PENNSTATE

HRP-503f - Protocol for Human Subject Research

Protocol Title: Post-operative analgesia following elective soft-tissue surgery of the hand: A randomized, double blind comparison of Acetaminophen/Ibuprofen versus Acetaminophen/Hydrocodone

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1.0 Objectives

1.1 Study Objectives

- Compare the efficacy of acetaminophen/hydrocodone (AH) to acetaminophen/ibuprofen (AIBU) in providing adequate post-operative pain relief in elective, soft-tissue hand surgery patients.
- Review the adverse events related to administration of AH or AIBU
- Subcategorize patients based on anatomic location, surgery performed, and perioperative variables

1.2 Primary Study Endpoints

- Compare the efficacy of acetaminophen/hydrocodone (AH) to acetaminophen/ibuprofen (AIBU) in providing adequate post-operative pain relief in elective, soft tissue hand surgery patients
    - VAS, Pain Catastrophizing Scale, medication pain relief [Likert pain score], mean daily pain values

1.3 Secondary Study Endpoints

- Incidence of adverse effects
- Patient satisfaction (yes/no)
- Time to stopping medication
- Incidence of medication discontinuation
- Need for additional analgesics
- Subcategorize patients
    - Surgery performed
    - Propofol dose
    - Fentanyl dose
    - Surgery time
    - Local anesthetic dose
    - Local anesthetic composition
    - Perioperative NSAIDs
    - PHQ-9 questionnaire score

2.0 Background

2.1 Scientific Background and Gaps

Currently, there are no randomized, controlled trial data to suggest a superior post-operative pain regimen in elective soft-tissue hand surgery. As opioids have been associated with adverse effects such as abuse, overdose and dependency, we wish to determine if their use can be limited in favor of non-opioid analgesics such as acetaminophen and ibuprofen for elective soft tissue hand surgery. Use of non-steroidal anti-inflammatory drugs is contraindicated in procedures where osseous healing is required.

2.2 Previous Data

The study drugs have been studied extensively and have been shown to provide reproducible analgesia and a low rate of severe side effects or adverse events.

2.3 Study Rationale

See study objectives

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

- Age: 21 – 90
- Gender: male or female (non-pregnant)
- Elective, soft-tissue hand surgery indicated based on diagnosis made by either clinical exam or diagnostic studies (i.e. nerve conduction study, EMG) or a combination of the two
    - Carpal tunnel release, trigger finger release, first dorsal compartment release, ganglion cyst excision
- Subjects are capable of giving informed consent

3.2 Exclusion Criteria

- Allergy to study medication
- Any preexisting pain condition requiring analgesia
- Fibromyalgia
- Recent upper gastrointestinal bleeding
- Coagulopathy (primary or medication-related)
- Renal impairment
- Liver disease
- Pregnancy
- Patients who consent to the study but who require unexpected admission, including those requiring admission resulting from operative complications, will be excluded before randomization.

3.3 Early Withdrawal of Subjects

3.3.1 Criteria for removal from study

Patients will be withdrawn from the study for safety reasons including severe adverse reactions, failure of subject to adhere to protocol requirements, or subject consent withdrawal.

3.3.2 Follow-up for withdrawn subjects

If a patient is withdrawn from the study, data collection will be terminated from that time point forward. All prior data collected will be included in the analysis. These subjects will not be replaced, but instead more subjects may need to be enrolled. These new data will be recorded and analyzed as would any other new enrollee. No further follow up of withdrawn subjects is necessary as the study follow-up terminates at two weeks following surgery.

4.0 Recruitment Methods

4.1 Identification / Recruitment of subjects

Subjects will be identified as part of their initial or routine evaluation by one of the study investigators in the Bone & Joint Institute. These patients would normally be treated at the Penn State Hershey Medical Center and will be receiving the same operative care as those not enrolled in the study.

4.2 Recruitment materials – N/A

4.3 Eligibility/screening of subjects - N/A

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent

Subjects presenting to the study investigators' practice site as part of their initial or routine evaluation will be given the opportunity to participate in the research study. Patients will be given information about the study and asked to participate. If eligible, based on inclusion and exclusion criteria, informed consent will be obtained at the time of the screening visit and the patient will be enrolled in the study.

5.1.1.2 Coercion or Undue Influence during Consent

Subjects will be given ample time to read and review the consent form on their own. All questions the patient may have will be answered, and written consent will be obtained. A member of the research team will assist in the explanation and obtaining of the written consent. A copy of the signed consent will be given to the patient and another copy sent to Medical Records.

5.1.2 Waiver or alteration of the informed consent requirement - N/A

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

A member of the research team will assist in the explanation and obtaining of the written consent. A copy of the signed consent will be given to the patient and another copy sent to Medical Records.

5.2.2 Waiver of Documentation of Consent - N/A

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects – N/A

5.3.2 Cognitively Impaired Adults - N/A

5.3.2.1 Capability of Providing Consent - N/A

5.3.2.2 Adults Unable To Consent - N/A

5.3.2.3 Assent - N/A

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission - N/A

5.3.3.2 Assent - N/A

6.0 Study Design and Procedures

6.1 Study Design

This will be a randomized, double-blind study in which physicians and patients are blinded to the treatment protocol.

Recruitment → Randomization → Surgery → Treatment (AH v AIBU)

AH → post-operative assessment at one week

AIBU → post-operative assessment at one week

Patient still having pain at one week → satisfied with medication regimen (yes/no)

Yes → continue current regimen

No→ prescription for oxycodone

Final study visit → data collection → discard unused study medication

6.2 Study Procedures

6.2.1 Visit 1 - Screening/Baseline Visit

Patients will be given information about the study and asked to participate. If eligible, based on inclusion and exclusion criteria, informed consent will be obtained at the time of the screening visit and the patient will be enrolled in the study. Baseline pain scale (VAS) measurements will be obtained as well as the PHQ-9 questionnaire and Pain Catastrophizing Scale. Patients will be provided instructions regarding study dosage and provided a patient diary with instructions.

Patients will be randomized to one of two recruitment groups (patient/PI blinded)

- AH – Acetaminophen 325 mg/Hydrocodone 5 mg
- AIBU – Acetaminophen 500 mg/Ibuprofen 400 mg

6.2.2 Visit 2 – Surgery Day

Instructions regarding study drug dosage will be reviewed with the patient and study drug provided to the patient.

The dose for the AH group will be two capsules containing a total of 325 mg of acetaminophen and 5 mg of hydrocodone – one study tablet contained within a capsule and one placebo tablet (cellulose will be used as a filler within the placebo to simulate the weight of an ibuprofen tablet) within a separate capsule.

The dose for the AIBU group will be two capsules – one study tablet containing acetaminophen 500 mg and the second capsule containing ibuprofen 400 mg.

Subjects will be instructed to take one dose (two capsules) of medication every four hours (maximum of 6 times per day) for 7 days or until pain free, whichever comes sooner.

6.2.3 Visit 3 - Phone call 1 – Post-operative day 7 (or next business day)

Patients will be contacted by research personnel at 7 days following surgery at which point they will be asked if they are still having pain requiring medication (yes/no).
If patients are still having pain, they will be asked if they are satisfied with the current pain regimen (yes/no). If "yes" then they will be asked to continue the current pain regimen. Unblinding will occur at this time. If they were randomized to the AH group, they will receive a prescription for one additional week of this medication. If they were randomized to the AIBU group, they will be instructed to take the Acetaminophen and Ibuprofen as directed on an as needed basis. If "no" (not satisfied with current regimen), they will be prescribed oxycodone 5 mg and instructed to take one or two tablets every 4 hours as needed for pain. Patients will be asked to record the date and time that they stopped taking the analgesic medication and asked to bring the opioid tablets with them to their final clinic visit. Data collection stops at this time.

6.2.4 Visit 4 – Final visit – Post-operative day 14

Patient will be asked to return to clinic approximately two weeks post-operatively (+/- 4 days) for suture removal and to conclude the study. Patient diary will be collected. Study medications will be counted and accuracy ensured. All study medication will be discarded by study personnel. Data collection ends one week postoperatively. Patient diaries with data will be collected at this final visit.

6.2.5 Study Visit Flowsheet

Screening visit	Surgery	1 week Post-operative phone call	2-week Post-operative visit
Enrollment; Randomization; Baseline VAS, Pain Catastrophizing Scale, PH-9 questionnaire via patient diary	Dispense study drug;	Pain assessment/continue medication? Finish patient diary completion.	Collect patient diary / dispose of study medication

6.3 Duration of Participation

Subjects will be asked to participate in the study through their two-week post-operative visit.

6.4 Test Article(s) (Study Drug(s) and/or Study Device(s))

6.4.1 Description

The study drugs consist of a combination of Acetaminophen 325mg / Hydrocodone 5 mg (AH) or Acetaminophen 500mg / Ibuprofen 400mg (AIBU). AH has been approved by the FDA under the trade name Norco. The mechanism of action of acetaminophen is to inhibit the synthesis of prostaglandins in the central nervous system and work peripherally to block pain impulse generation. The mechanism of action of hydrocodone is to block pain perception in the cerebral cortex by binding to specific receptor molecules (opiate receptors) within the neuronal membranes of synapses. The mechanism of action of ibuprofen is to reversibly inhibit cyclo-oxygenase 1 and 2 (COX-1 and COX-2), which results in decreased formation of prostaglandin precursors that cause inflammation and pain.

6.4.2 Treatment Regimen

The dose for the AH group will be two capsules containing a total of 325 mg of acetaminophen and 5 mg of hydrocodone – one study tablet contained within a capsule and one placebo tablet within a separate capsule. The non-opioid group (AIBU) will be given two

capsules per dose – one containing acetaminophen 500mg and the other containing ibuprofen 400mg. Patients will be instructed to take one dose (two capsules) of medication every four hours, as needed, for one week (7 days) or until pain free, whichever comes sooner. If patients have pain that is not controlled with the study medication, they will be given a prescription for oxycodone 5 mg and instructed to take one to two tablets every four hours as needed for pain. Anti-emetic medications will be prescribed if indicated. These patients will be analyzed in a subgroup analysis.

6.4.3 Method for Assigning Subject to Treatment Groups

Patients will be randomized to receive either AH or AIBU during their pre-operative clinic visit. Randomization will be conducted by the research coordinator (and not any study personnel who must remain blinded).

6.4.4 Subject Compliance Monitoring

Patients will be asked to record the time, in addition to a visual analog score (VAS) and Likert scale in their patient diary 6 times daily with every dose of medication (every 4 hours). They will not continue to record these measurements after no longer taking the study medication.

6.4.5 Blinding of the Test Article

The opioid and non-opioid analgesic regimen will be compounded by investigational pharmacy. Randomization will be performed prior to surgery and the study medication will be given to the patient by a member of the investigational pharmacy or clinical nursing not involved with the study after surgery. Physicians and other pertinent study personnel will be blinded to the treatment regimen.

6.4.6 Receiving, Storage, Dispensing and Return

6.4.6.1 Receipt of Test Article

The study drugs will be obtained by the investigational pharmacy.

6.4.6.2 Storage

The study drugs will be stored at room temperature monitored by investigational pharmacy.

6.4.6.2 Preparation and Dispensing

The study drugs will be packaged and stored by investigational pharmacy. The week-long supply of study drug will be dispensed to the patient after surgery.

Patients will be given 6 doses of medication per day, in two pill bottles – one containing yellow capsules and the other blue capsules. Each dose will consist of two capsules of acetaminophen 325 mg/hydrocodone 5 mg or acetaminophen 500 mg/ibuprofen 400 mg. The total number of capsules in the 2-week long pill bottles will be 84, or 12 per day. Patients will be instructed not to take more than 6 doses each day. Additional pain medication outside of the study medication will not be allowed. However, patients will be able to request oxycodone 5 mg if the study medication does not provide adequate pain relief.

6.4.6.3 Return or Destruction of the Test Article

Patients will be instructed to bring their pill containers with them to the final post-operative visit at which time study personnel will be responsible for discarding all remaining study medications.

6.4.6.4 Prior and Concomitant Therapy

Patients will be excluded from the study if they are currently being treated for any pain-related condition or are taking any pain medication regularly. All other concomitant medications will be allowed to continue.

7.0 Data and Specimen Banking

7.1 Data and/or specimens being stored

- Patient Name, MRN #, Date of Birth, Phone number, Gender, Ethnicity, Race, Occupation, Right or Left handedness, and link to identifier code
- VAS Scale
- Likert Scale
- PHQ-9 questionnaire
- Pain Catastrophizing Scale

7.2 Location of storage

All research data will be kept on a password-protected computer or in a locked filing cabinet and accessible only to the research personnel.

7.3 Duration of storage

All research data will be stored for length of time required by federal regulations/funding source and then destroyed (minimum 3 years).

7.4 Access to data and/or specimens

Only research personnel will have access to the study data.

7.5 Procedures to release data or specimens – N/A

7.6 Process for returning results - N/A

8.0 Statistical Plan

8.1 Sample size determination

Sample size was determined based on a review of prior studies that used the VAS as the main outcome tool. A total sample size of 147 was determined based on the number needed to detect a difference of 5 mm assuming a standard deviation of 10 mm in the VAS and when also considering a 15 % drop out rate. 147 total patients initially enrolled in the study would account for 64 patients per treatment arm (AH v AIBU).

8.2 Statistical methods

The daily average pain score (VAS) will be compared between AIBU and AH groups using either t-test or Wilcoxon test for each of the 6 days after the operation. The number of days till pain free will be compared between the two groups using survival techniques such as log-rank test. Chi-square tests will be used to compare treatment groups for categorical variables (satisfaction, change in pain regimen, adverse events). Level of significance will be set at $p < 0.05$.

Secondary statistical analysis will include multivariate analyses to determine which variables such as anatomic location, surgery performed, and perioperative medication will impact the daily average pain score or modify the effect of AIBU versus AH. These can be accomplished by adding these variables and their interaction with treatment groups in the regression model. As these are secondary analysis, any interesting findings will be subject to validation in future studies. We will also seek to determine which groups of patients, if any, will more frequently request to change to the hydrocodone arm during the study due to inadequate analgesia.

Any deviations from the previously described statistical plan will be described and justified in a protocol amendment.

9.0 Confidentiality, Privacy and Data Management

9.1 Confidentiality

9.1.1 Identifiers associated with data and/or specimens

9.1.1.1 Use of Codes, Master List

Patient Name, MRN #, Date of Birth, Phone number, and link to identifier code. A linking code list (identifiers will be linked to a unique code) will be kept in the study investigator's research office. Only research personnel will have access to the list.

9.1.2 Storage of Data and/or Specimens

All research data will be stored in the study investigator's research office for length of time required by federal regulations/funding source and then destroyed (minimum 3 years).

9.1.3 Access to Data and/or Specimens

Only research personnel will have access to the study data.

9.1.4 Transferring Data and/or Specimens – N/A

9.2 Privacy

Only the minimum necessary information will be requested for this study. All research data will be kept on a password-protected computer or in a locked filing cabinet and accessible only to the research personnel.

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

The research coordinator will complete the appropriate report form and logs; assist the principal investigator to prepare reports and notify the IRB and any applicable reporting agencies of all unanticipated problems / adverse events.

The research coordinator and principal investigator will confirm that all adverse events are correctly entered in the AE log; be available to answer any questions concerning AEs; notify the IRB and any applicable reporting agencies of unanticipated problems and AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

10.2 Data that are reviewed

Data to be reviewed includes the patient's diary (VAS, Likert scales, Pain Catastrophizing Scale, and PHQ questionnaire) as well as incidence of adverse effects, patient satisfaction, time to stopping medication, incidence of medication discontinuation, need for additional analgesics, surgery performed, propofol dose, fentanyl dose, surgery time, local anesthetic dose, local anesthetic composition, and perioperative NSAIDs. .

10.3 Method of collection of safety information

Data will be collected beginning after informed consent at time of enrollment through one –week postoperatively. All data will be collected at the patient's final visit (approximately two weeks post-operatively). Data will be collected via the patient's diary, phone script, and review of the medical record.

10.4 Frequency of data collection

Data collection begins immediately following informed consent through one-week post-operatively, with collection of all data completed at the patient's final visit (approximately 2 weeks post-operatively).

10.5 Individual's reviewing the data

All data will be reviewed by members of the research team at completion of study. Reporting of any adverse events will be reviewed as they occur.

10.6 Frequency of review of cumulative data

There will be no interim analysis in this study. The entire study period will be one week post-operatively where patients will be recording pain scores in their patient diaries. Adverse events will be reviewed as they occur.

10.7 Statistical tests

The daily average pain (VAS) will be compared between AIBU and AH groups using either t-test or Wilcoxon test for each of the 6 days after the operation. The number of days till pain free will be compared between the two groups using survival techniques such as log-rank test. Chi-square tests will be used to compare treatment groups for categorical variables (satisfaction, change in pain regimen, adverse events). Level of significant will be set at $p < 0.05$.

Secondary statistical analysis will include multivariate analyses to determine which variables such as anatomic location, surgery performed, and perioperative medication will impact the daily average pain score or modify the effect of AIBU versus AH. These can be accomplished by adding these variables and their interaction with treatment groups in the regression model. As these are secondary analysis, any interesting findings will be subject to validation in future studies. We w ill also seek to determine which groups of patients, if any, will more frequently request to change to the hydrocodone arm during the study due to inadequate analgesia.

Any deviation from the previously described statistical plan will be described and justified in a protocol amendment.

All analyses comparing the treatment groups will be conducted on an intention-to-treat basis. Two-tailed tests will be used at all times.

10.8 Suspension of research

There will be no stopping rules in this study, as all medications are FDA approved and safe for patient use.

If a patient, at any point in the post-operative course, demonstrates a significant adverse event related to the study medication (i.e. intractable nausea/vomiting), then they will have an opportunity to switch to the non-opioid pain regimen. If they are having pain that is not relieved with the AIBU regimen, they will have the opportunity to contact the study physician and obtain a prescription for oxycodone Anti-nausea medication will be prescribed as indicated. These patients will not be removed from the study, but will be included in a subgroup analysis. Study primary and secondary endpoints will continue to be monitored in a similar fashion.

11.0 Risks

The most common side effects associated with acetaminophen/hydrocodone include:

Nausea, vomiting, constipation, lightheadedness, dizziness, or drowsiness

Rare side effects/adverse events associated with acetaminophen/hydrocodone include but are not limited to:

Cardiovascular: Bradycardia, cardiac arrest, circulatory collapse, coma, hypotension

Central nervous system: Anxiety, dysphoria, euphoria, fear, lethargy, lightheadedness, malaise, mental clouding, mental impairment, mood changes, physiological dependence, sedation, somnolence, stupor

Dermatologic: Pruritus, rash

Endocrine & metabolic: Hypoglycemic coma

Gastrointestinal: Abdominal pain, constipation, gastric distress, heartburn, peptic ulcer, xerostomia

Genitourinary: Ureteral spasm, urinary retention, vesical sphincter spasm

Hematologic: Agranulocytosis, bleeding time prolonged, hemolytic anemia, iron deficiency anemia, occult blood loss, thrombocytopenia

Hepatic: Hepatic necrosis, hepatitis

Neuromuscular & skeletal: Skeletal muscle rigidity

Otic: Hearing impairment or loss (chronic overdose)

Renal: Renal toxicity, renal tubular necrosis

Respiratory: Acute airway obstruction, apnea, dyspnea, respiratory depression (dose related)

Miscellaneous: Allergic reactions, clamminess, diaphoresis

The most common side effects associated with ibuprofen include:

Dyspepsia, nausea, vomiting, diarrhea, abdominal pain, and flatulence

1% to 10% of patients may be at risk for these side effects:

Cardiovascular: Edema (1% to 3%)

Central nervous system: Dizziness (3% to 9%), headache (1% to 3%), nervousness (1% to 3%)

Dermatologic: Rash (3% to 9%), itching (1% to 3%)

Endocrine & metabolic: Fluid retention (1% to 3%)

Gastrointestinal: Epigastric pain (3% to 9%), heartburn (3% to 9%), nausea (3% to 9%), abdominal pain/cramps/distress (1% to 3%), appetite decreased (1% to 3%), constipation (1% to 3%), diarrhea (1% to 3%), dyspepsia (1% to 3%), flatulence (1% to 3%), vomiting (1% to 3%)

Otic: Tinnitus (3% to 9%)

<1% of patients may be at risk for these side effects:

(Limited to important or life-threatening): Acute renal failure, agranulocytosis, anaphylaxis, aplastic anemia, azotemia, blurred vision, bone marrow suppression, confusion, creatinine clearance decreased, duodenal ulcer, edema, eosinophilia, epistaxis, erythema multiforme, gastric ulcer, GI bleed, GI hemorrhage, GI ulceration, hallucinations, hearing decreased, hematuria, hematocrit decreased, hemoglobin decreased, hemolytic anemia, hepatitis, hypertension, inhibition of platelet aggregation, jaundice, liver function tests abnormal, leukopenia, melena, neutropenia, pancreatitis, photosensitivity, Stevens-Johnson syndrome, thrombocytopenia, toxic amblyopia, toxic epidermal necrolysis, urticaria, vesiculobullous eruptions, vision changes

The most common side effects associated with acetaminophen include:

Liver damage due to large doses, chronic use or concomitant use with alcohol or other drugs that also damage the liver. Chronic alcohol use may also increase the risk of stomach bleeding.

Rare side effects/adverse events associated with acetaminophen include but are not limited to:

Oral, Rectal: Frequency not defined:

Dermatologic: Skin rash

Endocrine & metabolic: Decreased serum bicarbonate, decreased serum calcium, decreased serum sodium, hyperchloremia, hyperuricemia, increased serum glucose

Genitourinary: Nephrotoxicity (with chronic overdose)

Hematologic & oncologic: Anemia, leukopenia, neutropenia, pancytopenia

Hepatic: Increased serum alkaline phosphatase, increased serum bilirubin

Hypersensitivity: Hypersensitivity reaction (rare)

Renal: Hyperammonemia, renal disease (analgesic)

I.V.:
>10%: Gastrointestinal: Nausea (adults 34%; children ≥5%), vomiting (adults 15%; children ≥5%)
1% to 10%:
Cardiovascular: Hypertension, hypotension, peripheral edema, tachycardia
Central nervous system: Headache (adults 10%; children ≥1%), insomnia (adults 7%; children ≥1%), agitation (children ≥5%), anxiety, fatigue, trismus
Dermatologic: Pruritus (children ≥5%), skin rash
Endocrine & metabolic: Hypervolemia, hypoalbuminemia, hypokalemia, hypomagnesemia, hypophosphatemia
Gastrointestinal: Constipation (children ≥5%), abdominal pain, diarrhea
Genitourinary: Oliguria (children ≥1%)
Hematologic & oncologic: Anemia
Hepatic: Increased serum transaminases
Local: Infusion site reaction (pain)
Neuromuscular & skeletal: Limb pain, muscle spasm
Ophthalmic: Periorbital edema

Respiratory: Atelectasis (children ≥5%), abnormal breath sounds, dyspnea, hypoxia, pleural effusion, pulmonary edema, stridor, wheezing

There is a risk of loss of confidentiality, but precautions will be taken to prevent this from happening.

Subjects will be assigned to a treatment program by chance. The treatment received may prove to be less effective or to have more side effects than the other research treatment(s) or other available treatments.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

There is no benefit to individual subjects. Subjects will play an important role in identifying a superior post-operative pain regimen in patients who will undergo similar surgical procedures following the study period.

12.2 Potential Benefits to Others

The results of this study will guide future treatment decisions. We seek to reduce unnecessary prescribing of opioid pain medications, if feasible, in order to prevent patients from having unwanted side effects and limit the overuse or abuse of these medications.

13.0 Sharing Results with Subjects - N/A

14.0 Economic Burden to Subjects

14.1 Costs

The acetaminophen/hydrocodone or acetaminophen/ibuprofen will be provided by the investigational drug pharmacy at no cost to subjects for the first week following surgery. A prescription will be provided for subjects that continue to need pain relief thereafter.

14.2 Compensation for research-related injury

It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

15.0 Number of Subjects

Approximately 150 people will take place in this research study at the Hershey Medical Center.

16.0 Resources Available

16.1 Facilities and locations

- Penn State Milton S. Hershey Medical Center, Bone & Joint Institute
- Hershey Outpatient Surgery Center

16.2 Feasibility of recruiting the required number of subjects – N/A

16.3 PI Time devoted to conducting the research - N/A

16.4 Availability of medical or psychological resources - N/A

16.5 Process for informing Study Team - N/A

17.0 Other Approvals

17.1 This study was approved by the PSHMC Scientific Review Committee on March 10, 2014, prior to IRB submission.

18.0 Subject Stipend and/or Travel Reimbursements - N/A

19.0 Multi-Site Research - N/A

20.0 Adverse Event Reporting

20.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

20.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

20.3 Unblinding Procedures

In most cases, the unblinding will be part of managing a serious adverse reaction, and will be reported with the serious adverse event. However, in cases were unblinding is not associated with a serious adverse event, such actions will be reported in a timely manner according to the timeline requirements for investigator reporting of adverse events to the IRB.

21.0 Study Monitoring, Auditing and Inspecting

21.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g. source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g. pharmacy, diagnostic laboratory, etc.).

21.2 Safety Monitoring

The **Principal Investigator** will confirm that all adverse events (AE) are correctly entered into the AE case report forms by the coordinator; be available to answer any questions that the coordinators may have concerning AEs; and will notify the IRB, FDA, sponsor and/or DSMB of all applicable AEs as appropriate. All assessments of AEs will be made by a licensed medical professional who is an investigator on the research.

The **research coordinator** will complete the appropriate report form and logs; assist the PI to prepare reports and notify the IRB, FDA, and/or DSMB of all Unanticipated Problems/SAE's.

22.0 References

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4. Emergency department visits involving nonmedical use of selected prescription drugs—United States, 2004–2008. Cai R, Crane E, Poneleit K, Paulozzi L. MMWR Morb Mortal Wkly Rep 2010:59:705–709.

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7. Severity and impact of pain after day-surgery. Beauregard L, Pomp A, Choiniere M. Can J Anaesth. 1998 Apr; 45(4): 304-11.

8. Analysis of statistical tests to compare visual analog scale measurements among groups. Dexter F, Chestnut DH. Anesthesiology 1995; 82:896-902.

23.0 Appendix – N/A