HRP-592 - Protocol for Human Subject Research with Use of Test Article(s)

Protocol Title:

The Efficacy of Local Anesthetics to Reduce Shoulder Pain Post-Steroid Injections

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1.0 Objectives

1.1 Study Objectives

The specific aim of this prospective study is to determine whether local anesthetics prior to subacromial steroid injections reduce pain and consequently if they are cost-effective in the treatment for shoulder pathology.

Hypothesis: Patients undergoing subacromial steroid injections without local anesthetics will have significantly increased pain than those who do use anesthetics prior to undergoing the injections.

Standard of Care: Giving local anesthetics in addition to the steroid injection. Both of these treatment options are available to patients even if they are not undergoing the study.

1.2 Primary Study Endpoints

The primary endpoint is to determine whether local anesthetics prior to subacromial injections reduce pain, quantified on a 1-10 pain scale.

1.3 Secondary Study Endpoints

Not applicable

2.0 Background

2.1 Scientific Background and Gaps

Shoulder pain is a common problem that can be estimated to be prevalent in up to 15 percent of the patient population registered to general practices and is second only to back pain in patients seeking treatment for musculoskeletal issues in the primary care setting. As a common source of distress, shoulder pain contributes significantly to health care costs. In the US, it directly attributes $7 billion to costs in the year 2000, with a mean cost per care episode of $1667 and $3011 for outpatient and hospital-based settings, respectively.

Rotator cuff disease due to impingement, tendonitis or bursitis is a frequent cause of shoulder pain and dysfunction. Initial treatment consists of a conservative approach of activity modification, oral nonsteroidal anti-inflammatory drugs (NSAIDs) and supervised physical therapy. However, if the patients' symptoms persist, subacromial injections of a local anesthetic such as lidocaine, and a corticosteroid may be indicated as a sequential treatment option.

The steroid injection itself can be a painful process, so administering a local anesthetic prior to the steroid injection is thought to mitigate pain or reduce possible discomfort during and immediately following the procedure. A survey of 835 rheumatologists found that 74.7 percent of those who trained after 1985 combined lidocaine and steroids for soft tissue and joint injections. Though there is evidence advocating for the benefits of combining local anesthetics and corticosteroids for the treatment of subacromial pathologies, it is not conclusive whether local anesthesia prior to steroid injections significantly enhances the pain relieving effect of steroids. Should local anesthesia not have a significant impact on the patient's pain intensity, then the use of corticosteroids alone could potentially result in reduced costs in care.

2.2 Previous Data

Not applicable

2.3 Study Rationale

Though there is evidence advocating for the benefits of combining local anesthetics and corticosteroids for the treatment of subacromial pathologies, it is not conclusive whether local anesthesia enhances the pain relieving effect of steroids. Should local anesthesia not have a significant impact on the patient's pain intensity as detected by self-assessment via pain scale, then the use of corticosteroids alone could potentially result in reduced costs in care.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

- Adults aged 18-70
- Shoulder pain lasting at least 4 weeks
- Inability to use arm with restriction of movement and loss of full function.
- Able to understand study and provide voluntary, written informed consent

3.2 Exclusion Criteria

- Less than 18 or greater than 70 years old
- Contraindications of previous injections and previous shoulder surgery
- Unable to understand consent form (in the opinion of the PI)
- Non-English speaking individuals
- Medication contradictions to lidocaine, corticosteroids

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

The subjects may withdraw at any point prior to the steroid injection. Additionally, they may elect not to participate in rating their pain right after they receive the injections. Subjects who withdraw and prefer to have a lidocaine injection, may still participate in rating their pain after the lidocaine + steroid injection. Any subject who is getting steroid injections for shoulder pain may replace subjects who withdrew.

4.0 Recruitment Methods

4.1 Identification 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.

4.2 Recruitment process

If steroid injections are indicated for subjects with shoulder pathologies who come to the Orthopedics department, they will be asked to participate in the study.

4.3 Recruitment materials

Not applicable.

4.4 Eligibility/screening of subjects

Adult patients presenting to the Bone & Joint Institute will be evaluated as part of standard of care. Those subjects meeting eligibility requirements will be presented with the opportunity to participate in the research study by a member of the research team.

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 investigator's 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. Subjects will be informed they do not have to participate in this research study. They will be informed that their current and future care at the PSHMC will not be affected by their decision to accept or decline participation.

5.1.2 Waiver or alteration of the informed consent requirement

Requesting a waiver to screen for eligibility prior to the informed consent document being signed.

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 (Implied consent, Verbal consent, etc.)

Not applicable.

5.3 Consent – Other Considerations

5.3.1 Non-English Speaking Subjects

Not applicable.

5.3.2 Cognitively Impaired Adults

5.3.2.1 Capability of Providing Consent

Not applicable.

5.3.2.2 Adults Unable To Consent

Not applicable.

5.3.2.3 Assent of Adults Unable to Consent

Not applicable.

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

5.3.3.1 Parental Permission

Not applicable.

5.3.3.2 Assent of subjects who are not yet adults

Not applicable.

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

☐ **Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study.** *[Mark all parts of sections 6.2 and 6.3 as not applicable]*

☒ **Authorization will be obtained and documented as part of the consent process.** *[If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]*

☒ **Partial waiver is requested for recruitment purposes only (Check this box if patients' medical records will be accessed to determine eligibility before consent/authorization has been obtained).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Full waiver is requested for entire research study (e.g., medical record review studies).** *[Complete all parts of sections 6.2 and 6.3]*

☐ **Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained).** *[Complete all parts of sections 6.2 and 6.3]*

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure

Information is included in the "Confidentiality, Privacy and Data Management" section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers

The list will be destroyed upon completion of the study.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI

Patient identifiers are necessary for identification and review of the patient's medical records. A unique study code number will be used for identification of study data. The linking list will be destroyed upon completion of the study.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization

Waiver is required to screen for eligibility.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.

The research team will collect only information essential to the study and in accord with the 'Minimum Necessary' standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design

The trial is a randomized, prospective study. Patients undergoing steroid injections will be randomized into three groups:

- Group A=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine
- Group B=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine after 2 ml in subcutaneous injection
- Group C=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine after applying ethyl chloride spray for 3 seconds

Patients' pre and post-procedural pain as well as the pain of the injection itself will be assessed with a visual pain scale and the results will be analyzed for statistical significance.

7.2 Study Procedures

The study consists of one visit in clinic during their standard of care 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.

After obtaining informed consent, the patient will be asked to rate their current pain on a visual 1-10 point scale before injection. They will then be randomized to one of three treatment groups. The study investigator will randomly draw a sealed envelope containing one of the three treatment groups. The sealed envelopes will be stored in a secure area within the clinic practice site. The subject will be randomized to one of three groups:

- Group A=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine
- Group B=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine after 2 ml in subcutaneous injection
- Group C=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine after applying ethyl chloride spray for 3 seconds

The needle size will be standardized:

- 25 gauge needle for the subcutaneous lidocaine injection
- 21 gauge needle for the combined injection

Immediately after and ten minutes after the injection is completed, they will also be asked to rate pain on the same 1-10 visual scale.

No long-term follow-up will be conducted.

7.3 Duration of Participation

The subject will only be participating from the time they receive the injection to when they indicate the level of pain on the pain scale; i.e. they will be seen in the clinic site once.

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

7.4.1 Description

All of these drugs and listed dosages are currently FDA approved and considered standard of care.

Lidocaine hydrochloride injection: USP is sterile, nonpyrogenic, aqueous solution that contains a local anesthetic agents and is administered parenterally by injection. It is FDA approved and indicated for production of local or regional anesthesia by infiltration techniques such as steroid injections

Ethyl Chloride spray: a vapocoolant (skin refrigerant) intended for topical application to control pain associated with injections. It is FDA approved.

Kenalog Injection (triamcinolone acetonide): a synthetic glucocorticoid corticosteroid with anti-inflammatory action. This formulation is FDA approved for intramuscular and intra-articular use only

7.4.2 Treatment Regimen

- Group A=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine
- Group B=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine after 2 ml in subcutaneous injection
- Group C=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine after applying ethyl chloride spray for 3 seconds

7.4.3 Method for Assigning Subject to Treatment Groups

The subjects will be randomized by drawing a treatment group from a sealed envelope.

7.4.4 Subject Compliance Monitoring

Subject compliance monitoring is not necessary as there will only be 1 treatment protocol for this study.

7.4.5 Blinding of the Test Article

Not applicable.

7.4.6 Receiving, Storage, Dispensing and Return

7.4.6.1 Receipt of Test Article

The compounds are used in the Bone & Joint Institute as standard of care.

7.4.6.2 Storage

The compounds will be stored at room temperature in the Bone & Joint Institute as per standard of care instructions.

7.4.6.3 Preparation and Dispensing

The study drug will be prepared by an investigator following standard of care protocols. Subject randomization will be performed prior to dispensing of any study drugs. Once the needle is in the proper location, the solution of steroid will be injected slowly. A 2 mL solution of 1% lidocaine without epinephrine will be injected subcutaneously prior to the steroid injection if the subject is randomized into group B. If subject is in group C, ethyl chloride spray will be applied for 3 seconds prior the steroid injection.

7.4.6.4 Return or Destruction of the Test Article

The study drug will be disposed of in clinic following standard procedure for disposal of needles.

7.4.6.5 Prior and Concomitant Therapy

No prior and concomitant therapy will be collected.

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Approximately 150 subjects (50 per treatment arm).

8.2 Sample size determination

The primary endpoint is the change in visual pain scale from baseline (pre-injection) to follow up (0- and 10-minutes after injection). The study contains 3 groups:

- Group A=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine
- Group B=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine after 2 ml in subcutaneous injection
- Group C=Injection of 1 ml of 40 mg Kenalog combined with 4 ml of 1% lidocaine after applying ethyl chloride spray for 3 seconds

Comparisons will be made for the primary outcome between all 3 study groups: Group B vs. A; Group C vs. A; and Group C vs. B. Thus, we used a Bonferonni corrected Type I error rate for 3 tests to determine the sample size required for 80% power.

A total of N=50 patients per group (N=150 total) yields 80% power for a t-test conducted at the Bonferonni corrected Type I error rate of 1.7%, which holds the overall Type I error rate for the study at 5%, to detect a 2-point difference in pain scale changes between groups, assuming a common standard deviation of 3 points. The standard deviation was calculated after making a conservative assumption that visual pain scores would be uniformly distributed across 0-10.

8.3 Statistical methods

A one-way analysis of variance (ANOVA) model will be used to test whether changes in pain scores differ by study group. The outcome variable for the model will be the change in pain scores, and the independent variables will be indicators of each study group. The overall F-test for study group will be used to determine whether study groups differ with respect to mean changes in visual pain scores. If the F-test is significant, then follow up tests comparing each set of groups will be conducted using the Bonferonni-adjusted Type I error rate of 1.7%.

9.0 Confidentiality, Privacy and Data Management

See the Research Data Plan Review Form

9.1 Confidentiality

9.1.1 Identifiers associated with data and/or specimens

9.1.1.1 Use of Codes, Master List

9.1.2 Storage of Data and/or Specimens

9.1.3 Access to Data and/or Specimens

9.1.4 Transferring Data and/or Specimens

9.2 Subject Privacy

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 incidence of adverse effects collected data.

10.3 Method of collection of safety information

Not applicable.

10.4 Frequency of data collection

Not applicable.

10.5 Individuals reviewing the data

Not applicable.

10.6 Frequency of review of cumulative data

There will be an interim analysis in this study after 50% of patients are enrolled and have completed all study requirements. Adverse events will be reviewed as they occur.

10.7 Statistical tests

A one-way analysis of variance (ANOVA) model will be used to test whether changes in pain scores differ by study group. The outcome variable for the model will be the change in pain scores, and the independent variables will be indicators of each study group. The overall F-test for study group will be used to determine whether study groups differ with respect to mean changes in visual pain scores. If the F-test is significant, then follow up tests comparing each set of groups will be conducted using the Bonferonni-adjusted Type I error rate of 1.7%.

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 course of their treatment demonstrates a significant adverse event related to the study medication, then the adverse event will be addressed.

11.0 Risks

Loss of confidentiality will be minimized as the research team will only have access to the research data and all information will be kept in a shared research file in Hersheymed.net on a password-protected computer, in the Orthopaedic research office locked filing cabinets.

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.

Ethyl Chloride - freezing may alter skin pigment

Kenalog - joint tissue damage, swelling in your veins, allergic reaction, infection, increase in blood sugar.

Lidocaine - itching, rash, swelling of the skin, pain at the injection site, numbness, dizziness, and allergic reactions. Rarely, when injected into the blood stream lidocaine can cause confusion, coma, seizures, respiratory arrest, heart beat irregularities, and toxicities; however, in this study lidocaine will not be injected into your bloodstream.

Nerve damage for a period of time after the injection.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

The treatment received may prove to be less or more effective or to have more side effects than the other research treatment or other available treatments.

12.2 Potential Benefits to Others

The potential benefit may be a way to reduce healthcare cost by decreasing the over-utilization of unnecessary materials/procedures. The results of this study will guide future treatment decisions.

13.0 Sharing Results with Subjects

The results will not be shared.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Not applicable

15.0 Economic Burden to Subjects

15.1 Costs

All procedures are standard of care and will be billed to insurance. The subjects will be liable for any co-pays, deductibles, or other fees associated with their insurance policy.

15.2 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.

16.0 Resources Available

16.1 Facilities and locations

Research will be conducted at the Penn State Hershey Bone and Joint Institute.

16.2 Feasibility of recruiting the required number of subjects

The Penn State Hershey Bone and Joint Institute cares for many patients with shoulder problems that need to get steroid injections to relieve pain. The PI does 1-2 injections per clinic and has 2 clinics a week. After 52 weeks the sample size would be around 150, which is above the 138 subject sample size calculated by the edited stats analysis.

16.3 PI Time devoted to conducting the research

Dr. Gallo has research time determined in his agreement with the Orthopaedic Department.

16.4 Availability of medical or psychological resources

If any medical or psychological care is needed for a subject, they will be directed for standard of care treatment at Hershey Medical Center.

16.5 Process for informing Study Team

All team members have been given copies of all IRB approved documents – protocol, data collection tools, approval memos, etc. The team meets regularly to review data and any updates.

17.0 Other Approvals

17.1 Other Approvals from External Entities

Not applicable.

17.2 Internal PSU Committee Approvals

Check all that apply:

☐ Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of the Use of Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available on the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/forms

☐ Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

☐ Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

☐ Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

☐ Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload the Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available on the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/forms

☐ IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

☒ Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

18.1 Communication Plans
not applicable

18.2 Data Submission and Security Plan
not applicable

18.3 Subject Enrollment
not applicable

18.4 Reporting of Adverse Events and New Information
not applicable

18.5 Audit and Monitoring Plans
not applicable

19.0 Adverse Event Reporting

19.1 Adverse Event Definitions

Adverse event	Any untoward medical occurrence associated with the use of the drug in humans, whether or not considered drug related
Adverse reaction	Any adverse event caused by a drug
Suspected adverse reaction	Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. Suspected adverse reaction implies a lesser degree of certainty about causality than "adverse reaction". • *Reasonable possibility.* For the purpose of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event.
Serious adverse event or Serious suspected adverse reaction	Serious adverse event or Serious suspected adverse reaction: An adverse event or suspected adverse reaction that in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate

	medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
Life-threatening adverse event or life-threatening suspected adverse reaction	An adverse event or suspected adverse reaction is considered "life-threatening" if, in the view of either the Investigator (i.e., the study site principal investigator) or Sponsor, its occurrence places the patient or research subject at immediate risk of death. It does not include an adverse event or suspected adverse reaction that had it occurred in a more severe form, might have caused death.
Unexpected adverse event or Unexpected suspected adverse reaction.	An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure, general investigational plan, clinical protocol, or elsewhere in the current IND application; or is not listed at the specificity or severity that has been previously observed and/or specified.

For device studies, incorporate the following definitions into the below responses, as written:	
Unanticipated adverse device effect	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or IDE application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

19.2 Recording of Adverse Events

All adverse events (serious or non-serious) and abnormal test findings observed or reported to study team believed to be associated with the study drug(s) or device(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.

An abnormal test finding will be classified as an adverse event if one or more of the following criteria are met:

- The test finding is accompanied by clinical symptoms
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy

NOTE: Simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an adverse event.

- The test finding leads to a change in study drug dosing or discontinuation of subject participation in the clinical research study

The test finding is considered an adverse event by the investigator.

19.3 Causality and Severity Assessments

The investigator will promptly review documented adverse events and abnormal test findings to determine 1) if the abnormal test finding should be classified as an adverse event; 2) if there is a reasonable possibility that the adverse event was caused by the study drug(s) or device(s); and 3) if the adverse event meets the criteria for a serious adverse event.

If the investigator's final determination of causality is "unknown and of questionable relationship to the study drug(s) or device(s)", the adverse event will be classified as associated with the use of the study drug(s) or device(s) for reporting purposes. If the investigator's final determination of causality is "unknown but not related to the study drug(s) or device(s)", this determination and the rationale for the determination will be documented in the respective subject's case history.

19.4 Reporting of Adverse Reactions and Unanticipated Problems to the FDA

19.4.1 Written IND/IDE Safety Reports
Not applicable.

19.4.2 Telephoned IND Safety Reports – Fatal or Life-threatening Suspected Adverse Reactions
Not applicable.

19.5 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.

19.6 Unblinding Procedures
Not applicable.

19.7 Stopping Rules
The study will be stopped if one method is found to be clearly superior or if there are adverse reactions.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Study Monitoring Plan

20.1.1 Quality Assurance and Quality Control
Study data will be recorded and kept in a shared folder on hersheymed.net in a restricted file accessible by investigators on the study. The Principal Investigator will oversee all aspects of the study including monitoring.

20.1.2 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.

The Monitor will confirm that the AEs are correctly entered into the case report forms. The Monitor will also confirm that the adverse events are consistent with the source documents and are reported to the appropriate regulatory bodies as required.

20.2 Data and/or specimens being stored
Regulatory work, paper copies of data, electronic copies of data.

20.3 Location of storage
Paper regulatory work and data will be kept at 30 Hope dr. suite 2900 in locked files.
Electronic data will be kept in hersheymed.net investigator accessible shared files.

20.4 Duration of storage

Data will be kept at least 6 years, and disposed as per the PI.

20.5 Access to data and/or specimens

Data will only be accessible by investigators listed on the study.

20.6 Procedures to release data or specimens

not applicable

20.7 Process for returning results

not applicable

21.0 References

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3. Burbank, K, Stevenson J, Czarnecki G, Dorfman J. Chronic Shoulder Pain: Part II. Treatment. Am Fam Physician. 2008 Feb 15;77(4):493-497.

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5. Centeno LM, Moore ME. Preferred intraarticular corticosteroids and associated practice: a survey of members of the American College of Rheumatology. Arthritis Care Res. 1994;7(3):151–155.

6. Arroll, B. and F. Goodyear-Smith (2005). "Corticosteroid injections for painful shoulder: a meta-analysis." Br J Gen Pract 55(512): 224-228.

7. Yu, C. M., et al. (2006). "Subacromial injections of corticosteroids and xylocaine for painful subacromial impingement syndrome." Chang Gung Med J 29(5): 474-479.

8. Gaujoux-Viala, C., et al. (2009). "Efficacy and safety of steroid injections for shoulder and elbow tendonitis: a meta-analysis of randomised controlled trials." Ann Rheum Dis 68(12): 1843-1849

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