PennState

HRP-591 - Protocol for Human Subject Research

Protocol Title:

Clinical Outcomes Following Randomization of Steroid Concentration in Patients with Glenohumeral Osteoarthritis

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Version Date:

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Clinicaltrials.gov Registration #:

Not Applicable

Important Instructions for Using This Protocol Template:

1. Add this completed protocol template to your study in CATS IRB (http://irb.psu.edu) on the "Basic Information" page, item 7.
2. This template is provided to help investigators prepare a protocol that includes the necessary information needed by the IRB to determine whether a study meets all applicable criteria for approval.
3. **Type your protocol responses below the gray instructional boxes of guidance language. If the section or item is not applicable, indicate not applicable.**
4. **For research being conducted at Penn State Hershey or by Penn State Hershey researchers only, delete the instructional boxes from the final version of the protocol prior to upload to CATS IRB (http://irb.psu.edu). For all other research, do not delete the instructional boxes from the final version of the protocol.**
5. When making revisions to this protocol as requested by the IRB, please follow the instructions outlined in the Study Submission Guide available in the Help Center in CATS IRB (http://irb.psu.edu) for using track changes.

If you need help…	
University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Fax number: 717-531-3937 Email: irb-hspo@psu.edu

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1.0 Objectives

1.1 Study Objectives

The purpose of this study is to determine the most effective intraarticular steroid dose for the treatment of glenohumeral osteoarthritis. We aim to randomize patients into low, medium, and high dose groups of injectable corticosteroids as these doses are typically used in the standard of care for our patients. To date there has been no study to evaluate which dose is most efficient with the fewest side effects for glenohumeral osteoarthritis. Our objectives will be to provide ultrasound guided intraarticular glenohumeral injections of these randomized concentrations and to evaluate pain and function before and following injection with the Shoulder Pain and Disability Index (SPADI). We hypothesize that the low dose steroid will provide equivalent improvement of the pain and function to the medium and high doses, while minimizing side effects.

1.2 Primary Study Endpoints

- Change in Overall SPADI scores at baseline compared to 2,4, and 6 months.
- Adverse reactions to the steroid

1.3 Secondary Study Endpoints

- Rate of Shoulder Arthroplasty following injection at 1 year
- SPADI scores for those receiving Shoulder Arthroplasty at 1 year

2.0 Background

2.1 Scientific Background and Gaps

Osteoarthritis (OA) affects 54.4 million US adults and 23.7 million (43.5%) have arthritis-attributable activity limitation[1]. As the condition progresses, pain and functional disability increase. Patients usually begin treatment with conservative measures including physical therapy and administration of nonsteroidal anti-inflammatory drugs before obtaining a corticosteroid injection[2]. Corticosteroid injections have a patient-specific duration that often provide relief for a month before the effects begin to taper with most individuals returning to baseline by 2-3 months post injection[3,4].

Unfortunately, data on intraarticular injections is not robust and primarily focused on hip, knee, and disease processes rather than the glenohumeral joint[6-8]. For example, steroid concentrations have been studied in adhesive capsulitis, where 20 and 40mg of triamcinolone acenotide were used with no statistical significance between the two[6]. When a placebo was added, both doses were better than the placebo, but once again no difference was seen between the two steroid concentrations[7]. Another study, looking at knee osteoarthritis, found that high dose steroids had a larger effect on duration[8], but other studies have shown no difference in duration between the 40mg and 80mg concentration of triamcinolone acetonide[9].

Intraarticular injections do have adverse effects. Similar to steroids taken orally or intravenously, intraarticular injections have a similar side effect profile. Fortunately, intraarticular injections are localized, by the nature of the procedure, and the chances of experiencing a significant side effect is rare[10,11]. The most common side effects are steroid flare, allergic reaction, facial erythema, hypo- pigmentation, fat pad necrosis, cutaneous atrophy, and a transient increase in blood glucose[11]. Some of the rare side effects have been seen in case reports include idiopathic central serous chorioretinopathy, decrease in breast milk production, sepsis, tendon rupture, and cataracts[11]. In addition, the administration of steroid injections are limited to being done every three months due to risk of weakening tendons, and acceleration of cartilage loss[11,12].

There is a void of literature for understating the ideal injectable steroid concentrations in glenohumeral osteoarthritis. Because of this, providers who perform intraarticular injections tend to perform them based on prior training experience or anecdotal evidence[13]. We aim to evaluate the ideal steroid concentration that will maximize treatment effect for glenohumeral osteoarthritis, but at the same time minimize side effects, and better train our future providers.

2.2 Previous Data

Not Applicable

2.3 Study Rationale

There have been no studies to date examining the optimal steroid concentration for injections of the glenohumeral joint for osteoarthritis. This is important because corticosteroid injections are not without risk. Better patient care hinges on the correct balance between an effective dose of steroid and minimizing potential adverse effects. Current practice is based completely on expert opinion and standard of care rather than scientific evidence.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria

- An X-ray with Radiographic evidence of OA
- 18 years of age or older
- Clinical diagnosis established due to symptoms that will include pain attributed to glenohumeral osteoarthritis, pain with range of motion, and/or functional limitations longer than 3 months.

3.2 Exclusion Criteria

- Previous guided steroid injection of the glenohumeral joint within 3 months
- Previous diagnosis of inflammatory arthritis, rotator cuff tear, or immunocompromised
- Previous shoulder surgery
- Allergy to steroid or lidocaine
- A Kellgren and Lawrence classification of 1 or less on radiograph
- Non-English Speaking
- Inability to provide informed consent

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 failure of subject to adhere to protocol requirements, or withdrawal of subject consent.

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. The new data will be recorded and analyzed as would any other new enrollee.

4.0 Recruitment Methods

4.1 Identification of subjects

Patients are normally scheduled for ultrasound guided injections as part of their normal care following referral. A member of the research team will review the schedules of the physician investigators who provide these injections to identify patients scheduled for ultrasound guided glenohumeral joint injections and pre-screen for eligibility.

4.2 Recruitment process

Potential candidates may be contacted via telephone prior to the scheduled appointment to determine interest in the study. If a patient expresses interest in the study a member of the research team will meet with the patient at their scheduled clinic appointment and informed consent will be obtained. If a potential patient is unable to be reached prior to the scheduled appointment, the study opportunity will be presented to the patient at the time of the clinic appointment.

4.3 Recruitment materials

Phone Script

4.4 Eligibility/screening of subjects

The clinic schedules of the investigators performing the injections will be reviewed to identify potential patients. A review of the medical record for inclusion and exclusion criteria will be completed to determine eligibility. This study is asking for waiver of authorization for the use of PHI to pre-screen potential subjects for eligibility.

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

- After the potential subject express interest in participating, the formal written consent process will occur. Written consent will occur on the day of the scheduled outpatient clinic visit for the ultrasound guided injection.

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 and ask any questions they may have. The researcher obtaining consent will review the consent form in entirety and will clearly indicate that participation is voluntary. The consent process will occur in a private setting and will be administered by a member of the research team who is not the treating physician. Consent will be obtained in accordance with principles of GCP and ICH guidelines.

5.1.2 Waiver or alteration of the informed consent requirement

Requested for the purpose of pre-screening medical records and patients schedules for eligibility.

5.2 Consent Documentation

5.2.1 Written Documentation of Consent

A member of the research team will assist in the explanation and obtaining written consent. A copy of the signed consent will be given to the patient and a copy will be placed in the medical record.

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

All SPADI data will be entered into Redcap with each patient receiving a patient identifier prior to being entered. All paper copies will be destroyed at the completion of the study and will stored in the locked office of the research coordinator until that time.

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

PHI is needed for identification of patients and determination of eligibility. 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

The study team would be unable to identify the appropriate patients to be included in this research study.

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

This is a prospective, randomized, three-arm, double-blind clinical trial comparing steroid concentrations in patients undergoing intraarticular glenohumeral joint injections.

7.2 Study Procedures

7.2.1 Pre-Clinic appointment

- A member of the research team will review the weekly clinic schedules of the contributing physicians to identify patients scheduled for a glenohumeral joint ultrasound guided injection. Patients will be pre-screened for eligibility by reviewing the medical record. The patients will need to meet the inclusion criteria with radiographic evidence of glenohumeral OA within the last year, 18 years or older, and will have already been evaluated by the referring physician and a clinical diagnosis established due to symptoms that will include pain attributed to glenohumeral osteoarthritis, pain with range of motion, and/or functional limitations longer than 3 months. The medical record will also be reviewed for exclusion criteria including previous guided steroid injection of the glenohumeral joint within 3 months, previous diagnosis of inflammatory arthritis, rotator cuff tear, or immunocompromised. Finally a previous shoulder surgery and allergy to steroid or lidocaine will exclude the patient. Patients meeting pre-screening criteria will be contacted via phone call and presented with the study opportunity. Patients will be asked a series of questions to assess eligibility based on whether they are English speaking and if they are able to provide informed consent. For patients expressing interest in the study, arrangements will be made for a member of the research team to meet with the patient at their scheduled clinic appointment where the full consent discussion will occur.

- Potential patients who were unable to be reached prior to their scheduled clinic visit will be met with by a member of the research team at the time of the clinic appointment and presented with the study opportunity. Patients expressing interest in the study will be assessed for eligibility based on the inclusion exclusion criteria and informed consent will be obtained.

  Once it has been determined that the patient is interested in participation and has met all inclusion/exclusion criteria thus far there will be one final step in accessing eligibility. The patient will be excluded if they have a Kellgren and Lawrence classification of 1 or less on radiograph. In order to make this assessment the research coordinator will contact our musculoskeletal radiologist who is a contributor to this project. They will then review the radiographs of the patient to make this assessment. If the patient meets the radiographic criteria they will be deemed eligible for the study.

7.2.2 Clinic appointment

A member of the research team will meet with the patient. The consent will be read and reviewed with the patient. After obtaining informed consent, the patient will be asked to complete the SPADI. This will be completed on paper and entered in to the REDCap database by a member of the research team. Patients will be asked questions regarding nicotine use, pain relievers use 24 hours prior to the injection, recent therapies for shoulder pain, and dominant arm. This data will be recorded in the research records. The coordinator will randomize the patient. The patient will be randomized into one of three study arms 1) 20 mg Triamcinolone with 3 cc of 1% Lidocaine, 2) 40 mg Triamcinolone with 3cc of 1% Lidocaine, or 3) 80mg Triamcinolone with 3cc of 1% Lidocaine. The injection will be prepared by a non-blinded investigator based on the study arm selected following standard of care protocols. Standard clinic protocol involves applying a patient label to the syringe. To assist with the blinding process, an additional label will be applied to the body of the syringe to ensure the volume of the syringe cannot be determined.

For the actual injection we will be using patients from 3 physicians who are investigators for this study. The same 3 physicians will administer the injection to their individual patients. Each of these investigators have performed a minimum of 800 injections and will be using the exact same methodology for providing the Ultrasound Guided injection. Since the injections will be performed under guidance and the approach of the injection will be identical we anticipate minimal operator effect on our study results.

An ultrasound unit will be used to identify the Glenohumeral joint with the patient in a lateral recumbent position. A posterior approach will be utilized to access the Glenuhumeral space. The joint will be scanned and a marking pen will be used to mark the area of approach. The skin and probe will then be sterilized. The probe will then be replaced on the previously marked position and a 22 gauge spinal needle will used to direct the injection into the glenohumeral space. The needle will be visualized throughout the procedure. Images will be taken of the joint before the injection, while the needle is in the joint, and post injection. They will be saved and uploaded into the medical record. Pre and post pain levels will be elicited from patient. The patient will be blinded to the study arm selected.

7.2.3 Post-Clinic appointment

Patients will be contacted via telephone at 2 weeks to determine if any significant adverse outcomes have occurred. Patients will be contacted at 2 months, 4 months, and 6 months following the injection by email and/or phone call for completion of the SPADI and assessment of any adverse events that may have occurred as a result of the injection. Patients will also be asked what, if any, pain medications have been used in the month prior to the phone call. Patients will be given the option to complete the SPADI using the REDCap system or on paper. Patients wishing to complete the survey online will be emailed a link to access REDCap. A paper version of the survey will be mailed to the patient if that is their preferred method. A self-addressed stamped envelope will be included with the mailings.
If the patient perceives that they have experienced an adverse effect the research coordinator will make a detailed record of the patient experience and the PI of the study will be contacted. .

At 12 months following the initial injection, in addition to a chart review, the patient will be contacted to determine the outcome of their shoulder pain and determine if the patient underwent any additional procedures and/or surgeries to the shoulder.

7.3 Duration of Participation

Patients will be followed for 1 year following the injection

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects

Total number of subjects will be 171 allowing for 10% loss to follow-up.

8.2 Sample size determination

This is a three arm trial comparing three different doses of steroid (20mg, 40mg, 80mg) in patients with glenohumeral arthritis. The primary endpoint is change in overall pain score on the SPADI at two, four, and six months from baseline. The sample size is determined based on assuming a minimal clinically meaningful difference in the 20mg vs 80mg groups as well as conducting non-inferioriorty tests in the 20mg vs 40mg and 40mg vs 80mg groups. Let d1, d2, and d3 be the average change in overall pain scale for the three different doses (low, medium, high). For the first part, in the 20mg vs 80mg groups, we wish to have sufficient statistical power based on the assumption of a moderate Cohen effect size of .5 (e.g. differences of 40 vs 20 with a standard deviation of 40). This requires a sample size 51 per group based on a two-sided 80%-power 5%-level t-test. For the non-inferiority test, we assume d1, d2, and d3 are 40, 36, and 32 (so d3-d2=d2-d1=4) with a standard deviation of 20. Allowing for a non-inferiority margin of 15 (so that differences less than 15 are deemed clinically non-inferior), a sample size of 52 per group based on an 80%-power 2.5%-level (since there are two tests) non-inferiority test (http://powerandsamplesize.com/Calculators/Compare-2-Means/2-Sample-Non-Inferiority-or-Superiority). Allowing for 10% loss to follow-up yields a final sample size calculation of **57 per group for each of the three groups**.

8.3 Statistical methods

The primary endpoint is change from baseline of the shoulder pain and disability index (SPADI). The low dose and high dose changes will be analyzed with a two-sided two-sample t-test. Noninferiority tests with a margin of .5 will be used to test for a clinically meaningful difference between 20mg and 40mg doses and the 40mg and 80mg doses. The three groups will be summarized with descriptive statistics and univariate statistical tests using analysis of variance for normally distributed continuous variables, Kruskal-Wallis test for non-normally distributed continuous variables, and the Fisher's exact test for categorical variables. The demographic data and SPADI data will be analyzed accordingly. All statistical analyses, graphics, and reports will be prepared following best practices in conducing reproducible research in statistics utilizing various software packages built around the R software platform. Arthur Berg, Ph.D., Associate Professor, will serve as the Biostatistician for this study.

9.0 Confidentiality, Privacy and Data Management

9.1 Confidentiality

See the Research Data Plan Review Form

10.0 Data and Safety Monitoring Plan

10.1 Periodic evaluation of data

The research coordinator will complete the appropriate report form and logs, and assist the principal investigator in preparing reports and notifying 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 AE's as appropriated. All assessments of AEs will be made by Dr Robert Gallo, MD a licensed medical professional who is an orthopedic surgeon and specializes in the treatment of shoulder injuries.

10.2 Data that are reviewed

Patients' overall health and physical function will be reviewed.

10.3 Method of collection of safety information

Safety information will be collected by phone interview during the follow up phone calls as well as review of the electronic medical record.

10.4 Frequency of data collection

Data will be collected beginning after informed consent at time of enrollment through 12 months post-injection. Adverse events will be collected as they occur.

10.5 Individuals reviewing the data

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

10.6 Frequency of review of cumulative data

There will be an interim analysis after 25% of patients are enrolled. Adverse events will be reviewed as they occur.

10.7 Statistical tests

Not Applicable

10.8 Suspension of research

Not Applicable

11.0 Risks

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

Other risks include those inherent to all steroid injections. These include pain and swelling at the site of injection, skin discoloration, increase in blood glucose, infection, and allergic reaction.

Risk of randomization

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects

There is no direct benefit to patients participating in this study.

12.2 Potential Benefits to Others

By finding the ideal concentration does of steroid to inject in the glenohumeral joint, we will be able to maximize pain relief and its duration while also reducing the likelihood of experiencing side effects associated with steroids.

13.0 Sharing Results with Subjects

The overall results of the study will not be shared with the patients. The results specifically as it pertains to the patient will be experienced as our outcomes are what the patients experience such as pain scale and functional outcomes recorded on the SPADI questionnaire.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

Not Applicable

15.0 Economic Burden to Subjects

15.1 Costs

There are no additional costs to patients as a result of their participation in this research. All charges associated with the standard of care treatment will be billed to the patient's insurance company.

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 the subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations

Penn State Hershey Medical Center

16.2 Feasibility of recruiting the required number of subjects

Based on current patient volume we feel that we will have approximately 10-15 patients a month to recruit. We do not foresee an issue in recruitment since these injections are very common in these clinics in order to reach our total of 171 in order to have the study sufficiently powered

16.3 PI Time devoted to conducting the research

The PI, Dr. Onks, and co-PI, Dr. Latorre, will work as a team to oversee the study. Research time will be used that has been granted by the chair of Family Medicine.

16.4 Availability of medical or psychological resources

Penn State Medical Center is a regional medical center with access to many specialty and sub-specialty programs that can provide any assistance we may need from experienced side effects from steroid injections. They will be contacted in the case that a side effect was to happen. It would be a rare circumstance that we would need these resources as these injections are performed routinely in our office on a daily basis.

16.5 Process for informing Study Team

Monthly meetings or secure emails will be used to update the study team as needed

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 HRP-902 - Human Tissue For Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ 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).

☐ Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ Clinical Research Center (CRC) Advisory Committee – All campuses – Research involves the use of CRC services in any way.

☐ 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 a copy of HRP-903 - Radiation Review Form on the "Supporting Documents" page in CATS IRB. This form is available in the CATS IRB Library.

☐ 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

Not Applicable

19.0 Adverse Event Reporting

19.1 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.

20.0 Study Monitoring, Auditing and Inspecting

20.1 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.).

21.0 Future Undetermined Research: Data and Specimen Banking

Not applicable

22.0 References

1. Barbour KE, Helmick CG, Boring MA, Brady TJ. Vital signs: prevalence of doctor-diagnosed arthritis and arthritis-attributable activity limitation --- United States, 2013—2015. *Morb Mortal Wkly Rep.* 2017 March 7.

2. McAlindon TE, Bannuru RR, Sullivan MC, et al. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage. 2014;22(3):363-388.

3. M Godwin and M Dawes. Intra-articular steroid injections for painful knees. Systematic review with meta-analysis. Can Fam Physician 2004; 50:241.

4. B Arroll and F Goodyear-Smith. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. BMJ 2004; 328:869.

5. Gaujoux-Viala C, Dougados M, Gossec L. Efficacy and safety of steroid injections for shoulder and elbow tendonitis: a meta-analysis of randomised controlled trials. Ann Rheum Dis. 2009;68(12):1843-1849.

6. Kim, Y. S., Lee, H. J., Lee, D. H., & Choi, K. Y. (2017). Comparison of high- and low-dose intra-articular triamcinolone acetonide injection for treatment of primary shoulder stiffness: a prospective randomized trial. J Shoulder Elbow Surg, 26(2), 209-215.

7. Yoon SH, Lee HY, Lee HJ, Kwack KS. Optimal dose of intra-articular corticosteroids for adhesive capsulitis: a randomized, triple-blind, placebo-controlled trial. AM J Sports Med. 2013 May;41(5):1133-9.

8. Arroll B, Goodyear-Smith F. Corticosteroid injections for osteoarthritis of the knee: meta-analysis. Bmj. 2004;328(7444):869.

9. Popma, J. W., Snel, F. W., Haagsma, C. J., Brummelhuis-Visser, P., Oldenhof, H. G., van der Palen, J., & van de Laar, M. A. (2015). Comparison of 2 Dosages of Intraarticular Triamcinolone for the Treatment of Knee Arthritis: Results of a 12-week Randomized Controlled Clinical Trial. J Rheumatol, 42(10), 1865-1868.

10. Intra-articular injections for osteoarthritis of the knee. Med Lett Drugs Ther. 2006;48(1231):25-27.

11. Smuin DM, Seidenberg PH, Sirlin EA, Phillips SF, Silvis ML. Rare Adverse Events Associated with Corticosteroid Injections: A Case Series and Literature Review. Curr Sports Med Rep. 2016;15(3):171-176.

12. McAlindon TE, LaValley MP, Harvey WF, et al. Effect of Intra-articular Triamcinolone vs Saline on Knee Cartilage Volume and Pain in Patients With Knee Osteoarthritis: A Randomized Clinical Trial. Jama. 2017;317(19):1967-1975.

13- Kegel G, Marshall A, Barron OA, Catalano LW, Glickel SZ, Kuhn M. Steroid injections in the upper extremity: experienced clinical opinion versus evidence-based practices. Orthopedics. 2013;36(9):e1141-1148.