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THE STATE UNIVERSITY
OF NEW JERSEY

INTERVENTIONAL
RESEARCH PROTOCOL TEMPLATE

(HRP-503a)

STUDY INFORMATION

- **Title of Project:**
  OARS Protocol Pilot- Multi-site
- **Principal Investigator Name**
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- **Protocol Version and Date:**
  Vr.0.4.06.28.2021

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1.0 Research Design

1.1 Purpose/Specific Aims

The purpose of this study is to test protocols being developed for the conduct of a large sale multi-site clinical trial which will compare opioids to non-opioids for managing post-surgical impacted 3rd molar extraction pain.

A double-blind randomized clinical trial is being designed. Subjects will be randomly assigned to either the OPIOID or NON-OPIOID group. Analgesic agents for both the OPIOID and NON-OPIOID group are commonly used in practice today. The OPIOID analgesic (hydrocodone 5mg/acetaminophen 300mg) is available in a combination tablet and is the most commonly prescribed opioid analgesic in dentistry. The NON-OPIOID analgesic (ibuprofen 400 mg and acetaminophen 500mg) is not available as a combination tablet in the US at that dosage, however components are available separately in the dosages which will be used. All analgesics are FDA approved and are being used according to label.

A. Objectives

The objectives of this study are to:

1. Test refined OARS study instruments. These instruments include:
    a. Eligibility form
    b. Enrollment form
    c. Pre-surgical questionnaire
    d. Post-surgical questionnaire
    e. eDiary
2. Test REDCap for:
    a. Texting subjects eDiary entry invitations via Twillo
3. Test Actigraph for:
    a. Capturing activity and sleep activity data
4. Test SMRxT bottle for:
    a. Capturing date/time that pill removal from the SMRxT bottle
    b. Texting investigator messages based upon changes in the number of pills in the SMRxT bottle
5. Test the steps for querying the Prescription Database Monitoring Program (PDMP) database.
6. Test whether female patients are amenable to take a pregnancy test to determine eligibility.

B. Hypotheses / Research Question(s)

The following research questions will be answered:

1. Are patients able to answer the proposed questions on the pre-surgical and post-surgical questionnaire?
2. Are patients able to consistently make the eDiary entries via their smart phones?
3. Is REDCap easy to use?
4. Are patients willing to wear the Actigraph for 72 hours and can data be easily downloaded?
5. Is data provided by SMRxT reliable and can Nomi accurately send text messages to study investigators?
6. Are patients willing to consistently take 3 capsules per dose?
7. Do patients comply with instructions to take one capsule from Bottle #1 and 2 capsules from Bottle #2?
8. Are female patients willing to take a pregnancy test to determine eligibility to participate?

1.2 Research Significance

Patients and their clinicians select analgesics to prevent and/or manage post-surgical and acute pain.[3] Many young, vulnerable, opioid-naive, patients undergoing 3rd molar extraction, and adults experiencing a dental emergency or undergoing osseous dental surgery, are exposed to unnecessary opioids.[3,4] These exposures create unnecessary dangers[5-10] and result in unused tablets that may be abused.[11-14] Completed studies are limited as they compare the analgesic against a placebo, frequently are single dose studies or follow patients for just several hours.[15-17] None

of those studies demonstrate non-inferiority; are pragmatic (prescribe the analgesics as used in practice); follow a patient through the entire pain episode; determine tablets remaining in the patient's household; and compare the patient's propensity for obtaining future opioid prescriptions. This pilot will test methodology for a pragmatic clinical trial which could demonstrate that a combination of ibuprofen and acetaminophen is at least as good as the most commonly prescribed opioid by dentists in managing post-surgical pain.

1.3 Research Design and Methods

This pilot study consist of two phases intended to test procedures and instruments that will be used in a large scale, multi-site clinical study. The research design and methods will be identical for subjects enrolled in each of the phases.

- Phase 1: Enrolling 24 subjects (12 male and 12 female) at Rutgers School of Dental Medicine Oral Surgery Clinic
- Phase 2: Enrolling 8 (4 male and 4 female) subjects at each of the additional clinical sites
    - University of Rochester
    - University of Maryland
    - University of Illinois
    - University of Michigan

Phase 2 will begin any time after the first 10 participants in Phase 1 (at RSDM) have completed Visit 2.

Subjects, who have presented to the Dental Clinic to have at least one impacted lower 3rd molar extracted, will be followed at surgery then for 9 (-/+5) days post-surgery in this pilot study. As this is a pragmatic clinical trial, subjects are able to determine when and how much of the study analgesic to use. Subject compliance is based upon completion of the eDiary morning and evening entries and at the post-operative visit.
Subjects will complete a questionnaire prior to surgery related to their pre-operative pain.

Immediately following surgery, subjects will be given a study material package which contains the following items:

- Pain Medication in SMRxT bottles: Two combination analgesics will be used and subjects will be randomly assigned to either the OPIOID (Hydrocodone 5 mg/acetaminophen 300 mg) or NON-OPIOID group (ibuprofen 400 mg/acetaminophen 500mg). Study analgesics will be formulated from powder by the compounding pharmacy and provided in 2 different size/color capsules.

Capsule Number	OPIOID Content PROTOCOL Z	NON-OPIOID Content PROTOCOL A	Quantity for a Dose	Total Dispensed	Capsule Size	Color
1	Hydrocodone 5mg / Acetaminophen 300 mg	Ibuprofen 400 mg	1	20	AA	Brown
2	Placebo	Acetaminophen 500 mg	1	20	00	White

* All analgesics are FDA approved and are being used according to label.

Each study package will contain 20 doses. Subjects will be asked to take the first dose before leaving the office as long as they are accompanied. If they are not accompanied, subjects will be asked to take their first dose when they get home. The remaining study analgesic will be self-administered. Pain medication will be contained in 2 SMRxT bottles, electronic bottles which enable the tracking of capsule removal at any given time.

- Actigraph- sleep/ activity monitor worn like a watch that tracks and transmits daily activity data

In addition to managing their post-operative pain as needed, subjects will be asked to actively participate over the post-operative period (time between surgery visit and post-operative visit). Subjects will be asked to complete a pain eDiary twice a day during the post-operative period and wear an Actigraph activity/sleep monitor continuously for the first 72 hours of the post-operative period.

- eDiary:

  - Subjects will receive automatic reminders to complete a survey which is linked to their file in REDCap
  - Using their smart phones, subjects will self-report pain levels, sleep activity, and medications used.
  - Frequency: once in the morning and once in the evening during each day of the post-operative period
- Actigraph- electronically captures activity and sleep data
  - Data will be downloaded when the Actigraph is returned

Subjects will return for the post-operative visit, during which they will complete a PostOp Subject Questionnaire and a Pilot Participation Questionnaire. At this visit, subjects will be required to return the Actigraph and 2 SMRxT medication bottles containing all unused study medication. The Clinical Research Coordinator will count, record in REDCap, and collect/store all unused medication in the double locked drug cabinet. All unused study medication will be collected by to Rutgers School of Dental Medicine (External sites will ship unused study product to Rutgers) and destroyed in accordance with policies set forth by Rutgers Environmental Health Services at the conclusion of the study.

A follow-up PDMP query taking place 30 days +/- 7 days after completing Visit 1 if permitted by state law. If the subject filled an additional opioid prescription within that month, subject will be offered addiction counseling. Contact will be initiated by phone, however, if phone contact is unsuccessful, subject will be emailed the counseling information.

A. Research Procedures

The follow is the order of occurrence:

Order	Research Procedure	When	Research Protocol	Where	By Whom
1	Informed consent obtained	Visit 0	Yes	Dental Clinic	Clinical Site Research Coordinator/ Clinical Co-Investigator
2	Eligibility determination	Visit 0	Yes	Dental Clinic	Clinical Site Research Coordinator/ Clinical Co-Investigator
3	Urine Pregnancy Test	Visit 1	Yes	Dental Clinic	Clinical Site Research Coordinator/ Clinical Co-Investigator
4	Protocol Training and SMS Test	Visit 1	Yes	Dental Clinic	Clinical Site Research Coordinator/ Clinical Co-Investigator
5	Pre-Op questionnaire administered	Visit 1	Yes	Dental Clinic	Clinical Site Research Coordinator/ Clinical Co-Investigator
6	Treatment or surgery performed	Visit 1	Standard of Care	Dental Clinic	Clinical Co-Investigator
7	Surgical Care Report completed	Visit 1	Yes	Dental Clinic	Clinical Site Research Coordinator/ Clinical Co-Investigator
8	Loading Dose taken before leaving office	Visit 1	Yes	Dental Clinic	Subject
9	Analgesics taken and eDiary completed	Days 1-10	Yes	Subject's Home	Subject
10	Post-operative Examination	Visit 2 (Day 10 +/- 5 days after Visit 1)	Standard or Care	Dental Clinic	Clinical Co-Investigator
11	Post-Operative Care Report completed	Visit 2	Yes	Dental Clinic	Clinical Site Research Coordinator/ Clinical Co-Investigator

12	Post-Op questionnaire administered	Visit 2	Yes	Dental Clinic	Clinical Site Research Coordinator/ Clinical Co-Investigator
13	Unused analgesia tablets collected	Visit 2	Yes	Dental Clinic	Clinical Site Research Coordinator/ Clinical Co-Investigator
14	PDMP Query (if permitted by state law)	30 days +/- 7 days after Visit 1	Care offered to participants	Dental Clinic	Clinical Site Research Coordinator/ Clinical Co-Investigator

B. Data Points

Data elements to be collected include:

When	Data Points Collected
Eligibility/Consent Visit - Visit 0	• Name • Date of birth • Positive substance abuse history • Presence of any chronic pain problem • Previous adverse reactions to analgesics • PDMP history (previous opioid Rx's) • Significant medical history preventing eligibility • Self-reported Pregnancy (if female)
Treatment Visit (including Surgery) - Visit 1	**Gender & Pregnancy** • Gender/gender identify • Pregnancy Test Results (if female) **Pre-Operative Questionnaire** • Race/Ethnicity • Education Achieved • Sleep ability • Swelling • Smoking • Height/Weight/BMI • Current pain level • Overall ability to withstand pain • Pain Interference **Protocol Knowledge Test Questionnaire (SMS Test and Training Form)** • Knowledge of study protocol **Treatment/Surgery Record** • Teeth extracted • Impaction type • Surgical difficulty • Surgical treatment time duration • Anesthesia • Antibiotics • Anti-Inflammatory agents
Days 1-10 +/- 5 days (At home)	**Patient Diary (for the first 7 evenings and days)** • Ability to sleep • Time/date and # of study medication capsules taken • Other OTC pain medication taken (drug/dosage/tablets) • Side effects/adverse events • Sleep ability • Pain interference • Time/date and # tablets taken • Pain levels • Ability to perform daily functions (pain interference)
Post Operative Visit- Visit 2	**Post Op Report**

(Day 10 +/1 5 days)	• Date • Complications **End of Study Data Collection** • Pain Interference • Post-op visit time • Sleep quality • # tablets returned • Overall satisfaction with pain control • Diary ease of use • Suggestions for protocol improvement
PMDP Query (21 days after Visit 2 +/- 7 days)	**Query** • Date • Opioid prescription found (y/n) • Date of prescription • Prescription details

In addition, should an emergency call be received or an emergency visit take place during the post-operative period, the date of the call/visit, reason for the call/visit and any treatment/recommendations provided will be recorded. Should a subject elect to terminate their participation in the study or should the subject be hospitalized, the date the subject is terminated from the study along with the reason will be recorded.

C. Study Duration

The study will be completed over a 4-month period. Each subject will participate in the study for 10 +/- 5 days. A follow-up PDMP query taking place 30 days +/- 7 days after completing Visit 1 if permitted by state law.

D. Endpoints

Study will end after the PMDP query.

1.4 Preliminary Data

Not applicable.

1.5 Sample Size Justification

As this is a pilot to test clinical trial instruments and protocols, no sample size calculation was performed.

1.6 Study Variables

A. Independent Variables, Interventions, or Predictor Variables

Independent variables include:

- Intervention group
- Type of smartphone utilized
- Internet carrier

Note: The surgical treatment provided to the patient is NOT a study intervention. Subjects are being recruited to participate in this study after patients have decided to receive their surgical treatment based upon normal clinical practice and is part of normal standard of care. The intervention in this study is usage of a combination of over-the-counter non-opioid analgesics versus the usage of an analgesic containing the most commonly prescribed opioid for pain management.

B. Dependent Variables or Outcome Measures

Source	Outcome Measure

REDCap	• Completeness of data fields on the questionnaires • Accuracy of the data • Accuracy of the Interface with eDiary • Usability among end-users
eDiary	• Number of entries by subject • Frequency of entries by subject • Completeness of entries

Actigraph	• Utilization (Subject wearing the device)
	  ○ Total duration
	  ○ Interrupted verses constant
	• Accuracy of data output
	  ○ Monitoring activity verses sleep

SMRxT Bottle	• Accuracy of the data
	  ○ Date/time record for capsule removal
	  ○ Discernibility of # of Capsules removed per time point
	  ○ Nomi text alert to investigator

PDMP website	• PDMP Data Completeness

1.7 Drugs/Devices/Biologics

OPIOID group contains hydrocodone 5mg/acetaminophen 300mg and a placebo. The NON-OPIOID group contains ibuprofen 400mg and acetaminophen 500mg. The OPIOID and NON-OPIOID groups will be made by over-encapsulating existing FDA approved caplets currently sold in the United States. Two different color capsules will be used.

COLOR	OPIOID GROUP	NON-OPIOID GROUP
Brown	Hydrocodone 5mg/acetaminophen 300mg	Ibuprofen 400mg
White	Placebo	Acetaminophen 500mg

Each dose of study analgesic will consist of two capsules, one brown and one white. Subjects will be instructed to take one brown capsule and one white capsule when taking study medication as needed for pain.

Study medication will be purchased from Liberty Drug Compounding Center in Chatham, NJ. Liberty Drug will prepare the study product by over-encapsulation. Capsules used for over-encapsulation will be bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE) free. These FDA approved analgesics will be used according to label. Two capsules will be required for each dosage.

- For OPIOID:
  - One capsule will contain hydrocodone 5mg/acetaminophen 300 mg encapsulated in a 00 capsule
  - One capsule will contain the placebo formed into a 0 capsule
- For NON-OPIOID:
  - One capsule will contain acetaminophen 500 mg encapsulated into a 00 capsule
  - One capsule will contain ibuprofen 400 mg encapsulated into a 0 capsule

Study product will be shipped to the Rutgers School of Dental Medicine Coordinating Core in bottles of 20 capsules. Each bottle will contain a barcode which contains a unique bottle number, the contents (drug), quantity, batch/lot number, manufacture date, and expiration date. Rutgers School of Dental Medicine Coordinating Core will be responsible study package assembly for each participant at each site. These study participant packages will be organized in the randomization order generated by the statistician and shipped to the sites, ensuring that site personnel are blinded.

When preparing a packet of materials for an OPIOID subject, twenty (20) capsules of hydrocodone/acetaminophen will be transferred to at SMRxT bottle and twenty (20) capsules of the placebo

will be transferred to a second SMRxT bottle. For a NON-OPIOID subject, twenty (20) capsules of acetaminophen will be transferred to a SMRxT bottle and twenty (20) capsules of ibuprofen will be transferred to a second SMRxT bottle. A label will be affixed to each SMRxT bottles which includes instructions to be followed by the subject.

SMRxT bottles are child proof, light protected bottles which weigh the capsules contained within the bottle. Each time a pill is removed or replaced and the bottle placed on a flat service, the number of capsules removed is transmitted via cellular service to the SMRxT secure cloud. This enables the research staff to track usage of capsules in real time.

A. Drug/Device Accountability and Storage Methods

Study product will be purchased from Liberty Drug Compounding Pharmacy. The compounding pharmacy has the license needed to provide the quantity of study medication needed. All medications (Ibuprofen 400mg, Acetaminophen 500mg, Hydrocodone 5mg/Acetaminophen 300mg are commercially available in the US and will be used according to their labels. Capsules used to over-encapsulate will be bovine spongiform encephalopathy/transmissible spongiform encephalopathy (BSE/TSE) free. These FDA approved analgesics will be used according to label.

Receipt from the Pharmacy

Liberty Pharmacy will ship study product to the Rutgers School of Dental Medicine in bottles of 20 capsules. Each bottle will be clearly marked with a unique ID number, the contents (drug), quantity, batch/lot number, manufacture date, and expiration date. Shipments will be recorded as received by scanning each bottle into REDCap. All study product will be stored in a medication safe in the Rutgers Coordinating Core at RSDM (Newark, NJ).

Radom assignment

Subjects will be randomized to either the opioid or non-opioid analgesic group at the 1:1 ratio, stratified by gender. Pre-determined random number sequences, will be generated by the statistician. The randomization code will be generated and labels will be created during the preparation phase when the treatment packets are prepared so that each packet will be prepared and the labeled with the packet identification number will be generated and put on the packets according to the randomization sequence. Complete randomization code for each site will be stored in REDCap and only the DCC staff have access to it.

Subject Package Preparation

When a subject package is ready to be prepared, the OPIOID/NON-OPIOID designation is obtained by looking up on the randomization list for the next site/gender to be prepared. Study package ID (PID) labels will be printed for all materials to be placed into the packet.

Medication Transfer

When preparing a packet of materials for a participant, there will be a one to one transfer from the manufacturer's bottle to the SMRxT bottles. Specifically, for OPIOID participant, twenty (20) capsules of hydrocodone/acetaminophen will be transferred to at SMRxT bottle and twenty (20) capsules of the placebo will be transferred to a second SMRxT bottle. For a NON-OPIOID participant, twenty (20) capsules of acetaminophen will be transferred to a SMRxT bottle and twenty (20) of ibuprofen will be transferred to a second SMRxT bottle. Immediately following the medication transfer, the Coordinator will scan the bar code on the manufacturer bottle then the barcode on the SMRxT bottles to record the transfer of study product in REDCap, enabling the system to track the study product which has now been placed into a subject package. The manufacturer bottles will then be discarded.

Shipment to the Sites

Subject packages will be shipped to each site in denominations of 4. When packaging a shipment, the study packet being packed will be scanned into REDCap to register the package being sent to a clinical site.

Storage
Each clinical site will have three locked metal cabinets which will be exclusively used for this study: one cabinet will be used to store study materials which have been shipped to the sites by Rutgers, one for placement of study materials, including study product, when recharging the SMRxT bottles and Actigraph prior to release to a participant and the third cabinet will maintain study materials (including study product) which have been returned by the participant and are awaiting shipment to the Rutgers Coordinating Core.

Return of Study Packages to Rutgers Core
Study packages will be shipped back to the Rutgers Core for processing and medication disposal. Contents of the returned study packages (2 SMRxT bottles with unused study medication and the Actigraph) will be individually scanned upon receipt at the Core. Unused study medication will be transferred into a storage bins awaiting disposal through REHS.

1.8 Specimen Collection

A. Primary Specimen Collection
- **Types of Specimens**: N/A
- **Annotation**: N/A
- **Transport**: N/A
- **Processing**: N/A
- **Storage**: N/A
- **Disposition**: N/A

B. Secondary Specimen Collection
- **Types of Specimens**: N/A
- **Annotation**: N/A
- **Transport**: N/A
- **Storage**: N/A
- **Disposition**: N/A

1.9 Data Collection

A. Primary Data Collection
- **Location**: Eligibility form, consent, pre-operative questionnaire, gender/pregnancy form, surgical case report form, post-operative case report form, post-operative questionnaire will be collected in the dental clinic. Subjects will complete their eDiary on their smart-phones at home.

- **Process of Data Collection**: There will be several mechanisms and applications through which the data will be collected:

- REDCap
  The majority of the data will be collected electronically via REDCap forms/surveys. The eligibility form, consent, pre-operative questionnaire and post-operative questionnaire will be administered by study personnel. The surgical case report form and post-operative case report form will be completed by study personnel. The eDaily will be completed by the subject via REDCap web-based surveys on their smart phones.

- NOMI through the use of SMRxT bottles

To collect data on the usage of study analgesics, each study subject will be given 2 SMRxT bottles with study product. SMRxT bottles are electronic bottles which record the date time capsules are removed from the bottle or replaced back into the bottle. One SMRxT will contain the color 1 capsules and the 2nd SMRxT bottle the color 2 capsules. SMRxT bottles connect via cellular technology to the NOMI website which provides real-time monitoring of study product usage. No patient identifiers will be stored in the NOMI system which operates the SMRxT bottles.

- Actigraph
  To collect data on a subject's activity level and sleep, subjects will be asked to wear the Actigraph activity/sleep monitor. Data from the Actigraph will be downloaded from the Actigraph website into REDCap. No patient identifiers will be stored in the Actigraph system.

- **Timing and Frequency**: Time and frequency for each instrument is shown in the Study Instruments Table below.
- **Procedures for Audio/Visual Recording**: N/A
- **Study Instruments**: The following data collection study instruments will be used:

Instrument	Methodology	Measures	Time	Frequency	Location
Informed Consent	REDCap form		15 minutes	Once	Dental Clinic
Eligibility Form	REDCap form		5 minutes	Once	Dental Clinic
Pre-Operative Questionnaire	REDCap form	Demographics pain, swelling,	5 minutes	Once	Dental Clinic
Surgical Treatment Case Report	REDCap form	Extractions Surgical time Difficulty Pharmaceuticals used	5 minutes	Once	Dental Clinic
eDiary	REDCap Surveys	Pain Sleep Pain Interference Adverse Effects	2 minutes per entry	7 evening entries 7 mid-day entries 7 evening entries	At Home
Post-Operative Case Report	REDCap form		3 minutes	Once	Dental Clinic
Post Operative Questionnaire	REDCap form	Pain Sleep Pain Interference Adverse Effects Pain Interference Adverse Effects Satisfaction	10 minutes	Once	Dental Clinic

- **Ethnographic Studies, Interviews, Or Observation**: N/A

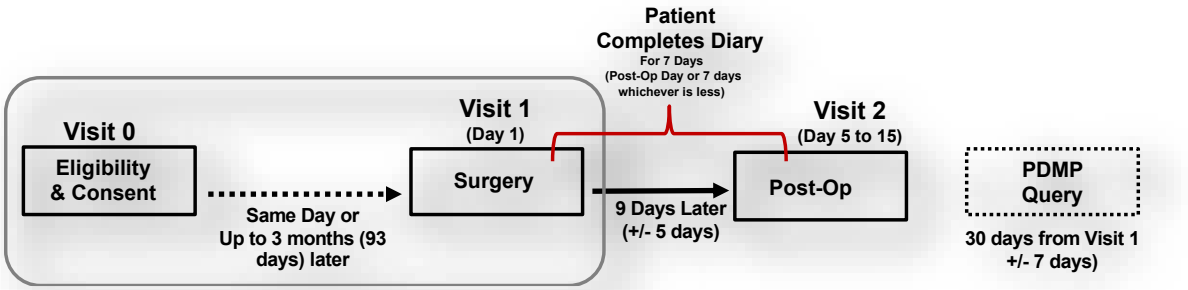
- **Subject Identifiers**: Once a patient is enrolled, a study ID code will be assigned and used on all study materials, eliminating the need to place identifiable information on the forms. Thus, no other study material will not contain the patients name or any other identifiable information. Once the study is completed, the log containing patient names will be shredded.

B. Secondary Data Collection

- **Type of Records**: N/A
- **Location**: N/A
- **Inclusion/Exclusion**: Medical records will be utilized to pre-screen for study eligibility.
- **Data Abstraction Form(s):** N/A

1.10 Timetable/Schedule of Events

The following is the study timetable:



2.0 Project Management

2.1 Research Staff and Qualifications

Research Staff	Training	Experience	Role
Cecile A. Feldman	DMD, MBA	Dr. Feldman is a professor in the department of Community Health and has participated in many research protocols over the course of her career.	**PI** As PI, Dr. Feldman is responsible for oversight of this pilot project; obtaining patient payment cards, collecting study instruments, entering data, calculating descriptive statistics and developing final report.
Janine Fredericks-Younger	DMD	Dr. Fredericks-Younger is an assistant professor in the Department of Restorative at the Rutgers School of Dental Medicine.	**Co-Investigator** As co-investigator, Dr. Fredericks-Younger will serve as the Chief Clinical Officer responsible for overseeing adherence to the study protocol and providing support to the Clinical Co-Investigators.
Shou-en Lu	PhD	Dr. Lu is an associate professor in the department of epidemiology and biostatistics at the Rutgers School of Public Health.	**Co-Investigator/Statistician** As co-investigator, Dr. Lu will assist with data management, statistical analysis and developing the final report
Patricia Greenberg	MS	Ms. Greenberg is the administrative manager and senior biostatistician at the Rutgers School of Public Health.	**REDCap Developer and Statistician** Ms. Greenberg will provide REDCap support and assist in data management.
Vincent Ziccardi	DMD, MD, Certificate in Oral and Maxillofacial Surgery	Dr. Ziccardi is the chair of the Oral and Maxillofacial Surgery Department and has been involved in several analgesia pain studies. He will serve as a Clinical Co-Investigator.	**Clinical Co-Investigator** Clinical Co-Investigators are responsible for subject recruitment, determining eligibility, performing necessary treatment, providing patient instructions, and completing post-operative treatment.
Brahmleen Kaur	DMD	Dr. Kaur is a faculty member in the department of Oral and Maxillofacial Surgery.	**Clinical Co-Investigator** Clinical Co-Investigators are responsible for subject recruitment, determining eligibility, performing necessary treatment, providing

			patient instructions, and completing post-operative treatment.
Megan Ogden	BSN	Ms. Ogden is a nurse in the Oral and Maxillofacial Surgery Clinic and will serve as Clinical Research Coordinator.	**Clinical Research Coordinator** Ms. Ogden is a nurse in the Oral and Maxillofacial Surgery Clinic and will serve as Clinical Research Coordinator.
Yosmery Garcia	RDH	Ms. Garcia is a dental hygienist/research coordinator at the Rutgers School of Dental Medicine and will serve as Clinical Research Coordinator.	**Clinical Research Coordinator** Clinical Research Coordinator is responsible for subject recruitment, obtaining consent, providing patient instructions, completing REDCap forms, and administering subject surveys.
Sandi Grace		Ms. Grace is a dental student at the Rutgers School of Dental Medicine	**Data Quality Analyst** Data Quality Analyst is responsible for reviewing the data for accuracy and completeness
Jonathan Vacca		Jonathan Vacca is an RSDM dental student	**Data Analyst**
Ayodeji Awopegba		Ayodeji Awopegba is an RSDM dental student	**Data Analyst**
Anthony Bishoy Doss		Anthony Bishoy Doss is an RSDM dental student	**Data Analyst**
Phase 2 Personnel			
Gary Warburton	DDS, MS	Dr. Warburton is a faculty member in the department of Oral and Maxillofacial Surgery at the University of Maryland, Baltimore. Dr. Warburton will serve as a Clinical Co-Investigator.	**Site Clinical Co-Investigator** Clinical Co-Investigators are responsible for subject recruitment, determining eligibility, performing necessary treatment, providing patient instructions, and completing post-operative treatment.
Jane Phillips	MS	Ms. Phillips is a research coordinator at the University of Maryland, Baltimore and will serve as Site Clinical Research Coordinator.	**Site Clinical Research Coordinator** Site Clinical Research Coordinator is responsible for subject recruitment, obtaining consent, providing patient instructions, completing REDCap forms, and administering subject surveys.
Michael Miloro	DMD, MD	Dr. Miloro is the Chair of the Oral and Maxillofacial Surgery Department at the University of Illinois at Chicago, College of Dentistry. Dr. Miloro will serve as a Clinical Co-Investigator.	**Site Clinical Co-Investigator** Clinical Co-Investigators are responsible for subject recruitment, determining eligibility, performing necessary treatment, providing patient instructions, and completing post-operative treatment.
Susan Ferguson	MS	Ms. Ferguson is a research coordinator at the University of Illinois at Chicago and will serve as Site Clinical Research Coordinator.	**Site Clinical Research Coordinator** Site Clinical Research Coordinator is responsible for subject recruitment, obtaining consent, providing patient instructions, completing REDCap forms, and administering subject surveys.
Brent Ward	DMD, MD	Dr. Ward is the Chair of the Oral and Maxillofacial Surgery Department at the University of	**Site Clinical Co-Investigator** Clinical Co-Investigators are responsible for subject recruitment, determining eligibility, performing

		Michigan. Dr. Ward will serve as a Clinical Co-Investigator.	necessary treatment, providing patient instructions, and completing post-operative treatment.
Jennifer Lay-Luskin	Other	Ms. Lay-Luskin is a research coordinator at the University of Michigan and will serve as Site Clinical Research Coordinator.	**Site Clinical Research Coordinator** Site Clinical Research Coordinator is responsible for subject recruitment, obtaining consent, providing patient instructions, completing REDCap forms, and administering subject surveys.
Hans Malstrom	DDS	Dr. Malstrom is the Chair of Eastman Dental's General Dentistry Division at the University of Rochester. Dr. Malstrom will serve as a Clinical Co-Investigator.	**Site Clinical Co-Investigator** Clinical Co-Investigators are responsible for subject recruitment, determining eligibility, performing necessary treatment, providing patient instructions, and completing post-operative treatment.
Rita Crosier	Other	Ms. Crosier is a research coordinator at the University of Rochester and will serve as Site Clinical Research Coordinator.	**Site Clinical Research Coordinator** Site Clinical Research Coordinator is responsible for subject recruitment, obtaining consent, providing patient instructions, completing REDCap forms, and administering subject surveys.

2.2 Research Staff Training

Before patient recruitment begins, the principal investigator will meet with all Clinical Co-Investigators and the Clinical Research Coordinators to train them in the research protocol. Included will be the training that must be provided to subjects so that they know how to complete their diaries.

2.3 Resources Available

For Phase 1, emergency services through the Rutgers School of Dental Medicine and University Hospital will be available. For Phase 2 clinical sites, emergency services will be offered through the dental clinics at which care was provided. Note that surgical treatment and post-operative care is following normal standard of care.

2.4 Research Sites

Phase 1

Subjects will be seen at the Rutgers School of Dental Medicine, Oral and Maxillofacial Surgery Clinic.

Phase 2

Subjects will be seen at the following clinical sites:

- University of Maryland, School of Dentistry, Department of Oral and Maxillofacial Surgery
- University of Illinois at Chicago, College of Dentistry, Department of Oral and Maxillofacial Dentistry
- University of Michigan, School of Dentistry, Department of Oral and Maxillofacial Surgery
- University of Rochester, Eastman's School of Dentistry, General Practice Residency Clinic

3.0 Multi-Center Research

This pilot study is a single protocol that will be implemented at the following institutions: University of Maryland, School of Dentistry, Department of Oral and Maxillofacial Surgery, University of Illinois at Chicago, College of Dentistry, Department of Oral and Maxillofacial Dentistry, University of Michigan, School of Dentistry,

Department of Oral and Maxillofacial Surgery, and University of Rochester, Eastman's School of Dentistry, General Practice Residency Clinic.

4.0 Subject Considerations

4.1 Subject Selection and Enrollment Considerations

A. Method to Identify Potential Subjects

The schedule for patients being seen at the dental school for 3rd molar extracts will be reviewed by study investigators so that study personnel can be present when the patients reports for a consult and inquire about interest in participating in the study. The site may advertise for the study by word of mouth and/or advertising through flyers, social media, e-mail and/or ads in local/college newspapers.

B. Recruitment Details

The Clinical Co-Investigators will have identified patients presenting for impacted 3rd molar extraction. A Clinical Co-Investigator will approach the patient and determine if he/she is interested in finding out about a clinical trial about pain medications. After asking if the patient is interested in participating in the trial comparing the effectiveness of two pain medications, an explanation will be provided along with the consent form. The patient will be provided 15 minutes to review the informed consent and then discuss it with the clinical co-investigator associated with the respective clinic.

C. Subject Screening

If after reviewing the informed consent and discussing the trial with the clinical co-investigator the patient is still interested in participating, the patient will be asked to sign the informed consent. Screening will be initiated to determine if inclusions criteria have been meet and no exclusion criteria exist which would exclude them from the study. If during the eligibility process an exclusion is found, the patient will be deemed ineligible to participate.

- **Inclusion Criteria**

  Adult men and non-pregnant women who are at least 18 years of age, who are able to refrain from driving or operating heavy machinery while taking the study medication will be able to participate. Subjects who are English speaking and are able to provide consent will be considered. Subjects must be in generally good health and able to take ibuprofen, paracetamol (acetaminophen), and hydrocodone.

- **Exclusion Criteria**

  Subjects who self-report the following history will be excluded from participating:

  - Individual under the age of 18
  - History of gastrointestinal bleeding and/or peptic ulcer
  - History of renal disease (excluding kidney stones)
  - History of hepatic disease
  - History of bleeding disorder
  - History of respiratory depression
  - Any prior respiratory effect of an opioid or other anesthetic drug that required respiratory support postoperatively
  - Active or untreated asthma
  - History of known allergic reaction to ibuprofen, acetaminophen, hydrocodone, and/or anesthesia
  - Currently taking any of the following medications:
    - CYP3A4 inhibitor, such as macrolide antibiotics (e.g., erythromycin), azole-antifungal agents (e.g., ketoconazole), and protease inhibitors (e.g., ritonavir), which may increase plasma concentrations of hydrocodone bitartrate and acetaminophen and prolong opioid adverse reactions, and which may cause potentially fatal respiratory depression
    - CNS depressants.
  - Consumes 3 or more alcoholic drinks every day and/or has a history of alcoholism

- History of drug or alcohol abuse (excludes marijuana use)
- Family history of drug or alcohol abuse in a first degree relative
- Has had one or more opioid prescription filled within the past 6 months
- Currently pregnant or lactating

Patients would also be excluded due to any additional criteria that would place the individual at increased risk or preclude the individual's full compliance with or completion of the study which includes:

- Prior participation in this study
- Inability or refusal to provide informed consent

4.2 Secondary Subjects

N/A

4.3 Number of Subjects

A. Total Number of Subjects

Phase 1: A maximum of 24 subjects will be enrolled, 12 males and 12 females.
Phase 2: A maximum of 8 subjects will be enrolled, 4 males and 4 females at each clinical site.

B. Total Number of Subjects If Multicenter Study

Total study enrollment: 56 subjects

C. Feasibility

Phase 1: The RSDM Oral and Maxillofacial Surgery Clinic has performed previous 3rd molar pain studies. These studies have enrolled about 5 patients per week. Thus it is not anticipated that there will be any problem recruiting 24 patients over a 2 month period enabling the study to be completed within 4 months.

Phase 2: The other institutional sites are enrolling 8 patients each and, like RSDM, have adequate patient flow to meet the 8 subject enrollment over the student period.

4.4 Consent Procedures

A. Consent Process

- **Location of Consent Process**
  Consent will be obtained while the patient is being seen in the dental clinic. This is the same location in which informed consent is obtained for all dental procedures being performed at the dental school.
- **Ongoing Consent**
  Study objectives, risks and benefits will be reviewed with the patient at the beginning of the Treatment Visit if the Treatment Visit is Separate from the Screening Visit and at the beginning of the Post-Operative Visit. While patients can withdraw their consent at any time, it is not expected that this will happen as the study protocol lasts for only 10 days. Should a patient withdraw their consent, they will be instructed to immediately stop taking the study medication and return all unused medication to the Clinical Co-Investigator.
- **Individual Roles for Researchers Involved in Consent**
  The Clinical Co-Investigators and the Research Coordinator will obtain the informed consent.
- **Consent Discussion Duration**
  It is estimated that it will take about 10-15 minutes to discuss the study purpose and obtain informed consent.
- **Coercion or Undue Influence**
  The Clinical Co-Investigators will be asked to emphasize that participation in this study protocol is purely voluntarily. They will be told to emphasize, that the dental treatment they will receive will not

be influenced in any way by their participation or non-participation in the study. Patients participating in this pilot study will not be given free care, thus limiting the possibility of coercion or undue influence.

- **Subject Understanding**
  Subjects will be asked to summarize in their own words the purpose of the study, the risks and the benefits in order to ensure their understanding and willingness to participate.

B. Waiver or Alteration of Consent Process

- **Waiver or Alteration Details**
  N/A
- **Destruction of Identifiers**
  N/A
- **Use of Deception/Concealment**
  N/A
  a. **Minimal Risk Justification**
     N/A
  b. **Alternatives**
     N/A
  c. **Subject Debriefing**
     N/A

C. Documentation of Consent

- **Documenting Consent**
  Consent will be obtained by electronic signature in REDCap. A printed copy of the signed consent will be provided to the patient.
- **Waiver of Documentation Of Consent (i.e., will not obtain subject's signature)**
  N/A

4.5 Special Consent/Populations

A. Minors-Subjects Who Are Not Yet Adults

- **Parental Permission**
  N/A
- **Non-Parental Permission**
  N/A
- **Assent Process**
  N/A
- **Documentation of Assent**
  N/A.
- **Reaching Age of Majority During Study**
  N/A

B. Wards of the State

N/A

- **Research Outside of NJ Involving Minors**
  N/A

C. Non-English-Speaking Subjects

Only English speaking subjects will be enrolled.

- **Process for Non-English-Speaking Subjects**
  N/A
- **Short Form Consent for Non-English Speakers**
  N/A

D. Adults Unable to Consent / Cognitively Impaired Adults (for interventional studies)
N/A]

- **NJ Law-Assessment of Regaining the Capacity to Consent**
  N/A
- **Capacity to Consent**
  N/A
  - **a. NJ Law-Selecting A Witness**
    N/A
  - **b. Removing a Subject**
    N/A

4.6 Economic Burden and/or Compensation for Subjects

A. Expenses

Subjects will not be responsible for any costs associated with this research or for any expenses above what they would normally be responsible for should they not be a participant in this research.

B. Compensation/Incentives

Subjects will receive $125 in compensation in the form of a Visa gift card to compensate for the time in completing all of the following: the pre-operative survey, e-Diary entries (at least the first 3 morning and 3 evening entries), and the post-operative survey.

C. Compensation Documentation

The principle investigator will obtain all payment cards. Subjects will provide an electronic signature (on a REDCap form) to indicate receipt of their payment card. This will be done as the last question on the post-operative REDCap survey form.

4.7 Risks of Harm/Potential for Benefits to Subjects

A. Description of Risks of Harm to Subjects

- **Reasonably Foreseeable Risks of Harm**

Each proposed analgesic has potential side effects. These side effects include:

- excessive fatigue or drowsiness
- inability to concentrate
- dizziness
- euphoria (intense feeling of well-being & happiness)
- headache
- nausea
- vomiting
- diarrhea
- constipation
- stomach aches
- heartburn
- itching
- skin rashes
- urinary retention
- unintentional weight gain

Should these side effects become significant or bothersome, the patient will be instructed to stop taking the prescribed medication. If additional analgesia is required, the subject will be instructed to call the emergency number. Should the subject experience shortness of breath, or tachycardia, the subject will be instructed to immediately stop taking the study medication and call the emergency number. Subjects will also be counseled on the addictive nature of opioids.

- **Risk of Harm from an Intervention on a Subject with an Existing Condition**
  All study analgesics are commonly used to control post-operative pain today. To be eligible to participate, subject must meet all inclusion and not have any exclusion criteria. Thus subjects with existing conditions are not eligible to participate.
- **Other Foreseeable Risks of Harm**
  Opioids provided are minimal number of capsules and unused capsules will be collected to minimize the possibility of diversion. Care provided will include a PMDP query 30 days after surgery. If an opioid prescription has been filled, the subject will be able to speak to an addiction counselor. Other foreseeable risks may include risks associated with a possible loss of confidentiality.
- **Observation and Sensitive Information**
  All information will be as confidential. .

B. Procedures which Risk Harm to Embryo, Fetus, and/or Pregnant Subjects

Third molar surgery is the standard of care for patients who require third molar removal. All study analgesic medication is part of normal standard of care for post-surgical pain management for men and for women who self-report not being pregnant. Exposure is limited to a short post-operative period, generally 2-5 days as needed.

While not a universal standard of care, female subjects will be required to take a point-of-service pregnancy test on the day of surgery to provide an extra level of safety. Only females testing negative will be allowed to participate. In addition, while not a standard of care, female subjects will be counseled on the importance of not becoming pregnant while taking study medication and that they should use some form of birth control if sexually active. Standard post-op procedures are being followed which includes a clinical exam at one week post-op.

C. Risks of Harm to Non-Subjects

Subjects will be instructed to not allow others, including members of their household, to use their study medication. Medication will be dispensed with childproof caps. If patients follow these instructions, there are no known risk to non-subjects.

D. Assessment of Social Behavior Considerations

Individuals who have an individual or immediate family history (parents, siblings, children or spouse) of substance abuse are not eligible to participate as subjects thereby minimizing any foreseeable risks. Subjects will be instructed to not allow others, including members of their household, to use their study medication. Medication will be dispensed with childproof caps. If patients follow these instructions, there are no known risk to non-subjects.

E. Minimizing Risks of Harm

To minimize risks, patients are being instructed to take their assigned analgesic medication only as needed after the first dose. This will minimize exposure to subjects. In addition, Individuals who have a personal or immediate family history (parents, siblings, children or spouse) of substance abuse are not eligible to participate as subjects thereby minimizing any foreseeable risks. Subjects will be instructed to not allow others, including members of their household, to use their study medication. Medication will be dispensed with childproof caps.

- **Certificate of Confidentiality**
  A Certificate of Confidentiality will be issued automatically by NIH as the study utilizes identifiable, sensitive information.
- **Provisions to Protect the Privacy Interests of Subjects**
  Data will be de-identified to protect subjects.

F. Potential Benefits to Subjects

There is no direct benefit to subjects.

5.0 Special Considerations

5.1 Health Insurance Portability and Accountability Act (HIPAA)

The following data will be utilized in this study:

- Gender, race, ethnicity, age
- Eligibility criteria
- Pain levels, ability to sleep, ability to perform daily functions, overall satisfaction
- Treatment procedures and treatment notes
- Medications taken
- Any opioid prescriptions filled after surgery

As the study protocol includes the prescribing of an opioid, the state Prescription Data Monitoring Program (PDMP) database will be consulted before enrolling a subject into the study. New Jersey, New York, Illinois, Michigan, and Maryland all currently have an operational PDMP that is collects data from dispensers and reporting information from the database to authorized users. The patient's name and birth date is required for this inquiry. The inquiry will be conducted by the Clinical Co-Investigator. The subject's number of previous opioid prescriptions will be recorded on the Subject Eligibility Form. A second query will be done 30 days after surgery if the state PDMP allows. The PDMP query will be discussed with the subject during the consent process and subjects will consent to the prescription drug database will be queried 30 days after surgery on the research study consent form if permitted by state regulations. Study participants should be aware that opioids can be addictive. If the state's Prescription Drug Monitoring Database query reflects an opioid being prescribed after the surgical visit, the subject will be offered the ability to talk to an addiction counselor. If state regulations prohibit a post-surgery PDMP query at 30 days, an email will be send to all subjects from that locale 30 days after surgery to remind them of the availability of an addiction counseling session if needed.

The research team may use or share the subject's information collected or created for this study with the following people and institutions:

- Rutgers University Investigators Involved In the Study
- The Rutgers University Institutional Review Board and Compliance Boards
- Study personnel and institutional review boards form the following institutions:
    - University of Maryland, School of Dentistry
    - University of Illinois at Chicago, College of Dentistry
    - University of Michigan, School of Dentistry
    - University of Rochester, Eastman School of Dentistry
- The Office for Human Research Protections in the U.S. Dept. of Health and Human Services
- Federal Drug Administration
- National Institutes of Health (NIH) - National Institute of Dental and Craniofacial Research (NIDCR)

Those persons or organizations that receive your information may not be required by Federal privacy laws to protect it and may share your information with others without your permission, if permitted by the laws governing them.

The subject's name and birthday will be deleted 3 months after the last patient completes the protocol or 1 year from the date the first enrolled subject completed the protocol, whichever comes first.

5.2 Family Educational Rights and Privacy Act (FERPA)

N/A

5.3 NJ Access to Medical Research Act (Surrogate Consent)

N/A

5.4 General Data Protection Regulation (GDPR)

N/A

5.5 Code of Federal Regulations Title 45 Part 46 (Vulnerable Populations)

N/A

A. Special Populations

- N/A

6.0 Data Management Plan

6.1 Data Analysis

As the main purpose of this pilot study is to test the pragmatic study methodology, descriptive statistics including frequencies and means will be calculated for the independent and dependent variables. No power analysis was completed.

6.2 Data Security

Study data will be collected using REDCap, a secure system housed on Rutgers University servers. System access requires a NetID and is password protected. Personal identifiers are required in order to contact the subject during the research protocol. Links to personal identifiers (name, e-mail address, mobile phone number) will be deleted once all subjects have completed the protocol or a year from completing the first subject, whichever comes first.

There could a breach of confidentiality but measures are in place to try and protect the subjects' privacy. Provision of identifiable personal information will be limited to the log maintained should the need to un-blind the medication become necessary. Once a patient is enrolled, a study ID code will be assigned and used on all study materials, eliminating the need to place identifiable information on the forms. Thus, no other study material will not contain the patients name or any other identifiable information. Once the study is completed, the log containing patient names will be shredded.

All study personnel have taken both HIPAA and CITI training. All paper records, including the informed consents, subject logs, screening forms, medication logs, and patient diaries, will be stored in the PI's office in locked file cabinets. Electronic data will only be stored on drives which follow university security policies. Transmission of data will be through the RBHS e-mail system which transmits data in encrypted format. Data will only be used on university computers which are password protected. No identifiable patient information will be stored in any of the electronic files.

6.3 Data and Safety Monitoring

All Unanticipated problems (UP) and SAEs and will be reported to NIDCR, and the IRB.

A. Data/Safety Monitoring Plan

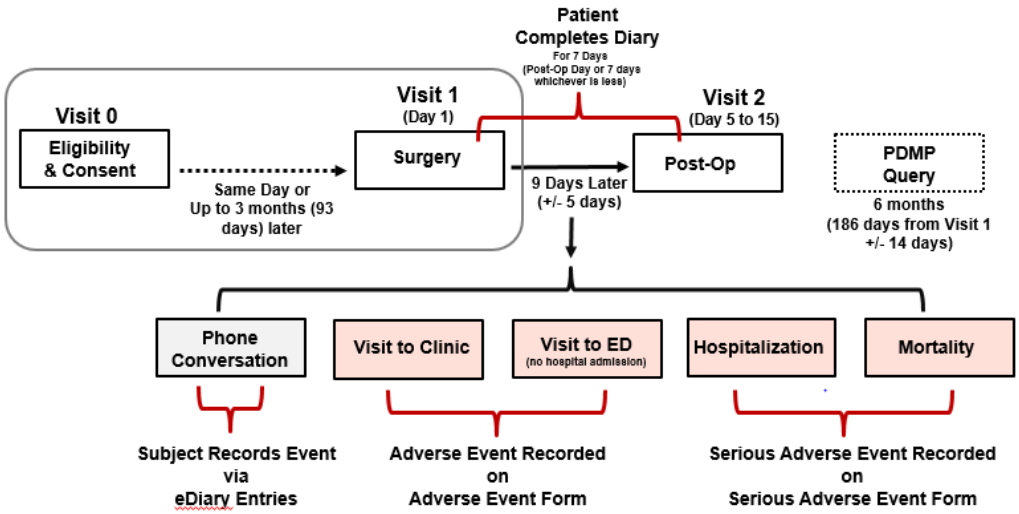
Subject record review activities are done in real-time via checks programmed into REDCap, as well as, manual reviews conducted by the Research Coordinator.

Pre-programmed quality checks

- *Structured responses are required for the CRFs so only valid responses can be recorded. In addition, REDCap has been programmed with all responses being required at time of completion.*
- *Validation rules are employed where possible*
- *Eligibility Criteria and Prohibited Medications: On the Eligibility Determination Form branching logic has been employed to sequentially review eligibility requirements and eliminate subjective eligibility scoring by the Research Coordinator*
    - *As an extra measure of quality control, before eligibility determination is started, the Research Coordinator will confirm the subject received a printed signed copy of the informed consent form. This attestation is contained on the Eligibility Determination REDcap form.*

Quality management activities will also include a real-time review of subject records, adherence to the protocol, adherence to onboarding of study personnel protocols, and proper tracking of study product. These reviews will be conducted after the first 10 subjects have competed the protocol. As part of this record review audit, the Research Coordinator and the PI will review of all forms, questionnaires and case reports which make up a participant's study record for the 10 subjects. Results of the review and corrective actions will be provided in a summary report. The data query process will be managed in REDCap via the Query Form and utilized to rectify identified issues in an appropriate time frame.

AE and SAE Identification and Reporting: Adverse events are expected due to the known nature of the FDA approved analgesics. An adverse event will be documented the Adverse Event form while a serious adverse event (SAE) will be recorded on the Serious Adverse Event form in REDCap. Likewise, unanticipated problems will be reported on the Unanticipated Problems Form in REDCap. Protocol Deviations and violations will be recorded on the Protocol Deviation/Violation Reporting Form in REDCap. Reporting information is found below:



Characteristics of an Adverse Event

Each event will be recorded on an appropriate case report form that includes assessment of the characteristics defined below. These characteristics, along with the frequency of an event's occurrence, will be considered in determining if the event is an unanticipated problem.

To assess relationship of an event to study intervention the following guidelines are used:

1. Related (Possible, Probable, Definite)
   a. The event is known to occur with the study intervention, and/or
   b. There is a temporal relationship between the intervention and event onset and/or
   c. The event abates when the intervention is discontinued, and/or
   d. The event reappears upon a re-challenge with the intervention.
2. Not Related (Unlikely, Not Related)
   a. There is no temporal relationship between the intervention and event onset, and/or
   b. An alternate etiology has been established.

The Study PI and/or study-appointed, clinically/medically responsible individual will determine whether an AE is expected or unexpected. The following are considered expected adverse events (associated with known adverse events from the study product):

   a. excessive fatigue or drowsiness

b. inability to concentrate
c. dizziness
d. euphoria (intense feeling of well-being & happiness)
e. headache
f. nausea
g. vomiting
h. diarrhea
i. constipation
j. stomach aches
k. heartburn
l. itching
m. skin rashes
n. urinary retention
o. unintentional weight gain

Other Adverse Events will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

Severity of Adverse Event
The severity of the adverse events will be graded by the extent to which the subject is bothered by the event. Subject will determine whether they were bothered by the event to a minor (no impact or minimal impact on activities of daily living and no intervention required) or major extent (moderate or significant impact on activities of daily living which may require the subject to stop taking the study analgesic or subject seeks medical attention.)
Serious adverse events will be considered severe in extent as the symptoms are significant requiring hospitalization and invasive intervention.

Item	Definition	Who completes REDCap form	Who Makes Report to Monitors	Time Frame For Reporting Occurrence of Event to Monitor	Which Monitors Reported to	Summary Report Prepared by	Timing for Issuing Report	Summary Report Issued to
Adverse Events	Any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research	• If clinic or ED visit Is not required - subjects self-report via eDiary entries; • If visit/ED visit is required - reported via adverse event form by clinical research coordinator	Reportable if event is: unexpected, related, and potentially places subject at greater risk	5 business days from the date of discovery		Statistical Core Chief	Once at end of pilot trial	IRB NIDCR Medical Monitor CROMS (Rho)
Serious Adverse Events	Event which requires hospitalization and/or causes mortality	Site Director or Clinical Research Coordinator	PI or Clinical Protocol Coordinating Chief	• 24 hours for hospitalization • 24 hours for fatalities	IRB NIDCR Medical Monitor CROMS (Rho)	Statistical Core Chief	Once at end of pilot trial	IRB NIDCR Medical Monitor CROMS (Rho)
Unanticipated Problems	Any problem or event which in the opinion of the local investigator was unanticipated, reflects new or increased risk to the subjects and was possibly related to the research procedures.	Site Director or Clinical Research Coordinator	PI or Clinical Protocol Coordinating Chief	5 business days from the date of discovery	IRB NIDCR Medical Monitor CROMS (Rho)	Statistical Core Chief	Once at end of pilot trial	IRB NIDCR Medical Monitor CROMS (Rho)
Protocol Deviations	Any change, divergence, or departure from the study design or procedures of a research protocol that is under the investigator's control and that has not been approved by the IRB.	Site Director or Clinical Research Coordinator	PI or Clinical Protocol Coordinating Chief	5 business days from the date of discovery	IRB NIDCR Medical Monitor CROMS (Rho)	Statistical Core Chief	Once at end of pilot trial	IRB NIDCR Medical Monitor CROMS (Rho)
Protocol Violation	Any deviation from the IRB approved protocol that may affect the subject's rights, safety, or well-being and/or the completeness, accuracy and reliability of the study data	Site Director or Clinical Research Coordinator	5 business days from the date of discovery	5 business days from the date of discovery	IRB NIDCR Medical Monitor CROMS (Rho)	Statistical Core Chief	Once at end of pilot trial	IRB NIDCR Medical Monitor CROMS (Rho)

B. Data/Safety Monitoring Board Details

N/A

6.4 Reporting Results

A. Individual Subjects' Results
Individual subject results will not be made available.

B. Aggregate Results
Aggregate results will not be made available to the subjects as this is a pilot study to test out study methodology only.

C. Professional Reporting
Results of this study will be used to finalize methodology for grant documentation to NIH. In addition, results of this pilot project may be published as abstract or journal articles and/or presented at professional meetings.

D. Clinical Trials Registration, Results Reporting and Consent Posting
This pilot study to test methodology. All analgesics are FDA approved and are being used according to label. Thus, this protocol will not be registered on clinicaltrials.gov.

6.5 Secondary Use of the Data
There is no planned secondary use of the data.

7.0 Research Repositories – Specimens and/or Data

N/A

8.0 Approvals/Authorizations

HRP 1812 and SMART IRB are being used to obtain a reliance agreement.

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