investigational Drugs and Biologics (ICH Focus) - Basic Course
04/24/21 - 04/23/24
Expired

Biomedical Investigators - Basic Course
02/18/17 - 02/17/22
Expired

Biomedical Investigators - Refresher Course
03/03/22 - 03/02/27

To promote the objectivity of the research, all researchers are required to disclose their **related disclosable financial interests**, per the IRB COI Policy. If you have any questions about the COI process in general, contact the COI team.

Each member of the study team for this protocol must be asked the following question to comply:

"Do you, your spouse/registered domestic partner, and dependent children have any disclosable financial interests* (i) that would reasonably appear to be affected by this research study; or (ii) in entities whose financial interests would reasonably appear to be affected by this research study?"

No

Degree

MD

Degree Other

Position/Title

Chair

Department

IR-7459 - ORTHOPEDIC SURGERY (Lead Unit)

Affiliation

UCI Faculty

Specify other UCI affiliation:

Researcher Role

Co-Researcher

Permissions

Full Access

Duties

Research Procedures
Screen/Recruit Subjects
Finalize Informed Consent
Access/Analyze Identifiable Information

Describe additional research procedures below:

Data analysis and manuscript writing

Specify relevant training and experience for the referenced duties/responsibilities:
Dr. Bhatia is the chair of the orthopedic surgery department as well as the UCI's Chief of spine surgery. Dr. Bhatia has over 20 years of research experience and is active in multiple research projects including federally funded spinal cord injury research. He has also been nominated for the prestigious Russell Hibbs research award by the Scoliosis Research Society. Dr. Bhatia is the only academic surgeon in Orange County to be selected for the exclusive Cervical Spine Research Society which has granted admission to less than 20 physicians in the state of California.

Are RP tracked outside the approved protocol, in accordance with the RP Heat Map?
Yes, RP are tracked on a Study Team Log or other comparable log

Supplemental Documents

Does this study include supplemental documents?
No

Background & Purpose of the Research

Describe the purpose, specific aims or objectives and specify the hypotheses or research questions to be studied:
Opioid antagonists at ultra-low doses have been used with opioid agonists to prevent or limit opioid tolerance. Remifentanil, a rapid onset/offset opioid that is often used as an anesthesia adjunct intraoperatively, has been associated with the development of hyperalgesia and opioid tolerance postoperatively. [1-4] Opioid-induced hyperalgesia (OIH) induced by remifentanil intraoperatively may be a factor contributing to an increase in postoperative pain as well as difficulty in controlling such pain. The

purpose of this study will be to evaluate whether an ultra-low dose of naloxone, an opioid antagonist, could block remifentanil-induced hyperalgesia and tolerance following surgery.

Provide the scientific or scholarly rationale for the research and describe the relevant background information and the specific gaps in current knowledge that this study intends to address:

This research will help elucidate the degree of OIH after surgeries involving remifentanil and determine if a new technique can be employed to decrease remifentanil-induced OIH. By mitigating OIH, patients should have a decrease in postoperative pain and an increase in patient satisfaction at UCI and other hospitals where such a technique is employed.

Provide relevant preliminary data (animal and/or human):

Attempts have been made with various agents to reduce the development of tolerance and hyperalgesia following remifentanil. Postoperative hyperalgesia and its prevention has been studied with ketamine[10, 11, 15-36] , Magnesium [12, 34, 37], Gabapentin[16], Clonidine[19, 38], Lornoxicam [18], Dextromethorphan [39], Paracetamol [40, 41], Morphine [42], Dexmedetomidine [43], Adenosine [44, 45], COX inhibitors [46, 47], Amantadine [48], Nitrous oxide [49], Fentanyl [50], Pregabalin [51], Buprenorphine [52], Midazolam [53], Dexamethasone [36]. Relevant to our current hypothesis is the report that concomitant administration of ultra-low dose naloxone [13] and naltrexone [54] with remifentanil prevented OIH. However, there are no studies on reducing the adverse effects of remifentanil with ultra-low dose naloxone in human subjects. While the traditional role of opiate antagonists have been in cases of opioid overmedication, recent evidence is emerging regarding their use in pain management. Gan et al. 1997 used an ultra-low dose naloxone infusion (0.00025 mg/kg/h or 0.001 mg/kg/h) in postoperative patients receiving IV morphine via a patient-controlled analgesia (PCA) device. Good pain relief was experienced in all groups, however consumption of PCA morphine was significantly reduced in patients that received the lowest infusion of naloxone and opioid-induced side effects (nausea, vomiting, pruritus) were reduced by naloxone at both dose.

Describe the primary outcome variable(s), secondary outcome variables, and predictors and/or comparison groups as appropriate for the stated study objectives/specific aims:

The primary outcome variable of the study will be to determine the occurrence of OIH in high dose remifentanil treatment group compared to a low dose Remifentanil group and a high dose Remifentanil dose with ultralow dose naloxone. OIH will be determined by assessing evoked pain thresholds. Secondary outcomes will include verbal assessment of overall pain levels via validated standard pain questionnaires and post-operative opioid consumption to determine presence of opioid analgesic tolerance. The predicted outcome is that ultralow dose naloxone will attenuate the development of remifentanil-induced OIH. Primary outcome: Mechanical pain threshold, determined by von Frey filaments, around the incision site at 24 and 48h post-surgery. Primary hypothesis: The mechanical pain thresholds at 48h in the HN group is higher than in the HI group. Secondary

hypotheses: 1. The mechanical pain thresholds at 48h in the LO group is higher than in the HI group. 2. The mechanical pain thresholds at 24h in both HN and LO group is higher than in the HI group. Secondary outcomes: - Opioid consumption required to control pain over the first 24 and 48h post-operatively. - Cold pressure test for pain threshold and pain tolerance - VAS pain scores measured prior to surgery and at 4, 8 and 12h after extubation and again at 24h and 48h post-operatively. - McGill short form questionnaire to be filled out prior to surgery and at 48h post-operatively - Brief Pain Inventory questionnaire to be filled out prior to surgery and at 48h post-operatively Other data collected will include a baseline history questionnaire (for demographics, age, sex, weight, income level) and the Public Health Questionnaire (PHQ-9) to measure depression as mood greatly influences pain perception. The PHQ-9 will be used to determine whether groups have been stratified appropriately.

List up to ten relevant references/articles to support the rationale for the research:

1. Bekhit, M.H., Opioid-induced hyperalgesia and tolerance. Am J Ther, 2010. 17(5): p. 498- 510. 2. Lin, S.L., et al., Co-administration of ultra-low dose naloxone attenuates morphine tolerance in rats via attenuation of

NMDA receptor neurotransmission and suppression of neuroinflammation in the spinal cords. Pharmacol Biochem Behav, 2010. 96(2): p. 236-45. 3. King, T., et al., Is paradoxical pain induced by sustained opioid exposure an underlying mechanism of opioid antinociceptive tolerance? Neurosignals, 2005. 14(4): p. 194-205. 4. Vinik, H.R. and I. Kissin, Rapid development of tolerance to analgesia during remifentanil infusion in humans. Anesth Analg, 1998. 86(6): p. 1307-11. 5. Guignard, B., et al., Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology, 2000. 93(2): p. 409-17. 6. Hansen, E.G., et al., Intra-operative remifentanil might influence pain levels in the immediate post-operative period after major abdominal surgery. Acta Anaesthesiol Scand, 2005. 49(10): p. 1464-70. 7. Ma, J.F., et al., [Cohort study of remifentanil-induced hyperalgesia in postoperative patients]. Zhonghua Yi Xue Za Zhi, 2011. 91(14): p. 977-9. 8. Cahill, C.M., S.V. Holdridge, and A. Morinville, Trafficking of delta-opioid receptors and other

G-protein-coupled receptors: implications for pain and analgesia. Trends Pharmacol Sci, 2007. 28(1): p. 23-31. 9. Holdridge, S.V., et al., Behavioural and morphological evidence for the involvement of glial cell activation in delta opioid receptor function: implications for the development of opioid tolerance. Mol Pain, 2007. 3: p. 7. 10. Yalcin, N., et al., A comparison of ketamine and paracetamol for preventing remifentanil induced hyperalgesia in patients undergoing total abdominal hysterectomy. Int J Med Sci, 2012. 9(5): p. 327-33.

Subject Population(s) (Individuals/Records/Biospecimens)

Check all subject populations/data sources that apply to the research:

Adults Competent to Provide Informed Consent

Maximum and Expected Number of Persons/Records/Biospecimens to be Enrolled

1. **Click "Add Line" button above Enrollment Table to add a Category/Group**
    a. **To change visibility of columns, click "Columns" button above Enrollment Table and select which Column rows to view.**

2. **Specify the maximum and expected numbers of individual-level information and/or biospecimens to be accessed/analyzed within each Category/Group**

Category/Group

Adults

Age Range

18 and over

Maximum Number of Subjects, Subjects to be Consented or Reviewed/Collected

115

Number Expected to Complete the Study or Needed to Address the Research Question

105

Will this study only take place at UCI and does not involve other sites?

Yes

Eligibility Factors (Inclusion/Exclusion Criteria)

1. Click "Add Line" button above Eligibility Factors Table to add a inclusion/exclusion criteria
    a. To change visibility of columns, click "Columns" button above Eligibility Factors Chart and select which Column rows to view.
2. Identify the factors for limited eligibility and provide a scientific rationale. Include additional rows for factors, as needed.

Category/Group Eligibility

Adult subjects over 18 years old undergoing posterior spinal fusion surgery will be recruited to participate in this study. There is no upper age limit for inclusion.

Inclusion Criteria

1. Subjects who provide written informed consent. 2. Age 18 years old or

1. Subjects who provide written informed consent. 2. Age 18 years old or older (no upper age limit for inclusion) 3. Gender: male or female. 4. Surgery: Posterior spinal fusions

Exclusion Criteria

1. Allergy to opiates 2. Chronic pain other than the primary indication for surgery 3. Psychiatric illness 4. History of substance abuse problem including alcohol &/or cannabis 5. BMI > 35 6. Subjects under 18 years of age. 7. Subject without the capacity to give written informed consent. 8. Female subjects who are pregnant

Is eligibility based on age, gender, pregnancy/childbearing potential, social/ethnic group, or language spoken (e.g., English Speakers only)?

Yes

Limited Eligibility Factors (Special Populations)

1. Click "Add Line" button above Limited Eligibility Factors Table to add a special population
    a. To change visibility of columns, click "Columns" button above Limited Eligibility Factors Table and select which Column rows to view.
2. Identify the special populations and provide a scientific rationale. Add additional rows, as needed.

Eligibility Limited to the Following Factors
Age

Specify the rationale for this group:
Subjects under the age of 18

Eligibility Limited to the Following Factors
Pregnancy/Childbearing Potential

Specify the rationale for this group:
pregnant female subjects will be excluded from this study due to concerns regarding consent/assent, possible unknown risks and the fact

concerns regarding consent/assent, possible unknown risks and the fact that these patient groups are not typically among those patients recruited for spinal fusion surgery at our institution.

Pre-Screening and Determining Eligibility without Informed Consent

Will Identifiable information be obtained for the purpose of screening, recruiting, or determining eligibility of prospective subjects?

Yes

The 2018 Common Rule allows for Pre-Screening activities (i.e., determining if potential subjects may be eligible to participate in research) performed without the written informed consent of the prospective subject or legally authorized representative (LAR). This means that the IRB does not need to grant a waiver of informed consent.

Provide a complete list of the data points, variables, and/or information that will be collected during Pre-Screening (i.e. data abstraction form):

Check here if the list will be submitted as a separate document [i.e. case report form (CRF; eCRF) or data abstraction form]

Check all the Pre-Screening activities that apply:

Study team will screen medical records to determine subject eligibility

Select Medical Record Source (check all that apply):

Study team will access their own UCI patients' records and abstract data directly from those records

Will the study team screen stored identifiable biospecimens?

No

Will the study team contact subjects for eligibility or recruitment purposes?

Yes

REQUIRED! Submit the pre-screening script in the Attachments Section.

UCI IRB requires the pre-screening script meets the Recruitment Requirements.

Recruitment Methods

Will this study involve **NO** direct contact with participants (i.e., passive observation of public behavior)?

No

Indicate all methods that will be used to recruit subjects for this study:

Recruitment Method

Clinicaltrials.gov

Specify Where Posted

Type of Space

Confirm that applicable consent documents will include reference to the use of SONA

Confirm that the ClinicalTrials.gov statement is in all applicable consent documents

Confirm that the study from the Center for Clinical Research (CCR) Find a Trial web page is registered on ClinicalTrials.gov

Specify how contact information will be obtained:

Specify how these individuals granted permission and enter HS#:

Examples:

- Individuals who are economically or educationally disadvantaged
- Individuals that have impaired decision-making capacity

- Individuals that have impaired decision making capacity
- Physician's own inpatients and/or outpatients
- Students (undergraduate, graduate, and medical students)
- Employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.)

IRB requires that:

1. Subjects will be approached with an emphasis that participation is voluntary; and
2. Subject will be informed in a caring manner that no matter their decision, it will NOT affect:
    a. Their relationship with UCI
    b. How their doctor cares for them as a patient or their care at UC Health in general and/or
    c. How their instructor grades their participation in the course; and
3. A statement attesting the information above in item b will be included in applicable recruitment and/or consent documents.

Confirm that colleagues may provide a copy of the consent and other UCI IRB approved materials but do not obtain subjects' consent for the research or act as representatives of the investigators

Confirm that:

1. The recruitment letter to be signed by the treating physician will be submitted in the Attachments Section
2. Colleagues do not obtain subjects' consent for the research or act as representatives of the investigators

Specify 'Other' recruitment methods:

Specify the precautions taken to avoid compromised objectivity:

Recruitment Method

Other recruitment methods

Specify Where Posted

Type of Space

Confirm that applicable consent documents will include reference to the use of SONA

Confirm that the ClinicalTrials.gov statement is in all applicable consent documents

Confirm that the study from the Center for Clinical Research (CCR) Find a Trial web page is registered on ClinicalTrials.gov

Specify how contact information will be obtained:

Specify how these individuals granted permission and enter HS#:

Examples:

- Individuals who are economically or educationally disadvantaged
- Individuals that have impaired decision-making capacity
- Physician's own inpatients and/or outpatients
- Students (undergraduate, graduate, and medical students)
- Employees of UCI (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.)

IRB requires that:

1. Subjects will be approached with an emphasis that participation is voluntary; and
2. Subject will be informed in a caring manner that no matter their decision, it will NOT affect:
    a. Their relationship with UCI
    b. How their doctor cares for them as a patient or their care at UC Health in general and/or
    c. How their instructor grades their participation in the course; and
3. A statement attesting the information above in item b will be included in applicable recruitment and/or consent documents.

Confirm that colleagues may provide a copy of the consent and other UCI IRB approved materials but do not obtain subjects' consent for the research or act as representatives of the investigators

Confirm that:

1. The recruitment letter to be signed by the treating physician will be submitted in the Attachments Section

2. Colleagues do not obtain subjects' consent for the research or act as representatives of the investigators

Specify 'Other' recruitment methods:

The coordinator will prescreen patients and introduce the study in person. The surgical team will also assist with identifying potential eligible subjects. When possible, the coordinator will then attend the pre-surgical appointment to fully consent the patient. Occasionally, pre-surgical appointments are telemedicine appointments where the coordinator may not be available and introduce the study over the phone and email the consent form if patients wish to review the consent form. The coordinator will obtain full consent on the day of surgery. Please note that even if the patient has previously consented, the coordinator will confirm their continued consent on the day of surgery.

Specify the precautions taken to avoid compromised objectivity:

Informed Consent Process

Does this study involve the creation, use, or disclosure of Protected Health Information (PHI)?

Yes

Methods of Health Insurance Portability and Accountability Act (HIPAA) Authorization

Identify the HIPAA authorization process (Check all that apply):

Partial waiver of HIPAA authorization for screening/recruitment purposes only. Signed authorization obtained prior to further access to PHI

Methods of Informed Consent

Identify the consent or assent process as applicable for each participant population (check all that apply):

Paper-based signed informed consent/assent

Paper-based Signed Informed Consent

Indicate the paper-based signed informed consent/assent (check all that apply):

Signed Informed Consent

REQUIRED! Submit the Adult Consent Form, Child Assent Form and/or Parental Permission Form in the Attachments Section.

Circumstances of Consent

Indicate the location where the consent process will take place (**check all that apply**):

Over the phone
Private room

Specify how the research team will assure that subjects, their parents, or their legally authorized representative (LAR) have sufficient time to consider whether to participate in the research:

Subjects or their LAR will be allowed to take home the unsigned consent form for review prior to signing it

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This study does NOT include Non-English Speaking Participants. Scientific justification/rationale is required in the Eligibility Criteria Section for Subject Populations.

Waiver of HIPAA Authorization

You requested a Partial Waiver of HIPAA Authorization

When a partial waiver is requested, the Lead Researcher is requesting the HIPAA research authorization be waived for a portion of the study, such as a waiver for subject identification or recruitment purposes.

Please specify for what purpose the partial waiver is requested:

Partial waiver of HIPAA authorization requested for screening/recruitment purposes only. Signed authorization obtained prior to further access to PHI.

Justification for a Waiver of HIPAA Authorization

Does the use or disclosure of personal health information involve more than minimal risk?

No

Would the granting of the waiver adversely affect privacy rights and welfare of the individuals whose records will be used or disclosed?

No

Explain (justify) the answer:

The use of personal health information (PHI) in this study involves minimal risk, as it is limited to screening and recruitment purposes. Identifiable information will only be accessed by the research team and will be de-identified before further use. Privacy protections, including the destruction or anonymization of personal identifiers, will be implemented once the data is no longer needed. Therefore, granting the waiver will not adversely affect the privacy rights or welfare of the individuals, as appropriate safeguards will be in place.

Could the research practicably be conducted without a waiver of HIPAA authorization?
No

Explain the answer:
The research cannot be practically conducted without a waiver of HIPAA authorization because accessing personal health information (PHI) is essential for identifying and recruiting eligible participants. The study relies on reviewing PHI, such as patient names and contact information, to determine whether individuals meet the eligibility criteria for the study. Without this information, the research team would not be able to approach potential subjects or effectively recruit participants. Therefore, a waiver is critical to ensure the study can proceed as planned, particularly during the initial phase of recruitment.

Could the research practicably be conducted without access to, use or disclosure of the personal identifiers listed in the PHI question?
No

Explain the answer:
The research relies on personal identifiers, such as patient names and

contact information, to identify and screen potential participants who meet the study's eligibility criteria. These identifiers are essential for reaching out to eligible individuals and recruiting them into the study. Without access to this information, the research team would be unable to efficiently select participants, making it impractical to conduct the study. Therefore, access to personal identifiers is necessary for the study to proceed as planned.

Are the privacy risks reasonable relative to the anticipated benefits of the research?
Yes

Describe the risk/benefit analysis performed to explain the answer above:
The privacy risks in this study are considered minimal because personal health information (PHI) will only be used for screening and recruitment, and strict safeguards will be in place. Only the research team will have

access to identifiable information, and any PHI will be de-identified or destroyed once no longer needed. The study will not involve sensitive data that could significantly impact participants' privacy if disclosed. The anticipated benefits, such as advancing scientific understanding and potentially improving patient care, justify the minimal risks to privacy. Given the protections in place, the risk of improper disclosure is low, and the potential benefits to the participants and the broader medical community make the risks reasonable.

Describe the plan to protect the personal identifiers from improper use and disclosure (i.e., describe data security methods):

Personal identifiers will be protected through a combination of physical, technical, and administrative safeguards. Data will be stored in secure, password-protected electronic systems with restricted access, ensuring only authorized research team members can view or use the information. Physical records containing personal identifiers will be kept in locked, secure locations. Any data transmitted electronically will be encrypted to prevent unauthorized access. Additionally, personal identifiers will be removed or de-identified as soon as they are no longer necessary for the study. These measures will ensure that personal identifiers are

safeguarded from improper use and disclosure throughout the research process.

Describe the plan to destroy the personal identifiers at the earliest opportunity, or provide a health or research justification for retaining the identifiers:

Personal identifiers will be destroyed or anonymized as soon as they are no longer necessary for the study. If a participant decides not to continue in the study, any identifying information will be promptly removed from the data and securely destroyed. For participants who consent to continue, personal identifiers will be retained only as long as needed for study procedures, such as tracking surgery dates or patient outcomes. Once the data collection phase is complete or identifiers are no longer required for analysis, all personal identifiers will be securely destroyed or de-identified. This approach ensures that personal information is retained only for the

minimum time necessary to achieve the research objectives and is disposed of in accordance with HIPAA guidelines.

Describe how potential subjects will be identified:
Potential subjects will be identified by reviewing the surgical schedule for patients undergoing posterior spinal fusion surgery at UCI Medical Center. The research team will cross-reference the schedule with the study's inclusion and exclusion criteria. Eligible patients must be 18 years or older, undergoing posterior spinal fusion surgery, and willing to sign the consent and HIPAA forms. Patients who meet the inclusion criteria and do not have any of the exclusion criteria (such as allergies to opiates, chronic pain unrelated to the surgery, psychiatric illness, substance abuse history, BMI over 35, pregnancy, or inability to provide informed consent) will be approached during their preoperative consultation. The research team will explain the study, address any questions, and obtain written consent from those who are interested in participating.

Research Procedures

Check all boxes that apply to the research:
Analysis of Existing Identifiable or Coded Data, Specimens, Records, Charts, and Datasets
Clinical Investigation involving on Investigational Drug or Biological Product (including the on or off label use of an FDA approved drug)
Surveys/Questionnaires/Interviews/Oral Histories

Clinical Phase of Study

Indicate the phase(s) of the study, if applicable:
N/A

Will deception or incomplete disclosure be involved in the research?

Will deception or incomplete disclosure be involved in the research?

No

Study Design

Include an explanation of the study design (e.g., randomized placebo-controlled, cross-over, cross-sectional, longitudinal, etc.) and, if appropriate, describe stratification/ randomization/blinding scheme:

This is a prospective, randomized, double-blinded study. The surgical team will screen for and identify potential patients undergoing posterior spinal fusion surgery using the UCI Medical Center surgical schedule. If the subject is deemed ineligible based on the inclusion and exclusion criteria after reviewing their medical history, his/her record will be discarded. If a subject is deemed eligible, information regarding their next visit prior to their surgery will be relayed to the research team. A member of the study team will speak with patients during their preoperative consultation in a private room and review the details of the study with them. The patient may choose to have their relatives in the room during this consent process. The patient will be enrolled in the study only after one of the investigators reviews the consent form with the patient, ensuring the patient

understands the study, answers all questions, and written informed consent is obtained. Subjects will be informed that their participation is voluntary and will not impact their patient care. The subject's privacy will be protected. Only the information relevant to study will be obtained. Occasionally, patients are approved for surgery via a telehealth visit or during an otherwise standard clinical visit. The study team will review the surgical schedule and screen for potential patients. As these surgeries are often scheduled 3-4 weeks after they are cleared for surgery, the study team will call to introduce the study and email the consent documents at minimum 48 hours prior to surgery but typically the patient will have those 3-4 weeks to review the consent document and ask questions. The study team will obtain full written informed consent on the day of surgery, in their private room within the pre-op area. The details of the study will be re-reviewed to ensure the patient fully understands. The subject's information will be kept confidential; if data is written on paper, the paper will be either

kept in the research folder, which is kept in the hospital or shredded when it is not needed. If subject data is kept on a computer, the data will only be stored on hospital computers. Subject information will not be shared beyond the IRB approved research team as listed in Section 2 of this protocol narrative. Once consented, the subjects will be randomized by the study team into one of the three study groups: (1) low dose remifentanil, (2) high dose remifentanil combined with ultra-low dose naloxone or (3) high dose remifentanil combined with placebo. The randomization list will be prepared before the study starts using a random number table generator and the study coordinator will obtain the information for each subject after consent. Personnel directly involved in subject care will be blinded as to naloxone or placebo administration. The pain assessors (second blinded group) will be blinded. Surgical procedures will not be altered and subjects will still receive standard subject care. Following consent, a packet of questionnaires (includes baseline questionnaire, Public Health Questionnaire (PHQ-9), VAS, McGill Short Form, Brief Pain Inventory) will be provided to subjects by study staff. All subjects will be required to complete a baseline questionnaire to obtain subject demographics prior to surgery. Opioid-induced hyperalgesia OIH will be measured by determining experimentally induced pain thresholds and clinically meaningful outcomes of pain via validated pain questionnaires and post-operative opioid consumption. These outcomes have previously been used and validated to assess remifentanil-induced hyperalgesia; pain thresholds to cold and static mechanical stimulation are the most common pain modalities altered by remifentanil infusion. Experimentally induced pain will be performed in pre-op by quantitative sensory testing via von Frey filaments applied in ascending order to the dorsal surface of the subject's non-dominant hand and 5cm from the incision site. Subjects will be instructed to indicate when stimulus produces a painful sensation as well as when the stimulus becomes unpleasant. In addition to determination of mechanical pain thresholds, cold pain threshold and tolerance will be determined. Subjects will be instructed to immerse their hand in a bucket of ice water and indicate when they first experience a painful sensation (threshold) and to remove their hand from the ice water when they can no

longer tolerate the pain (tolerance). The time for pain tolerance and threshold will be recorded. Validated pain questionnaires will be administered to subjects prior to surgery and 48h after cessation of remifentanil infusion. These questionnaires will include the McGill Short Form pain questionnaire and the Brief Pain Inventory (short form). The McGill questionnaire provides an assessment of pain quality and descriptors, whereas the Brief Pain Inventory assesses both pain intensity and pain unpleasantness (the emotional component of pain is considered to be a better metric of subject satisfaction and quality of life). A research assistant blind to treatment will administer both experimentally induced pain assessments and pain questionnaires before surgery and after the surgery. As part of the study, subject demographics (age, gender, surgery type) and hemodynamics (heart rate, blood pressure, etc) that are obtained as standard operating room procedure will be accessed. Measures will be taken to protect subject privacy by only allowing IRB approved research personnel to access records as needed. The table below indicates the timing and outcome measures that will be determined. Pre-op Consult Presurgery Post-surgery 4h 8h 12h 24h 48h PHQ-9 x x VAS x x x x x x McGill Pain Questionnaire x x UCI IRB Approved: 08-26-2021 | MOD# 29836 | HS# 2014-1345 Baseline History x Brief Pain Inventory x x Von Frey Testing x x x Cold Pressor Test x x x Opioid Consumption x x x x x x B. Statistical Considerations 1. Statistical Analysis Plan: Describe the statistical method(s) for the stated specific aims and hypotheses described in Section 1. Note: Required for scientific review. 2. Explain how the overall target sample size was determined (Provide power / sample size justification for the study). If a statistical analysis plan is not appropriate for your study design, please describe a plan for assessing your study results. Statistical Analysis Plan For the primary outcome, the 2-sample t-test will be applied to compare the difference in mechanical pain thresholds at 24 and 48h between HN and HI group, and between LO and HI group. For the secondary outcomes, the continuous variables will also be analyzed using 2-sample t-test to identify the difference between HN and HI group, and between LO and HI group. The mean level and corresponding 95% confidence interval (CI) will be obtained for each study

group. The categorical outcomes will be analyzed T Pre-op Consult Subjects screened for inclusion/exclusi on criteria Study introduction during surgical consult visit Subjects provided with consent form and study information sheet 2 Lab Visit Initiate subject consent Hamilton Rating Scale, VAS, McGill Pain Questionnaire, Brief Pain Inventory Finalize Consent 3 Pre-Surgery Subject is greeted in preop area Von Frey Testing, Cold Pressor Test, Opioid Consumption Pre-surgery medication: standard-of-care 4 Surgery Group 1 (LO): Induction dose per anesthesiologist (no ketamine); Maintenance: 0.1mcg Remifentanil Group 2 (HI): Induction dose per anesthesiologist (no ketamine): Maintenance: 0.4mg Remifentanil + Saline Group 3 (HN): Induction dose per anesthesiologist (no ketamine); Maintenance: 0.4mg Remifentanil + 0.004mcg/kg/min Nalaoxone 5 Post-Surgery Post-surgery medication: standard-of-care @4H, @8H, @ 12H: VAS, Opioid Consumption @24H: VAS, Von Frey Testing, Cold Pressor Test, Opioid Consumption @48H: Hamilton, VAS, McGill, Brief Pain Inventory, Von Frey, Cold Pressor, Opioid Consumption UCI IRB

Provide precise definitions of the study endpoints and criteria for evaluation; if the primary outcomes are derived from several measurements (i.e., composite variables) or if endpoints are based composite variables, then describe precisely how the composite variables are derived:

see above

Statistical Considerations

Is a statistical analysis plan appropriate for this qualitative study design?

Yes

Describe the statistical methods for the stated specific aims and hypotheses. Your analysis plans should match the stated study specific aims and hypotheses:

For the primary outcome, the 2-sample t-test will be applied to compare the difference in mechanical pain thresholds at 24 and 48h between HN and HI group, and between LO and HI group. For the secondary outcomes, the continuous variables will also be analyzed using 2-sample t-test to identify the difference between HN and HI group, and between LO and HI group. The mean level and corresponding 95% confidence interval (CI) will be

obtained for each study group. The categorical outcomes will be analyzedusing the chi-square test and the odds ratio (compare to HI group) and corresponding 95% CI will also be obtained.

Describe the statistical method(s) that will be used to analyze the primary outcome(s) or endpoints:

see above

If appropriate describe secondary or post hoc analyses of primary outcome(s) or other exploratory analysis and if necessary, provide a breakdown of the methods used per outcome or endpoint:

Secondary outcomes: - Opioid consumption required to control pain over the first 24 and 48h post-operatively. - Cold pressure test for pain threshold and pain tolerance - VAS pain scores measured prior to surgery and at 4, 8 and 12h after extubation and again at 24h and 48h post-operatively. - McGill short form questionnaire to be filled out prior to surgery and at 48h post-operatively - Brief Pain Inventory questionnaire to be filled out prior to surgery and at 48h post-operatively

Sample Size Determination: **Explain how the overall target sample size was determined** (e.g., power analysis; precision estimation), providing justification of the effect size for the primary outcome based on preliminary data, current knowledge/literature and/or cost consideration; if appropriate, provide sample size justification for secondary outcomes. Power analysis should (at least) match the primary outcome/endpoint:

The sample size determination and power analysis was based on a 2-sided 2-sample t-test with a significant level of 0.05. The following table shows the minimum effect size to detect for various sample size and power. We propose to recruit a total of 105 subjects (35 per group) and expect to have 96 subjects (account for 8% attrition) for final analysis. The proposed sample size will provide the study 80% power to detect an effect size of 0.71 and 90% power to detect an effect size of 0.82.

Research Procedures

Provide a detailed chronological description of the clinical or treatment plan:

see above

Specify the total duration of a subject's participation in the study and clearly outline the duration of participation for each study visit and sub-study, as applicable:

see above

List data collection tools (e.g., measures, questionnaires, observational tool) below by clicking the 'Add Line' button. Include additional rows for study instruments, as needed:

The 'Columns' button allows you to display or hide columns in the Study Instrument List.

Name of Tool:

Cold Pressor Test

Is the data collection tool standardized or validated?

Yes

Please provide data collection tool citation:

https://www.jpain.org/article/S1526-5900(04)00746-1/fulltext

Name of Tool:

PHQ 9

Is the data collection tool standardized or validated?

Yes

Please provide data collection tool citation:

https://www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/patient-health

Name of Tool:

Pain Scores (VAS, SF McGill, Brief Pain Inventory)

Is the data collection tool standardized or validated?

Is the data collection tool standardized or validated?
Yes

Please provide data collection tool citation:
https://pubmed.ncbi.nlm.nih.gov/22588748/

Name of Tool:

Von Frey

Is the data collection tool standardized or validated?
Yes

Please provide data collection tool citation:
https://www.sciencedirect.com/topics/medicine-and-dentistry/von-frey-hair

Name of Tool:

Hamilton Rating Scale

Is the data collection tool standardized or validated?
Yes

Please provide data collection tool citation:
https://academic.oup.com/occmed/article/65/7/601/1733495

Will this study require clinical items/ services from UC Irvine Health?
No

Does the research involve the use of identifiable private information?
Yes

Use of Identifiable Private Information as Part of the Main Study

Indicate the types/sources of identifiable private information (Check all that apply):
UCI Health Medical Records

Indicate whether the information was originally collected for research purposes:
Not originally collected for research

Explain how the information were originally collected (e.g., clinical care):
Standard-of-Care

Provide a complete list of the data points, variables, and/or information that will be collected (i.e. data abstraction form):
Check here if the list will be submitted as a separate document [i.e. case report form (CRF; eCRF) or data abstraction form]

Specify the time-frame of the data to be accessed (e.g. January 2002 to 2024):
N/A; prospective study looking at recent medical record information

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This study will use medical records, indicate the source:
Study team will access their own UCI patients' records and abstract data directly from those records

Does the research involve the use of identifiable biospecimens?
No

Sharing Results with Subjects

Will Individual results be shared with subjects?
No

Will overall study results will be shared with subjects?
The overall study results will be listed on Clinicaltrials.gov

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Investigational Drug or Biologic

Investigational Drug or Biologic

Trade Name/Biologic:

Narcan

Generic Name:

Naloxone

Drug Manufacturer:

Hospira, Inc

Identify the regulatory status of the agent(s) to be used in this study:

The agent is approved by the FDA and will be used according to the FDA label

REQUIRED! Submit a copy of the FDA determination letter in the Attachments Section.

Provide a copy of the FDA determination letter if available. Acknowledgement Evidence of the IND number on the Master Protocol serves as a protocol – specific reference and is acceptable evidence of the IND. Note: Researchers must provide documentation of a valid IND number prior to IRB approval. If the study is not externally funded or if a UCI investigator holds the IND, a copy of the FDA IND Application is required prior to IRB review. Upload copies in the Attachments Section.

IND Number:

IND Filing Date:

See example on how to select a date.

No date entered

Holder of the IND:

Enter IND Lead Researcher:

Other IND Holder (e.g., NIH, GOG, CTEP):

Does the IND allow billing of subjects?

Is the investigation intended to support FDA approval of a new indication or a significant change in the labeling of the agent?

Is the investigation intended to support a significant change in the advertising of the lawfully marketed agent?

Does the investigation involve a route of administration or dosage level or use in a patient population or other factor (e.g., formulation) that *significantly increases the risks to subjects* (or decreases the acceptability of the risks) associated with the use of the agent?

Is the investigation intended to promote or commercialize the investigational new agent (i.e., make promotional claims of safety or effectiveness)?

Does the study require any change in the approved formulation, dosage, or route of administration of the agent?

For Cancer therapies only: Does the investigation involve a new use, dosage, schedule, route of administration, or new combination of marketed cancer products in a population with cancer where based on the scientific literature and generally known clinical experience, there is no significant increase in the risk associated with the use of the agent(s)?

An IND application must be filed with the FDA.

For Cancer therapies only, an IND may NOT be required.

You may reference the section title and page number(s) of the Investigator Brochure or Package Insert rather than pasting or transcribing the relevant information in the following agent information questions.

REQUIRED! Submit the Investigator Brochure or Package Insert in the Attachments Section

Specify the product description:

Treats opioid emergencies or narcotic medicine overdoses; used for the complete or partial reversal of opioid depression, including respiratory depression.

Specify the clinical pharmacology:

Naloxone prevents or reverses the effects of opioids including respiratory depression, sedation, and hypotension. It can also reverse the psychotomimetic and dysphoric effects of agonist-antagonists such as pentazocine. Naloxone functions as a pure opioid antagonist and therefore has no effect without opioids in the system.

Specify the indications for use:

Naloxone is indicated for the complete or partial reversal of opioid depression, including respiratory depression, induced by natural and synthetic opioids, including propoxyphene, methadone, and certain mixed agonist-antagonist analgesics: nalbuphine, pentazocine, butorphanol, and cyclazocine. Naloxone hydrochloride is also indicated for the diagnosis of suspected or known acute opioid overdosage.

Specify the dosage and guidelines for administration (Optional):

Best administered intravenously with an initial dose of 0.4 mg to 2 mg with overdose suspicion. If no response is observed, the dose may be repeated every 2-3 minute intervals, but no more than 10 mg should be administered. Doses are recommended in 0.4-0.8 mg increments via IV. Intramuscular or subcutaneous administration may be necessary if IV is unavailable.

Specify the dosage and administration in this investigation (if different from approved):
N/A

Specify the toxicity and known side effects:
Postoperative use can lead to hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. An excessive dose may lead to a reversal of analgesia and agitation. Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events.

Specify the precautions and contraindications:
Naloxone is contraindicted in patients who are hypersensitive to naloxone. Use can lead to withdrawal from a dependency on opioids and a reversal of dependency. Abrupt postoperative reversal of opioid depression may result in nausea, vomiting, sweating, tremulousness, tachycardia, increased blood pressure, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest which may result in death. Excessive doses of naloxone in postoperative patients may result in significant reversal of analgesia and may cause agitation.

Describe how the investigational agent will be prepared, controlled and who will be responsible for management of the agent:
UCI Health IDS Pharmacy

IMPORTANT! **All investigational product (IP) utilized at UCI Health must be under the control of UCI Health Investigational Drug Services (IDS) Pharmacy. This includes storage**

control of UCI Health Investigational Drug Services (IDS) Pharmacy. This includes storage, control, and distribution of IP.

REQUIRED! Submit the IDS pharmacy waiver in the Attachments Section.

Describe your plan to ensure that the investigational agent is used only in accordance with the UCI IRB approved protocol:

Describe who will access to the agent and how access will be controlled to secure the drug/biologic:

Specify how records for control of the agent will be recorded:

REQUIRED! Submit Sponsor Drug/Biologic Log in the Attachments Section

Specify why no log will be used:

Specify whether investigational agent is prepared or manufactured in UCI research labs:

Identify the lab:

Trade Name/Biologic:

Ultiva

Generic Name:

Remifentanil

Drug Manufacturer:

Hospira, Inc.

Identify the regulatory status of the **agent(s) to be used in this study:**

The agent is approved by the FDA and will be used according to the FDA

label

REQUIRED! Submit a copy of the FDA determination letter in the Attachments Section.

Provide a copy of the FDA determination letter if available. Acknowledgement Evidence of the IND number on the Master Protocol serves as a protocol – specific reference and is acceptable evidence of the IND. Note: Researchers must provide documentation of a valid IND number prior to IRB approval. If the study is not externally funded or if a UCI investigator holds the IND, a copy of the FDA IND Application is required prior to IRB review. Upload copies in the Attachments Section.

IND Number:

IND Filing Date:

See example on how to select a date.

No date entered

Holder of the IND:

Enter IND Lead Researcher:

Other IND Holder (e.g., NIH, GOG, CTEP):

Does the IND allow billing of subjects?

Is the investigation intended to support FDA approval of a new indication or a significant change in the labeling of the agent?

Is the investigation intended to support a significant change in the advertising of the lawfully marketed agent?

Does the investigation involve a route of administration or dosage level or use in a patient population or other factor (e.g., formulation) that *significantly increases the risks to subjects* (or decreases the acceptability of the risks) associated with the use of the agent?

Is the investigation intended to promote or commercialize the investigational new agent (i.e., make promotional claims of safety or effectiveness)?

Does the study require any change in the approved formulation, dosage, or route of administration of the agent?

For Cancer therapies only: Does the investigation involve a new use, dosage, schedule, route of administration, or new combination of marketed cancer products in a population with cancer where based on the scientific literature and generally known clinical experience, there is no significant increase in the risk associated with the use of the agent(s)?

An IND application must be filed with the FDA.

For Cancer therapies only, an IND may NOT be required.

You may reference the section title and page number(s) of the Investigator Brochure or Package Insert rather than pasting or transcribing the relevant information in the following agent information questions.

REQUIRED! Submit the Investigator Brochure or Package Insert in the Attachments Section

Specify the product description:

Ultiva (remifentanil hydrochloride) is a sterile, nonpyrogenic, preservative-free, white to off-white lyophilized powder for intravenous (IV) administration after reconstitution and dilution. Remifentanil is a potent ultra short-acting synthetic opioid analgesic drug used for surgical anesthesia.

Specify the clinical pharmacology:

Remifentanil is a μ-opioid agonist with rapid onset and peak effect, and short duration of action. The μ-opioid activity of remifentanil is antagonized by opioid antagonists such as naloxone. Unlike other opioids, remifentanil is rapidly metabolized by hydrolysis of the propanoic acid-methyl ester linkage by nonspecific blood and tissue esterases. Remifentanil is not a substrate for plasma cholinesterase (pseudocholinesterase) and, therefore, patients with atypical

cholinesterase are expected to have a normal duration of action.

Specify the indications for use:

Remifentanil is indicated for IV administration as an analgesic agent for use during the induction and maintenance of general anesthesia for inpatient and outpatient procedures; for continuation as an analgesic into the immediate postoperative period in adult patients under the direct supervision of an anesthesia practitioner in a postoperative anesthesia care unit or intensive care setting; as an analgesic component of monitored anesthesia care in adult patients.

Specify the dosage and guidelines for administration (Optional):

Remifentanil is not recommended as the sole agent in general anesthesia because loss of consciousness cannot be assured and because of a high incidence of apnea, muscle rigidity, and tachycardia. Remifentanil is synergistic with other anesthetics; therefore, clinicians may need to reduce doses of thiopental, propofol, isoflurane, and midazolam by up to 75% with the coadministration of remifentanil. The administration of remifentanil must be individualized based on the patient's response.

Specify the dosage and administration in this investigation (if different from approved):

N/A

Specify the toxicity and known side effects:

Remifentanil produces adverse events that are characteristic of μ-opioids, such as respiratory depression, apnea, tachycardia, bradycardia,

hypotension, hypertension, and skeletal muscle (including chest wall) rigidity. Due to the presence of glycine in the formulation, remifentanil is contraindicated for epidural or intrathecal administration. Remifentanil is also contraindicated in patients with known hypersensitivity to fentanyl analogs.

Specify the **precautions and contraindications:**

Vital signs and oxygenation must be continually monitored during the administration of ULTIVA. Bradycardia has been reported with remifentanil and is responsive to ephedrine or anticholinergic drugs, such as atropine and glycopyrrolate. Hypotension has been reported with remifentanil and is responsive to decreases in the administration of remifentanil or to IV fluids or catecholamine (ephedrine, epinephrine, norepinephrine, etc.) administration. Intraoperative awareness has been reported in patients under 55 years of age when remifentanil has been administered with propofol infusion rates of ≤75 mcg/kg/min.

Describe how the investigational agent will be prepared, controlled and who will be responsible for management of the agent:

UCI Health IDS Pharmacy

IMPORTANT! **All investigational product (IP) utilized at UCI Health must be under the control of UCI Health Investigational Drug Services (IDS) Pharmacy. This includes storage, control, and distribution of IP.**

REQUIRED! **Submit the IDS pharmacy waiver in the Attachments Section.**

Describe your plan to ensure that the investigational agent is used only in accordance with the UCI IRB approved protocol:

Describe who will access to the agent and how access will be controlled to secure the drug/biologic:

Specify how records for control of the agent will be recorded:

REQUIRED! **Submit Sponsor Drug/Biologic Log in the Attachments Section**

Specify why no log will be used:

Specify whether investigational agent is prepared or manufactured in UCI research labs:

Identify the lab:

Risk Assessment

Risks and Discomforts

1. Describe and assess any reasonably foreseeable risks and discomforts associated with each procedure for each subject population — physical, psychological, social, legal or other:

2. If this study will involve the collection of identifiable private information, even temporarily, for which the disclosure of the data outside of the research could reasonably place the subjects at risk, include the risk of a potential breach of confidentiality:

With the exception of naloxone, the drug being studied, the medications and their dosages that the
patients are being administered are within the standard of care for an anesthesiologist caring for these
surgical patients.

Discuss what steps have been taken and/or will be taken to prevent and minimize any risks/potential discomforts to subjects:

Given that the study drug (naloxone) is an opioid (pain medication) antagonist, there is a theoretical risk that the analgesic effects of the intraoperative opioids are blocked. If this is the case, anesthesia will be maintained by modifying the dose of anesthetic so that no patient is subject to waking during the surgery. However, the dose of naloxone selected for the study is over 10,000 fold lower than the concentration

used UCI IRB Approved: 08-26-2021 | MOD# 29836 | HS# 2014-1345 to block the analgesic effects of the pain medications. Therefore the probability of such a risk is extremely low. Rare but serious High doses of naloxone, that are used to block the analgesic effects of pain medications or reverse respiratory depression in the event of an overdose, is associated with hypotension, hypertension, ventricular tachycardia and fibrillation, dyspnea, pulmonary edema, and cardiac arrest. An excessive dose may lead to a reversal of analgesia and agitation. Abrupt reversal of opioid depression may result in nausea, vomiting, sweating, tachycardia, increased blood pressure, tremulousness, seizures, ventricular tachycardia and fibrillation, pulmonary edema, and cardiac arrest. Death, coma, and encephalopathy have been reported as sequelae of these events. Since the dose of naloxone is over 10,000 fold lower in the present study, it is not expected that any of these side effects will occur. During this study there is a 33% chance that the patient will receive a placebo. Since placebo is introduced to the study to control for the effects of ultralow dose naloxone, there is no difference between placebo and standard of care for the operation the patient is undergoing. Thus, there will be no additional risk beyond the inherent risks of the operation posed to this group. The cold pressor test will be used to measure the pain threshold (when one feels pain) and pain tolerance (point when it becomes too painful to tolerate any

more). A clinical study published in Journal of Pediatric Psychology in 2010 reported that research ethic board approval is required by that both parents and children reported the test to be an acceptable method and adverse events were rare and transient. This test is also often used to assess cardiovascular function. A rare but adverse event associated with this test is constriction of blood vessels (less blood flow) in patients with atherosclerosis, where in healthy people it causes dilation of blood vessels (more blood flow). Another rare event associated with this test is the occurrence of seizures in patients with epilepsy. Although rare, there is the possibility that patients may have an allergic reaction to the study medication. There are no additional risks beyond the risks associated with the surgery. Breach of confidentiality: this is a very rare but possible risk. To

minimize this, all patients enrolled in this study will be given a unique identifier that only the study team members at UCIMC will have access to. Randomization: Patients will be assigned to a study group by chance (like a coin flip) rather than by a medical decision made by the researchers. The treatment subjects receive may prove to be less effective or to have more side effects than the other study group(s), or than standard treatments available for the patient's condition.

Certificate of Confidentiality

Is the research partially or wholly funded by NIH (including NIH Institutes and Centers), or does the research involve identifiable sensitive information that require CoC protections?
No

Potential Benefits

Is there the prospect of a direct benefit anticipated for subjects?
No

Specify the expected potential societal/scientific benefit(s) of this study:
This research will help elucidate the degree of opioid induced hyperalgesia after surgeries involving remifentanil and determine if a new technique can be employed to decrease remifentanil-induced OIH. The potential benefits to society include improved pain control, patient satisfaction, and decreased financial burden to society.

Alternatives to Participation

Describe the alternatives to participation in the study available to prospective subjects. Include routine (standard of care) options as well as other experimental options, as applicable (check all that apply):
No alternatives exist. The only alternative to study participation is not to participate in the study

Participant Compensation

Will subjects be compensated?
No

Will subjects be reimbursed for out-of-pocket expenses?
No

Participant Costs

Will subjects or their insurers be charged for study procedures?
No

Confidentiality of Research Data

Information and/or Biospecimens Storage

Indicate how information and/or biospecimens (including signed consent forms) will be stored (check all that apply):
Information will be maintained electronically. Information will be password protected and maintained in an encrypted format

Encrypted Format

Specify where the information will be maintained electronically:
Coded data; code key is kept separate from data in secure location

Will subject/patient identifiers be collected or retained?

No

Research Information and/or Biospecimens Retention

Indicate how long research information/biospecimens will be retained:

In accordance with UCOP policy, information/biospecimens will be retained for 10 years after the end of the calendar year in which the research is completed, unless otherwise specified in the award agreement

Will research information and/or biospecimens be shared?

No

Attachments

If required documentation is not provided, the submission is incomplete and your Application will be returned to you. Be sure to upload each document as required. If changes are needed, go back to the sub-section to revise your selections.

Maximum file size is 30MB

All UCI templates are available on the Human Research Protections Applications & Forms page or Human Stem Cell Research Applications & Forms page.

To access approval documents where UCI will rely on another IRB, including commercial IRBs, visit their respective online portals. Frequently used commercial IRB portals include:

- WIRB Copernicus Group's WCG IRB Connexus
- Advarra's CIRBI
- SMART Online Reliance System (ORS)

Attachment

2014-1345 Packet insert - Naloxone Hydrochloride (for reference)_normal_222590.pdf

Attachment Type

Package Insert

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

2014-1345 Packet insert - Remifentanil (for reference)_normal_222591.pdf

Attachment Type

Package Insert

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

2014-1345 PHQ9 Survey_normal_259429.pdf

Attachment Type

Data Collection Tool/Instrument

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

uci-hippa-document-spanish_April2023.pdf

Attachment Type

HIPAA Research Authorization Form

File Comments

Re-Translation Required to update study team & CT.gov language per Amendment Approved 11-17-22

File Name

Status (IRB/hSCRO Use Only)

Inactive

Attachment

20141345 HIPAA Authorization Form 09-22-23.docx

Attachment Type

HIPAA Research Authorization Form

HIPAA Research Authorization Form

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

Remi-Naloxone Subject Packet 08.24.21.pdf

Attachment Type

Case Report Form (CRF, eCRF)

File Comments

File Name

Status (IRB/hSCRO Use Only)

Approved

Attachment

HS2014-1345 Remi Naloxone Study Script 2023_02_03.docx

Attachment Type

Pre-Screening Script

Pre Screening Script

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

Spring 2025 DSMB and Certificate_merged.pdf

Attachment Type

Data Safety Monitoring Plan Documentation

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

Recruitment Placeholder.docx

Attachment Type

Recruitment Material

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

20141345 Consent Form 02-07-25.docx

Attachment Type

Consent Form

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

20141345 Consent and HIPAA Form 02-07-25.pdf

Attachment Type

Consent Form

File Comments

File Name

Status (IRB/hSCRO Use Only)

Attachment

20141345 Renew Amend Approval 02-07-25.pdf

Attachment Type

File Comments

File Name

Status (IRB/hSCRO Use Only)

Lead Researcher Certification

Investigator's Assurance

As Lead Researcher, I have ultimate responsibility for the performance of this study, the protection of the rights and welfare of the human subjects, and strict adherence by all co-investigators and research personnel to all Institutional Review Board (IRB) requirements, federal regulations, and state statutes for research involving human subjects.

I hereby assure the following:

1. The information provided in this application is accurate to the best of my knowledge.
2. The information provided in this application has been discussed and shared with my Department Chair. Any requests for changes based on this discussion are included in this application upon submission or will be initiated by the research team either during the IRB review process or via an amendment.
3. All named individuals on this project have read and understand the procedures outlined in the protocol and their role on the study.
4. All named individuals on this project have completed the required Educational research tutorials and have been made aware of the "Common Rule" (45 CFR Part 46), applicable Food and Drug Administration (FDA) regulations (21 CFR Parts 50, 56, 312 and 812), have read the Belmont Report, and UCI's Federalwide Assurance (FWA) that are available on the Human Research Protections Program (HRP) website.
5. All experiments and procedures involving human subjects will be performed under my supervision or that of another qualified professional listed on this protocol.
6. I understand that, if the study described in this IRB application is supported by a federal award or used as a basis for a proposal for funding, it is my responsibility to ensure that the description of human subjects activities in the proposal/award is identical in principle to that contained in this application. I will submit modifications and/or changes to the IRB as necessary to assure the proposal/award and application are identical in principle.

I and all co-investigators and research personnel agree to comply with all applicable requirements for the protection of human subjects in research including, but not limited to, the following:

1. Obtaining the legally effective informed consent of all human subjects or their legally authorized representatives (unless waived) and using only the currently approved, stamped consent form (if applicable).
2. Per federal regulations, once a human research study has received IRB approval, any subsequent changes to the study must be reviewed and approved by the IRB prior to implementation except when necessary to avoid an immediate, apparent hazard to a subject. See Reporting of Unanticipated Problems.
3. Reporting any unanticipated problems involving risk to subjects or others, including protocol violations per UCI IRB policy. In addition, HIPAA privacy violations must be PROMPTLY disclosed to the UCI Privacy Officer. There are time requirements for reporting these breaches of confidentiality, which, if not met, may result in monetary damages to the researcher and the institution.
4. Responding appropriately to subjects' complaints or requests for information about the study; and reporting to the IRB any subject complaints that are not resolvable by the study team.
5. Promptly providing the IRB with any information requested relative to the project.
6. Assuring the appropriate administration and control of investigational test articles (i.e.

6. Assuring the appropriate administration and control of investigational test articles (i.e., investigational drugs, biologics or devices) by a qualified investigator or other appropriate individual or entity (e.g., UCI Health pharmacy), and assuring use and maintenance of an Investigational Drug/Biologic Accountability Log or Device Accountability Log.
7. Registering applicable clinical trials with clinicaltrials.gov. For more information about this topic, visit the ClinicalTrials.gov web page or the HRP webpage. The consequences of not meeting the registration and reporting requirements include monetary damages to the researcher and the institution.
8. Obtaining continuing review prior to study expiration (I understand if I fail to apply for continuing review, approval for the study will automatically expire, and all human research activities must cease until IRB approval is obtained).
9. Promptly and completely complying with an IRB decision to suspend or terminate its approval for some or all research activities.
10. Submitting to a routine review of human subject research records. The Compliance & Privacy Office at UCI Health performs ongoing routine reviews of open biomedical research protocols, in an effort to ensure in part that human subject research activities are conducted in accordance with regulations, laws and institutional policies regarding the protection of human subjects. In addition, the HRP unit of the Office of Research has developed the Education Quality and Improvement Program (EQUIP). Through EQUIP, HRP staff conduct periodic quality improvement monitoring and educational outreach.
11. For clinical trials initially approved by the IRB on or after January 21, 2019, posting one (1) IRB-approved clinical trial consent form at a publicly available federal website. The consent form must be posted after recruitment closes, and no later than 60 days after the last study visit. For additional guidance, refer to the OHRP FAQs on Informed Consent.
12. Filing a final report with UCI HRP at the conclusion of this project.

As the Lead Researcher, I assure all of the above

Financial Disclosure

Investigators' Disclosure of Financial Interest

In order to inform research subjects of circumstances that may affect their decision to participate in this study, all researchers are required to disclose their financial interests with outside institutions.

The Lead Researcher of the protocol must ask the following question of all study team members:

“Do you, your spouse/registered domestic partner, and dependent children together have any

disclosable financial interests (i) that would reasonably appear to be affected by the research; or (ii) in entities whose financial interests would reasonably appear to be affected by the research?"

A member of the study team who answers in the affirmative will be contacted by the Conflict of Interest Oversight Committee (COIOC) to obtain additional information regarding their specific financial interest(s).

IMPORTANT! If there has been a change in the financial disclosures of the LR or the study team, please also request a 'Change in Financial Interests'.

As Lead Researcher, I certify that the disclosures for all study team members are accurate

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End of form. Please review responses for accuracy and completeness.

Please ignore the Admin Details Section below. This section is for IRB/hSCRO use only.

Administrative Details Form

Project Status

Committee:
IRB A

Project Status:
Approved

Date of Project Determination:
June 6, 2025

Amendment Status:
Approved

Date of Amendment Determination:
February 7, 2025

Date of ERA Transcription:
September 24, 2021

Pre-2018 Common Rule:
No

Date of Transition to 2018 Common Rule:
February 9, 2024