Document Coversheet

Study Title: Success of Long-acting Anti-inflammatories After Anterior Cruciate Ligament and Meniscal Injury

Institution/Site:	University of Kentucky
Document (Approval/Update) Date:	11/16/2022
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PROTOCOL TYPE (VERSION 4)

IRB Approval
11/16/2022
IRB # 53136
IRB6
CLOSED

Which IRB

(•) Medical ( ) NonMedical

Protocol Process Type

( ) Exemption
( ) Expedited (Must be risk level 1)
(•) Full

IMPORTANT NOTE: You will not be able to change your selections for "Which IRB" and "Protocol Process Type" after saving this section. If you select the wrong IRB or Protocol Process Type, you may need to create a new application.

See below for guidance on these options, or refer to ORI's "Getting Started" page. Please contact the Office of Research Integrity (ORI) at 859-257-9428 with any questions prior to saving your selections.

Which IRB

The **Medical IRB** reviews research from the Colleges of:

- Dentistry
- Health Sciences
- Medicine
- Nursing
- Pharmacy and Health Sciences
- and Public Health.

The **Nonmedical IRB** reviews research from the Colleges of:

- Agriculture
- Arts and Sciences
- Business and Economics
- Communication and Information
- Design; Education
- Fine Arts
- Law
- and Social Work

Note: Studies that involve administration of drugs, testing safety or effectiveness of medical devices, or invasive medical procedures must be reviewed by the **Medical IRB** regardless of the college from which the application originates.

Which Protocol Process Type

Under federal regulations, the IRB can process an application to conduct research involving human subjects in one of three ways:

- by exemption certification
- by expedited review.
- by full review;

The investigator makes the preliminary determination of the type of review for which a study is eligible. Please refer to ORI's "Getting Started" page for more information about which activities are eligible for each type of review.

The revised Common Rule expanded exemption certification category 4 for certain secondary research with identifiable information or biospecimens. The regulations no longer require the information or biospecimens to be existing. For more information see the Exemption Categories Tool.

53136
CLOSED

PROJECT INFORMATION

0 unresolved comment(s)

Title of Project: (Use the exact title listed in the grant/contract application, if applicable).
If your research investigates any aspect of COVID-19, please include "COVID19" at the beginning of your Project Title and Short Title

Success of Long-acting Anti-inflammatories after Anterior Cruciate Ligament and Meniscal injury

Short Title Description
Please use a few key words to easily identify your study - this text will be displayed in the Dashboard listing for your study.

SLAM

Anticipated Ending Date of Research Project: 1/22/2024

Maximum number of human subjects (or records/specimens to be reviewed) 100

After approval, will the study be open to enrollment of new subjects or new data/specimen collection? (•) Yes ( ) No

RISK LEVEL

0 unresolved comment(s)

Indicate which of the categories listed below accurately describes this protocol

- ○ (Risk Level 1) Not greater than minimal risk
- ◉ (Risk Level 2) Greater than minimal risk, but presenting the prospect of direct benefit to individual subjects
- ○ (Risk Level 3) Greater than minimal risk, no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition.
- ○ (Risk Level 4) Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of subjects.

*"Minimal risk" means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves from those ordinarily encountered in daily life or during the performance of routine physical or psychological examination or tests.

Refer to UK's guidance document on assessing the research risk for additional information.

53136
CLOSED

SUBJECT DEMOGRAPHICS **0 unresolved comment(s)**

Age level of human subjects: (i.e., 6 mths.; 2yrs., etc..) 18 to 99

Study Population:

Describe the characteristics of the subject population, including age range, gender, ethnic background and health status. Identify the criteria for inclusion and exclusion.

Provide the following information:

- A description of the subject selection criteria and rationale for selection in terms of the scientific objectives and proposed study design;
- A compelling rationale for proposed exclusion of any sex/gender or racial/ethnic group;
- Justification for the inclusion of vulnerable groups such as children, prisoners, adults with impaired consent capacity, or others who may be vulnerable to coercion or undue influence.

Please consider these resources:
NIH Diversity Policy
FDA Diversity Guidance

This study will recruit a sample of 30 skeletally mature male and female participants between the ages of 18 and 40 that have undergone arthroscopic ACL reconstruction with partial meniscectomy or meniscal repair. Participants will be recruited from the University of Kentucky's Department of Orthopaedic Surgery & Sports Medicine clinical patient population.

Complete subject inclusion and exclusion criteria are as follows, and patients will not be excluded on the basis of sex, race, or ethnicity:
Inclusion Criteria:
1. Written consent to participate in the study
2. Male or female greater than or equal to 18 years of age and less than 99 years of age
3. Has undergone arthroscopic ACL reconstruction with partial meniscectomy or meniscal repair in the past 4 weeks
4. Ambulatory and in good general health
5. Willing and able to comply with the study procedures and visit schedules and able to follow verbal and written instructions.
6. Willing to abstain from use of protocol-restricted medications during the study
7. Females and males who have reproductive potential: Must use highly effective contraception for at least 1 month prior to the study injection and agreement to use such a method during study participation (18 weeks; 8 to 26 weeks after surgery)
8. Demonstrate persistent inflammation defined as either synovial fluid IL-1alpha concentration >= 5 pg/mL at the time of surgery

Exclusion Criteria:
1. Known allergic reactions to components of the extended-release triamcinolone acetonide (Zilretta®)
2. Reactive arthritis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, or arthritis associated with inflammatory bowel disease
3. History of infection in either knee joint
4. Clinical signs and symptoms of active knee infection or crystal disease in either knee within 1 month of Screening
5. Other surgery or arthroscopy of either knee within 6 months of Screening
6. Intraarticular treatment of any joint with any of the following agents within six (6) months of Screening: any corticosteroid preparation or any biologic agent (e.g., platelet rich plasma (PRP) injection, stem cells, prolotherapy, amniotic fluid injection; investigational or marketed).
7. Intraarticular treatment in either knee with hyaluronic acid (investigational or marketed) within 6 months of Screening
8. Parenteral or oral corticosteroids (investigational or marketed) within 3 months of Screening
9. Inhaled, intranasal or topical corticosteroids (investigational or marketed) within 2 weeks of Screening
10. Females who are pregnant or nursing or plan to become pregnant during the study; men whose female partner plans to conceive during the study
11. Radiographic osteoarthritic changes defined as Kellgren-Lawrence grade 2 or greater (as determined by PI from patient's preoperative X-rays)
12. Inability to read and understand English

Attachments

Indicate the targeted/planned enrollment of the following members of minority groups and their subpopulations. Possible demographic sources: Census Regional Analyst Edition, Kentucky Race/Ethnic Table, Kentucky Population Data.
(Please note: The IRB will expect this information to be reported at Continuation Review time for Pre-2019 FDA-regulated Expedited review and Full review applications):

Participant Demographics

	Cisgender Man	Cisgender Woman	TGNB/TGE	Unknown/Not Reported
American Indian/Alaskan Native:				
Asian:				
Black/African American:				
Latinx:				
Native Hawaiian/Pacific Islander:				
White:				
American Arab/Middle				

Eastern/North African:				
Indigenous People Around the World:				
More than One Race:				
Unknown or Not Reported:				

If unknown, please explain why: It is not known at the time the demographics of the participants that will be recruited. This information will be updated at continuation review.

Indicate the categories of subjects and controls to be included in the study. You may be required to complete additional forms depending on the subject categories which apply to your research. If the study does not involve direct intervention or direct interaction with subjects, (e.g., record-review research, outcomes registries), do not check populations which the research does not specifically target. For example: a large record review of a diverse population may incidentally include a prisoner or an international citizen, but you should not check those categories if the focus of the study has nothing to do with that status.

Check All That Apply (at least one item must be selected)

- ☐ Children (individuals under age 18)
- ☐ Wards of the State (Children)
- ☐ Emancipated Minors
- ☐ Students
- ☐ College of Medicine Students
- ☐ UK Medical Center Residents or House Officers
- ☐ Impaired Consent Capacity Adults
- ☐ Pregnant Women/Neonates/Fetal Material
- ☐ Prisoners
- ☐ Non-English Speaking (translated long or short form)
- ☐ International Citizens
- ☐ Normal Volunteers
- ☐ Military Personnel and/or DoD Civilian Employees
- ☑ Patients
- ☐ Appalachian Population

ADDITIONAL INFORMATION:

Please visit the IRB Survival Handbook for more information on:

- Children/Emancipated Minors
- Students as Subjects
- Prisoners
- Impaired Consent Capacity Adults
- Economically or Educationally Disadvantaged Persons

Other Resources:

- UKMC Residents or House Officers [see requirement of GME]
- Non-English Speaking [see also the E-IRB Research Description section on this same topic]
- International Citizens [DoD SOP may apply]
- Military Personnel and/or DoD Civilian Employees

53136
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Assessment of the potential recruitment of subjects with impaired consent capacity (or likelihood):

☐ Check this box if your study does NOT involve direct intervention or direct interaction with subjects (e.g., record-review research, secondary data analysis). If there is no direct intervention/interaction you will not need to answer the impaired consent capacity questions.

Does this study focus on adult subjects with any conditions that present a high *likelihood* of impaired consent capacity or *fluctuations* in consent capacity? (see examples below)

○ Yes ◉ No

If Yes and you are not filing for exemption certification, go to "Form T", complete the form, and attach it using the button below.

Examples of such conditions include:

- Traumatic brain injury or acquired brain injury
- Severe depressive disorders or Bipolar disorders
- Schizophrenia or other mental disorders that involve serious cognitive disturbances
- Stroke
- Developmental disabilities
- Degenerative dementias
- CNS cancers and other cancers with possible CNS involvement
- Late stage Parkinson's Disease
- Late stage persistent substance dependence
- Ischemic heart disease
- HIV/AIDS
- COPD
- Renal insufficiency
- Diabetes
- Autoimmune or inflammatory disorders
- Chronic non-malignant pain disorders
- Drug effects
- Other acute medical crises

Attachments

53136
CLOSED

INFORMED CONSENT/ASSENT PROCESS/WAIVER

0 unresolved comment(s)

For creating your informed consent attachment(s), please download the most up-to-date version listed in "All Templates" under the APPLICATION LINKS menu on the left, and edit to match your research project.

Additional Resources:

- Informed Consent/Assent Website
- Waiver of Consent vs. Waiver of Signatures
- Sample Repository/Registry/Bank Consent Template

Consent/Assent Tips:

- If you have multiple consent documents, be sure to upload each individually (not all in a combined file).
- If another site is serving as the IRB for the project, attach the form as a "Reliance Consent Form" so the document will not receive a UK IRB approval stamp; the reviewing IRB will need to stamp the consent forms.
- Changes to consent documents (e.g., informed consent form, assent form, cover letter, etc...) should be reflected in a 'tracked changes' version and uploaded separately with the Document Type "Highlighted Changes".
- It is very important that only the documents you wish to have approved by the IRB are attached; DELETE OUTDATED FILES -- previously *approved* versions will still be available in Protocol History.
- Attachments that are assigned a Document Type to which an IRB approval stamp applies will be considered the version(s) to be used for enrolling subjects once IRB approval has been issued.
  Document Types that do NOT get an IRB approval stamp are:
  - "Highlighted Changes",
  - "Phone Script", and
  - "Reliance Consent Form",
  - "Sponsor's Sample Consent Form".

How to Get the Section Check Mark

1. You must:

   a) provide a response in the text box below describing how investigators will obtain consent/assent, and
   b) check the box for at least one of the consent items and/or check mark one of the waivers

2. If applicable attach each corresponding document(s) **as a PDF**.
3. If you no longer need a consent document approved (e.g., closed to enrollment), or, the consent document submitted does not need a stamp for enrolling subjects (e.g., umbrella study, or sub-study), only select "Stamped Consent Doc(s) Not Needed".
4. After making your selection(s) be sure to scroll to the bottom of this section and SAVE your work!

Check All That Apply

- ☐ Informed Consent Form (and/or Parental Permission Form and/or translated short form)
- ☐ Assent Form
- ☐ Cover Letter (for survey/questionnaire research)
- ☐ Phone Script
- ☑ Informed Consent/HIPAA Combined Form
- ☐ Debriefing and/or Permission to Use Data Form
- ☐ Reliance Consent Form
- ☐ Sponsor's sample consent form for Dept. of Health and Human Services (DHHS)-approved protocol
- ☐ Stamped Consent Doc(s) Not Needed

Attachments

Attach Type	File Name
Informed Consent/HIPAA Combined Form	SLAM ICF V9 12102021.pdf

Informed Consent Process:

Using active voice, describe how investigators will obtain consent/assent. Include:

- the circumstances under which consent will be sought and obtained
- the timing of the consent process (including any waiting period between providing information and obtaining consent)
- who will seek consent
- how you will minimize the possibility of coercion or undue influence
- the method used for documenting consent
- if applicable, who is authorized to provide permission or consent on behalf of the subject
- if applicable, specific instruments or techniques to assess and confirm potential subjects' understanding of the information

Note: all individuals authorized to obtain informed consent should be designated as such in the E-IRB "Study Personnel" section of this application.

Special considerations may include:

- Obtaining consent/assent for special populations such as children, prisoners, or people with impaired decisional capacity
- *Research Involving Emancipated Individuals*
  If you plan to enroll some or all prospective subjects as emancipated, consult with UK legal counsel **prior to submitting this application to the IRB**. Include research legal counsel's recommendations in the "Additional Information" section as a separate document.
- *Research Involving Non-English Speaking Subjects*
  For information on inclusion of non-English speaking subjects, or subjects from a foreign culture, see IRB Application Instructions for Recruiting Non-English Speaking Participants or Participants from a Foreign Culture.
- *Research Repositories*
  If the purpose of this submission is to establish a research repository describe the informed consent process. For guidance regarding consent issues, process approaches, and sample language see the Sample Repository/Registry/Bank Consent Template.

CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS
Consent forms describing in detail the study intervention, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/administering study intervention.

CONSENT PROCEDURES AND DOCUMENTATION
Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.
Participants are free to ask any question they may have about the study. Participants will be directed to contact the Principal Investigator or Study Coordinator if complaints, concerns, or questions arise. Participants will be provided with the Principal Investigator or Study Coordinator's name and current contact information at the time they are enrolled in the study and at the time of the informed consent process. Participants will also be advised to contact the staff of the Office of Research Integrity at 859-257-9428 or toll free at 1-866-400-9428 with any concerns.

☐ Request for Waiver of Informed Consent Process

If you are requesting IRB approval to waive the requirement for the informed consent process, or to alter some or all of the elements of informed consent, complete, Section 1 and Section 2 below.

Note: The IRB does not approve waiver or alteration of the consent process for greater than minimal risk research, except for planned emergency/acute care research as provided under FDA regulations. Contact ORI for regulations that apply to single emergency use waiver or acute care research waiver (859-257-9428).

SECTION 1.

Check the appropriate item:

☐ I am requesting a waiver of the requirement for the informed consent process.

☐ I am requesting an alteration of the informed consent process.

If you checked the box for this item, describe which elements of consent will be altered and/or omitted, and justify the

alteration.

SECTION 2.

Explain how each condition applies to your research.

a) The research involves no more than minimal risk to the subject.

b) The rights and welfare of subjects will not be adversely affected.

c) The research could not practicably be carried out without the requested waiver or alteration.

d) Whenever possible, the subjects or legally authorized representatives will be provided with additional pertinent information after they have participated in the study.

e) If the research involves using or accessing identifiable private information or identifiable biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format.

- Private information/specimens are “identifiable” if the investigator may ascertain the identity of the subject or if identifiers are associated with the information (e.g., medical records). This could be any of the 18 HIPAA identifiers including dates of service.
- If not using identifiable private information or identifiable biospecimens, insert N/A below.

Request for Waiver of Signatures

If you are requesting IRB approval to waive the requirement for signatures on informed consent forms, **your research activities must fit into one of three regulatory options**:

1. The only record linking the participant and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality (e.g., a study that involves participants who use illegal drugs).
2. The research presents no more than minimal risk to the participant and involves no procedures for which written consent is normally required outside of the research context (e.g., a cover letter on a survey, or a phone script).
3. The participant (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm, the research presents no more than minimal risk to the subject, and there is an appropriate alternative mechanism for documenting that informed consent was obtained.

Select the option below that best fits your study.

*If the IRB approves a waiver of signatures, participants must still be provided oral or written information about the study. To ensure you include required elements in your consent document, use the **Cover Letter Template** as a guide. There is an English and a Spanish version.*

Option 1

Describe how your study meets these criteria:

a) The only record linking the participant and the research would be the consent document:

b) The principal risk would be potential harm resulting from a breach of confidentiality (i.e., a study that involves subjects who use illegal drugs).

Under this option, each participant (or legally authorized representative) must be asked whether (s)he wants to sign a consent document; if the participant agrees to sign a consent document, only an IRB approved version should be used.

Option 2

Describe how your study meets these criteria:

a) The research presents no more than minimal risk to the participant:

b) Involves no procedures for which written consent is normally required outside of the research context (i.e. a cover letter on a survey, or a phone script):

Option 3

Describe how your study meets these criteria:

a) The subject (or legally authorized representative) is a member of a distinct cultural group or community in which signing forms is not the norm.

b) The research presents no more than minimal risk to the subject.

c) There is an appropriate alternative mechanism for documenting that informed consent was obtained.

53136
CLOSED

RESEARCH DESCRIPTION

0 unresolved comment(s)

You may attach a sponsor's protocol pages in the "Additional Information" section and refer to them where necessary in the Research Description. However, each prompt that applies to your study should contain at least a summary paragraph.

****!!!PLEASE READ!!!** Known Issue: The below text boxes do not allow symbols, web addresses, or special characters (characters on a standard keyboard should be ok). If something is entered that the text boxes don't allow, user will lose unsaved information.**

Workaround(s):

- **Save your work often to avoid losing data.**
- **Use one of the attachment buttons in this section, or under the Additional Information section to include the information with your application. During the document upload process, you will be able to provide a brief description of the attachment.**

Background

Include a brief review of existing literature in the area of your research. You should identify gaps in knowledge that should be addressed and explain how your research will address those gaps or contribute to existing knowledge in this area. For interventional research, search PubMed and ClinicalTrials.gov for duplicative ongoing and completed trials with same condition and intervention(s).

We have shown that anterior cruciate ligament (ACL) injury initiates a biochemical cascade that leads to cartilage degradation and the development of posttraumatic osteoarthritis (PTOA).5-8 ACL and acute traumatic meniscus tears have been linked the development and progression of PTOA.9-12 As such, there is an unmet need to identify treatments that may alter the progression of PTOA following ACL meniscus injury. Our overarching hypothesis is that intraarticular administration of long-acting anti-inflammatory agents will alter the progression of PTOA following ACL reconstruction.

The current standard of care for patients with combined ACL and meniscus injuries consists of surgical treatment often with a short course of postoperative physical therapy. However, the current mechanically-based standard of care does not address the persistent inflammatory process that promotes cartilage degradation and PTOA progression. We have demonstrated that pro-inflammatory stimulation of meniscus cells increases matrix metalloproteinase (MMP) and cytokine activity,13 and the combination of pro-inflammatory cytokines and compressive loading like what may be seen during sporting and high demand activities further results in degradative enzyme activity and increased production of pro-inflammatory mediators.14 In this way, the meniscus plays an active role in promoting the cycle of articular cartilage degradation and PTOA progression after ACL reconstruction.

Reducing MMP and cytokine activity after ACL and meniscus injury may alter the progression of PTOA for this at-risk patient population.15 Our recent results following ACL injury and reconstruction demonstrate that 1) triamcinolone acetonide effectively reduces cartilage degradation, 2) the inflammatory cascade and corresponding cartilage degradation are reinitiated after surgery, 3) hyaluronate treatment 1 week after surgery unsuccessfully mitigates the inflammatory and catabolic processes, and 4) pain and persistent postsurgical cytokine activity at 4 weeks were predictive of inferior knee biomechanics 6 months after surgery. In addition, long-acting agents may provide a greater treatment effect as temporal regulation of cytokine activity may more successfully alter the pro-inflammatory environment than shorter-duration treatments.17 These results identify that long-acting anti-inflammatory treatment is needed to alter the path of PTOA following meniscus injury and administration 8 weeks after surgery may offer the optimal timing of treatment.

We will test a model whereby femoral shape change and cytokine activity are mediated by a long-acting anti-inflammatory agent (extended-release triamcinolone acetonide). Femoral shape changes have been demonstrated after ACL injury and reconstruction, with shape changes in the first 6 months after surgery correlating with subsequent MRI evidence of cartilge degradation and inferior patient-reported outcomes 3 years postoperatively.

By identifying biologic treatment options, the proposed study will trigger a line of research to shift the treatment paradigm away from isolated surgical treatment of the ACL meniscus to a model in which both the joint and the modifiable postoperative pro-inflammatory state are treated to slow the progression of PTOA and prevent its associated sequelae. We will recruit a sample of 30 skeletally mature patients between the ages of 18 and 40 that have undergone ACL reconstruction with concomitant traumatic meniscus tears. At the time of surgery, patients will be screened for persistent inflammation by assessing synovial fluid IL-1alpha at that time. Those with elevated IL-1alpha will then be randomized to either extended-release triamcinolone acetonide or placebo (saline) 8 weeks after surgery. To assess the efficacy of extended-release triamcinolone acetonide, the following data will be collected at 8 week and 6 month follow-ups: 3T MRI, urinary and serum biomarkers of cartilage degradation, and patient-reported outcomes.

Objectives

List your research objectives. Please include a summary of intended research objectives in the box below.

Primary Objective: Determine if extended-release triamcinolone acetonide treatment alters the progressive changes in bone shape previously demonstrate after anterior cruciate ligament (ACL) reconstruction with partial meniscectomy or meniscal repair.

Secondary Objectives: Compare the change in patient-reported outcomes and a urinary biomarker of cartilage breakdown (uCTXII) between patients treated with extended release triamcinolone acetonide or placebo following ACL reconstruction with partial meniscectomy or meniscal repair.

Study Design

Describe and explain the study design (e.g., observational, secondary analysis, single/double blind, parallel, crossover, deception, etc.).

- *Clinical Research*: Indicate whether subjects will be randomized and whether subjects will receive any placebo.
- *Community-Based Participatory Research*: If you are conducting community-based participatory research (CBPR), describe strategies for involvement of community members in the design and implementation of the study, and dissemination of results from the study.
- *Qualitative research*: Indicate ranges where flexibility is needed, if a fixed interview transcript is not available, describe interview topics including the most sensitive potential questions.
- *Research Repositories*: If the purpose of this submission is to establish a Research Repository (bank, registry) and the material you plan to collect is already available from a commercial supplier, clinical lab, or established IRB approved research repository, provide scientific justification for establishing an additional repository collecting duplicate material. Describe the repository design and operating procedures. For relevant information to include, see the UK Research Biospecimen Bank Guidance or the UK Research Registry Guidance.

We will perform a Phase 2a, double-blind, placebo-controlled, randomized controlled trial to determine if a long-acting anti-inflammatory agent (extended-release triamcinolone acetonide) lessens progressive changes in bony shape, improves patient-reported outcomes, and/or reduces biomarkers of cartilage degradation when compared to placebo (saline). The single-site study is driven by the three guiding hypotheses:
Hypothesis 1: The shape changes of the femoral condyle between 8 weeks and 6 months after surgery will be significantly lower for patients treated with extended-release triamcinolone acetonide than the placebo group.
Hypothesis 2: Changes in patient reported-outcomes between eight and 6 months after surgery will be significantly greater for those treated with long-duration anti-inflammatory injections than the placebo group.
Hypothesis 3: Changes in a urinary biomarker of cartilage breakdown (uCTXII) between eight and 6 months after surgery will be significantly lower for those treated with long-duration anti-inflammatory injections than the placebo group.

Patient will provide informed consent prior to undergoing ACL reconstruction with meniscal involvement. At the time of surgery, a knee aspiration will be performed in the operating room after the patient has been anesthetized so that synovial fluid can be collected. Synovial fluid samples will be assessed for the concentration of pro-inflammatory cytokine IL-1alpha. This will be done to identify patients that present with persistent inflammation after injury that may be at increased risk of cartilage degradation. Patients with elevated IL-1alpha, defined as synovial fluid concentrations >= 5 pg/mL, will then be randomized to one of two groups. The synovial fluid threshold of 5 pg/mL was based on our previously published study of ACL patients that demonstrated that those with elevated IL-1alpha at the time of surgery less likely to achieve a successful clinical outcome at 2 years (Latttermann et al., Biomed Res Int, 2018).

Eight weeks after surgery, the knee will be aspirated and one group will receive a single 32 mg Zilretta injection and the other group will receive a 5 mL saline injection. The syringes will be blinded to ensure that both the investigator administering the injection and the patient will be blinded to the group assignment. Patients will then be seen again six weeks later. Both prior to injection and at the 6-month follow-up visit, patients will undergo 3T MRI scans so that femoral shape can be assessed and will also be asked to complete patient-reported outcomes questionnaires and provide a urine sample.

Attachments

Subject Recruitment Methods & Advertising

Describe how the study team will identify and recruit subjects. Please consider the following items and provide additional information as needed so that the IRB can follow each step of the recruitment process.

- How will the study team identify potential participants?
- Who will first contact the potential subjects, and how?
- Will you use advertisements? If so, how will you distribute those?
- How and where will the research team meet with potential participants?
- If applicable, describe proposed outreach programs for recruiting women, minorities, or disparate populations.
- How you will minimize undue influence in recruitment?
- Attach copies of all recruiting and advertising materials (emails, verbal scripts, flyers, posts, messages, etc.).

For additional information on recruiting and advertising:

- IRB Application Instructions - Advertisements
- PI Guide to Identification and Recruitment of Human Subjects for Research

This single site study will include 30 patients that have undergone ACL reconstruction with partial meniscectomy or meniscal repair. Our group performs 224 primary ACL reconstructions per year, with 154 (69%) patients/year meeting the inclusion criteria for this study. Based on our current and recent randomized trials assessing interventions prior to or following ACL reconstruction (ClinicalTrials.gov Identifiers: NCT02930122, NCT03364647, NCT03429140) we anticipate a similar rate of eligible patients that agree to participate in the current study (76%). Extrapolating from our annual patient volume, RCT agreement rate, and an approximate 30% rate of patients with persistent inflammation, we do not anticipate difficulty in enrolling 100 patients over an 18 month period in order to yield our desired sample size of 30 patients. Furthermore, our established relationship with other clinicians, dedicated research personnel with dedicated research space in our clinical facility also support the feasibility of successfully completing the proposed project.
• Accrual Rate: Enroll 10 patients per month with 3 patients per month with qualifying levels of IL-1alpha
• Patients will be recruited from the outpatient clinical populations of the UK HealthCare sports medicine surgeons at the UK HealthCare Orthopaedic and Sports Medicine Center
• Potentially eligible patients will be identified by their surgeon during a regularly scheduled preoperative visit. Patients will then meet with a member of the research team to discuss the study, determine eligibility, and provide informed consent.
• No advertisement will be used for this study.
• Since study visits coincide with routine standard of care follow-up visits 8 weeks and 6 months after surgery, patients will be reminded of their visit by the UKHealthCare automated phone reminder system. In addition, research personnel will contact patients via the patient's preferred method of contact (phone, text message, and/or email) 2 days prior to their visit to remind the patient of their upcoming visit.
• Caucasian patients account for 84% of our knee OA patient population; however, we take the inclusion of minorities very seriously. In a recently completed clinical trial of ACL reconstructed patients, our successful enrollment strategies have resulted in a greater representation of minorities than the general patient population for our area (29% vs. 16%). We aim to meet or exceed these proportions in the proposed study and will approach all eligible minority patients to ensure that at least 25% are non-white.
• Vulnerable populations including pregnant women, children, and prisoners will not be enrolled in this study.
• To promote retention, patients will be compensated $50 for completing Visit 2 (fluid collected at the time of surgery), and if they qualify for the study injection, participants will receive $75 for each of the 2 study visits that involve MRI scans. Compensation will be mailed to the participant by check within two weeks after they have completed study visits 2, 3, and 4. If they choose to withdraw early, or do not attend all study visits, payment will be prorated. Participants could earn up to $200 for participation in this study.
No advertisements will be used for this study.

Attachments

Research Procedures

Describe how the research will be conducted.

- What experience will study participants have?
- What will study participants be expected to do?
- How long will the study last?
- Outline the schedule and timing of study procedures.
- Provide visit-by-visit listing of all procedures that will take place.
- Identify all procedures that will be carried out with each group of participants.
- Describe deception and debrief procedures if deception is involved.

Differentiate between procedures that involve standard/routine clinical care and those that will be performed specifically for this research project. List medications that are explicitly forbidden or permitted during study participation.

EFFICACY ASSESSMENTS
PRIMARY OBJECTIVE
Determine if extended-release triamcinolone acetonide treatment alters progressive changes in bone shape after ACL reconstruction. The bone area of the medial femoral condyl has been shown to increase within the first few months after ACL reconstruction. This is clinically meaningful as similary bony changes have been previously associated with progressive OA and within 6 months of ACL reconstruction correlated with subsequent patient-reported outcomes and MRI markers of cartilage quality at 3 years. All subjects will undergo MRI examination prior to undergoing the study injection at Visit 3 and again at Visit 4. Sagittal and axial MRI images will be acquired with the knee in full extension using a 3.0-T MRI scanner and an 1Tx/15Rx phased array knee coil. Sagittal and axial T1-weighted spin echo images (FSE) will be acquired to allow semi-quantitative analysis at the conclusion of the study. These sequences will be followed by a sagittal high-resolution 3D dual echo steady state (DESS) sequence for cartilage segmentation and a sagittal combined T1?/T2 mapping for the quantification of cartilage composition.

Bone volume of the medial femoral condyle will be measured using previously validated methods. A single investigator experienced with quantitative and semi-quantitative assessments of knee MRIs41, will manually segment the medial femoral condyle on each slice of the MRI. Since the thickness of each slice is 3.5 mm, we will then calculate the medial condyle volume on each slice and then sum the volumes of all slices to generate the total medial condyle volume.

SECONDARY OBJECTIVES
Compare the change in patient-reported outcomes between patients treated with extended release triamcinolone acetonide or placebo following ACL reconstruction. The change in patient-reported outcomes (IKDC score, KOOSglobal score, and the Intermittent and Constant Osteoarthritis Pain (ICOAP) score) between the date of injection and the 6-month, 1-year, and 2-year postoperative follow-ups. The IKDC and KOOSglobal are knee-related patient-reported outcome tools. The IKDC has been validated in this specific patient population, and we developed and validated the KOOSglobal for use with young and potentially more active patient populations. The ICOAP was developed as part of the OARSI/OMERACT initiative and is a valid and reliable tool to assess OA-related pain.

Determine if extended-release triamcinolone acetonide treatment alters the progression of cartilage degradation following ACL reconstruction. The change in a urinary biomarker of cartilage degradation (CTXII) between baseline and the 4-month postoperative follow-ups be compared between the treatment and placebo groups. Following cartilage degradation, CTXII (C-terminal crosslinked telopeptide type II collagen) is released into the synovial fluid, is circulated and then filtered by the kidneys. CTXII has been identified as a biomarker for the diagnosis, staging, and evaluating the prognosis of hip and knee OA, and has also been demonstrated to be responsive over short testing periods (3 months). We have reported that CTXII correlates with the degree of joint destruction and increases significantly within 1 month after ACL injury. CTXII will be measured in the urine by ELISA (Cartilaps® (CTX-II); Immunodiagnostic Systems, Inc, Fountain Hills, AZ) and will be normalized to creatinine levels (Quidel, San Diego, CA).

Biological data quality control: To ensure data quality and fidelity, all data collection and analysis procedures will be detailed in a structured manual. OA biomarker data collected will be carefully analyzed with respect to variability, linear range of standard, and need for repeat analyses. Controls provided with commercially available ELISA kits will be used with every run. For assays for which no control is available or provided, aliquots of serum from normal human subjects have been aliquoted and frozen at -80oC for this purpose. Each assay day, a fresh aliquot of this control serum is thawed and used on every plate to calculate intra- and inter-assay variance of the assay. In addition to the standard curve run in duplicate, this control will be run with each assay and the results used to determine the precision of the assay and to establish an acceptable control range for the assay. The mean of the control sample for all assays ±2 standard deviations is defined as the acceptable control range. Any samples on a plate in which the control falls outside of this range will be excluded and repeated. Samples will be run in duplicate and reanalyzed if the coefficient of variation is > 15%. For values that are below the level of detection, a value equivalent to 0.5 lowest limit of detection will be recorded and used for statistical analyses. Our team in Kentucky has used this methodology in prior works.

COVARIATES
Biomarker concentrations have been previously shown to differ based on patient age, sex, race, and BMI.50 As such, these patient factors will be collected and used as covariates in our statistical analyses.

SAFETY AND OTHER ASSESSMENTS

• Limited Physical examination: Subject height and weight will be monitored, and the injection site will be closely r
of infection and/or allergic reaction.
• Vital signs: Blood pressure will be assessed per the standard of care
• Radiographic or other imaging assessments: The amount of arthritic changes to the knee will be assessed by the Principal Investigator from each patient's routine standard of care preoperative x-ray. Patients with more than Kellgren Lawrence grade I changes will be excluded from the study. These images will not be reviewed until after the patient has signed a HIPAA-approved informed consent form.
• Assessment of adverse events: Patients that develop AEs/SAEs will be closely monitored until conclusion of the event. For events that are ongoing at the 6-week study visit, we will continue to contact the patient on a monthly basis until the event has resolved or deemed to have reached maximum medical improvement.

All information garnered from safety assessments will be recorded in the patient's medical chart.

Attachments

Data Collection & Research Materials

In this section, please provide the following:

- Describe all sources or methods for obtaining research materials about or from living individuals (such as specimens, records, surveys, interviews, participant observation, etc.), and explain why this information is needed to conduct the study.
- For each source or method described, please list or attach all data to be collected (such as genetic information, interview scripts, survey tools, data collection forms for existing data, etc.).
- If you will conduct a record or chart review, list the beginning and end dates of the records you will view.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Hardcopies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant enrolled in the study. Clinical data will be entered onto paper case report forms provided by the sponsor. Clinical data will be transcribed directly from the source documents.

The investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the paper CRF entries. Monitoring standards require full verification for the presence of informed consent, adherence to the xclusion criteria, documentation of SAEs, and the recording of primary efficacy and safety variables. Additional checks of the consistency of the source data with the CRFs are to be performed according to the study-specific monitoring plan.

Attachments

Resources

Describe the availability of the resources and adequacy of the facilities that you will use to perform the research. Such resources may include:

- Staffing and personnel, in terms of availability, number, expertise, and experience;
- Computer or other technological resources, mobile or otherwise, required or created during the conduct of the research;
- Psychological, social, or medical services, including equipment needed to protect subjects, medical monitoring, ancillary care, or counseling or social support services that may be required because of research participation;
- Resources for communication with subjects, such as language translation/interpretation services.

Data collection will take place at the University of Kentucky's Orthopaedic and Sports Medicine Center and the Sports Medicine Research Institute. The participants will be followed by the principal investigator and their research team which includes physicians, certified nurses, and clinical research coordinators during the study. Emergency medical equipment, medications and supplies will be at the physician's disposal should the participant have an acute untoward reaction.

Potential Risks & Benefits

Risks

- Describe any potential risks – including physical, psychological, social, legal, ability to re-identify subjects, or other risks. Assess the seriousness and likelihood of each risk.
- Which risks may affect a subject's willingness to participate in the study?
- Describe likely adverse effects of drugs, biologics, devices or procedures participants may encounter while in the study.

- *Qualitative research* - describe ethical issues that could arise while conducting research in the field and strat
  to handle those situations.
- Describe any steps to mitigate these risks.

Benefits

- Describe potential direct benefits to study participants – including diagnostic or therapeutic, physical, psychological or emotional, learning benefits. This cannot include incentives or payments.
- State if there are no direct benefits.
- Describe potential benefits to society and/or general knowledge to be gained.

Describe why potential benefits are reasonable in relation to potential risks. If applicable, justify why risks to vulnerable subjects are reasonable to potential benefits.

Knee Aspiration: As with any invasive procedure, complications can occur. Some possible complications may include, but are not limited to, the following:
- Fever
- Pain or discomfort at the aspiration site
- Bruising at the aspiration site
- Redness, swelling, bleeding or other drainage from the aspiration site
- Infection at the aspiration site

MRI: The risks from MRI are minimal. The images taken will be taken of the knee cartilage. They are used only for research and are not read for any clinical interpretation.

Possible Risk/Side Effect from MR Scanning include Claustrophobia (It occasionally occurs, can be treated, and the volunteer is removed from the magnet) and Loud noise (It is expected to occur, is not serious, and participants wear ear protection).

KNOWN POTENTIAL RISKS OF ZILRETTA

Previous studies of animal models have suggested that repeated, high doses of intra-articular cortisosteroid injection can adversely affect articular cartilage. In human studies of older patients with knee OA, repeated triamcinoloine acetonide injections may result in cartilage thinning or loss of cartilage volume; however, little confirmatory evidence is available in human trials or when used intra-articularly at either lower doses or frequency following acute injury.

The following risks are copied directly from the Zilretta package insert:
CONTRAINDICATIONS: Patients with hypersensitivity to triamcinolone acetonide or any component of the product.

WARNINGS AND PRECAUTIONS
Warnings and Precautions Specific for ZILRETTA
ZILRETTA has not been evaluated and should not be administered by the following routes:
• Epidural
• Intrathecal
• Intravenous
• Intraocular
• Intramuscular
• Intradermal
• Subcutaneous

1. Serious Neurologic Adverse Reactions with Epidural and Intrathecal Administration: Serious neurologic events, some resulting in death, have been reported with epidural injection of corticosteroids. Specific events reported include, but are not limited to, spinal cord infarction, paraplegia, quadriplegia, cortical blindness, and stroke. These serious neurologic events have been reported with and without use of fluoroscopy. Reports of serious medical events have been associated with the intrathecal route of corticosteroid administration. The safety and effectiveness of epidural and intrathecal administration of corticosteroids have not been established, and corticosteroids are not approved for this use. In particular, the formulation of ZILRETTA should not be considered safe to use for epidural or intrathecal administration.

2. Hypersensitivity Reactions: Rare instances of anaphylaxis have occurred in patients with hypersensitivity to corticosteroids. Cases of serious anaphylaxis, including death, have been reported in individuals receiving triamcinolone acetonide injection, regardless of the route of administration. Institute appropriate care upon occurrence of an anaphylactic reaction.

3. Joint Infection and Damage: Intra-articular injection of corticosteroid may be complicated by joint infection. A marked increase in pain accompanied by local swelling, further restriction of joint motion, fever, and malaise are suggestive of septic arthritis. If this complication occurs and a diagnosis of septic arthritis is confirmed, institute appropriate antimicrobial therapy. Avoid injection of a corticosteroid into an infected site. Local injection of a corticosteroid into a previously infected joint is not usually recommended. Examine any joint fluid present to exclude a septic process. Corticosteroid injection into unstable joints is generally not recommended. Intra-articular injection may result in damage to joint tissues.

4. Increased Risk of Infections: Intra-articularly injected corticosteroids are systemically absorbed. Patients who are on corticosteroids are more susceptible to infections than are healthy individuals. There may be decreased resistance and inability to

localize infection when corticosteroids are used. Infection with any pathogen (viral, bacterial, fungal, protozoan, or location of the body may be associated with the use of corticosteroids alone or in combination with other immunosuppressive agents. These infections may be mild to severe. With increasing doses of corticosteroids, the rate of occurrence of infectious complications increases. Corticosteroids may also mask some signs of current infection. Advise patients to inform their health care provider if they develop fever or other signs or symptoms of infection. Advise patients who have not been vaccinated to avoid exposure to chicken pox or measles. Instruct patients to contact their health care provider immediately if they are exposed.

5. Alterations in Endocrine Function: Corticosteroids can produce reversible hypothalamic-pituitary-adrenal axis suppression, with the potential for adrenal insufficiency after withdrawal of treatment, which may persist for months. In situations of stress during that period (as in trauma, surgery, or illness), institute corticosteroid replacement therapy. Metabolic clearance of corticosteroids is decreased in hypothyroid patients and increased in hyperthyroid patients.

6. Cardiovascular Effects: Corticosteroids can cause elevations of blood pressure, salt and water retention, and increased excretion of potassium. These effects are less likely to occur with synthetic derivatives. Monitor patients with congestive heart failure or hypertension for signs of edema, weight gain, and imbalance in serum electrolytes. Dietary salt restriction and potassium supplementation may be necessary.

7. Renal Effects: Corticosteroids can cause salt and water retention, and increased excretion of potassium. These effects are less likely to occur with synthetic derivatives. All corticosteroids increase calcium excretion. Monitor patients with renal insufficiency for signs of edema, weight gain, and imbalance in serum electrolytes. Dietary salt restriction and potassium supplementation may be necessary.

8. Increased Intraocular Pressure: Corticosteroid use may be associated with development or exacerbation of increased intraocular pressure. Monitor patients with elevated intraocular pressure for potential treatment adjustment.

9. Gastrointestinal Perforation: Corticosteroid administration is associated with increased risk of gastrointestinal perforation in patients with certain GI disorders such as active or latent peptic ulcers, diverticulosis, diverticulitis, ulcerative colitis and in patients with fresh intestinal anastomoses. Avoid corticosteroids in these patients because signs of peritoneal irritation following gastrointestinal perforation may be minimal or absent.

10. Alterations in Bone Density: Corticosteroids decrease bone formation and increase bone resorption through their effect on calcium regulation and inhibition of osteoblast function. Special consideration should be given to patients with or at increased risk of osteoporosis (e.g., postmenopausal women) before initiating corticosteroid therapy.

11. Behavioral and Mood Disturbances: Corticosteroid use may be associated with new or aggravated adverse psychiatric reactions ranging from euphoria, insomnia, mood swings, and personality changes to severe depression and frank psychotic manifestations. Special consideration should be given to patients with previous or current emotional instability or psychiatric illness before initiating corticosteroid therapy. Advise patients and/or caregivers to immediately report any new or worsening behavior or mood disturbances to their health care provider.
The risks of the study, which include the known risks associated with triamcinolone acetonide and the risks associated with knee aspiration, are outweighed by the potential benefits. Sterile technique will be utilized for all knee aspirations and we have not noted any adverse events related to either intraarticular triamcinolone acetonide administration or repeated knee aspirations as part of two clinical trials (ClinicalTrials.gov identifiers NCT01692756 and NCT03429140). Patients in both the experimental and placebo groups have the potential benefit of pain relief, and there may also be a potential chondroprotective benefit of the study drug. As such, the risks of participation in the study outweigh the value of the information to be gained.

Available Alternative Opportunities/Treatments

Describe alternative treatments or opportunities that might be available to those who choose not to participate in the study, and which offer the subject equal or greater advantages. If applicable, this should include a discussion of the current standard of care treatment(s).

If the participant does not want to take part in the study, they can receive their normal (standard) care after knee surgery. They will be advised to discuss these treatment options with their doctor.

Back to Top

Records, Privacy, and Confidentiality

Specify where the data and/or specimens will be stored and how the researcher will ensure the privacy and confidentiality of both. Specify who will have access to the data/specimens and why they need access.

Describe how data will be managed after the study is complete:

- If data/specimens will be maintained, specify whether identifiers will be removed from the maintained information/material.
- If identifiers will not be removed, provide justification for retaining them and describe how you will protect confidentiality.
- If the data/specimens will be destroyed, verify that this will not violate retention policies and will adhere to applicable facility

requirements.

If this study will use de-identified data from another source, describe what measures will be taken to ensure that subject identifiers are not given to the investigator.

If applicable, describe procedures for sharing data/specimens with collaborators not affiliated with UK.

For additional considerations:
Return of Research Results or Incidental Research Findings
HIPAA policies
FERPA policies
Procedures for Transfer agreements
Information regarding multi-site studies
NIH Genomic Data Sharing (GDS) Policy
Digital Data

The investigative team maintains the right to keep, preserve, use and dispose of the findings of this investigation in accordance with Food and Drug Administration (FDA) guidelines. The FDA and the study sponsor, maintain the right to inspect the records of the study at any time. Investigational records from this study will be maintained in a confidential manner; participant names will not be associated with any published results.
Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsor(s) and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

All research activities will be conducted in as private a setting as possible.

The CCTS QA/QI auditor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Kentucky. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by University of Kentucky, Department of Orthopaedic research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the University of Kentucky.
Every precaution to prevent a direct study injury will be taken by medical personnel and the investigators. Should an adverse or serious adverse event occur, the research participant will be followed by physicians, registered nurses and other research staff members for the duration of the participant's hospitalization. Routine care will be provided by hospital staff. Emergency medical equipment, medications and supplies will be at the physician's disposal should the participants have an acute untoward reaction.

UK IRB policies state that IRB-related research records must be retained for a minimum of 6 years after study closure. Do you confirm that you will retain all IRB-related records for a minimum of 6 years after study closure?

◉ Yes ○ No

Back to Top

Payment

Describe the incentives (monetary or other) being offered to subjects for their participation. If monetary compensation is offered, indicate the amount and describe the terms and schedule of payment. Please review this guidance for more information on payments to subjects, including restrictions and expectations.

The participant will receive $50 for the baseline visit and $75 for each of the 2 study visits that involve MRI scans. Compensation will be paid by check after they have completed each of 3 specific study visits (visits 2, 3, and 4). If they choose to withdraw early, or do not attend all study visits, payment will be prorated. They can earn up to $200 for participation in this study. With a few exceptions, study payments are considered taxable income reportable to the Internal Review Service (IRS). A form 1099 will be sent if total payments for research participation are $600 or more in a calendar year.

Costs to Subjects

Include a list of services and/or tests that will not be paid for by the sponsor and/or the study (e.g., MRI, HIV). Kee
subject will not know what is “standard” – and thus not covered by the sponsor/study – unless you tell them.

The participant's insurance company, Medicare, or Medicaid will be responsible for the costs of all care and treatment that they would normally receive for any conditions they may have. These are costs that are considered medically necessary and will be part of the care they receive even if they do not take part in this study. The University of Kentucky may not be allowed to bill your insurance company, Medicare, or Medicaid for the medical procedures done strictly for research.

Therefore, these costs will be paid by the study:

• Knee aspirations performed at the time of surgery
• Pregnancy testing performed at Visit 3
• Administration of the study medication at Visit 3
• Limited physical examination performed at Visits 1, 3 and 4
• All questionnaires collected at Visits 3, 4, 5 and 6

The participant's insurance, Medicare, or Medicaid, may agree to pay for the costs. However, a co-payment or deductible may be needed.

Data and Safety Monitoring

The IRB requires review and approval of data and safety monitoring plans for greater than minimal risk research or NIH-funded/FDA-regulated clinical investigations.

- If you are conducting greater than minimal risk research, or your clinical investigation is NIH-funded, describe your Data and Safety Monitoring Plan (DSMP). Click here for additional guidance on developing a Data and Safety Monitoring Plan.
- If this is a non-sponsored investigator-initiated protocol considered greater than minimal risk research, and if you are planning on using a Data and Safety Monitoring Board (DSMB) as part of your DSMP, click here for additional guidance for information to include with your IRB application.

The DSMB is an independent multidisciplinary group with clinical research experience representing relevant specialties. This group will include a Research Subject Advocate (RSA) who is a Physician, a Pharmacist, an Internal Medicine Physician, Statistician, CCTS Representative and Executive Secretary. Ad-hoc members may be added when experience in specific disease areas or procedures is required.

The DSMB will meet tri-annually or as needed, and will review subject recruitment, AE’s, side effects, withdrawals, protocol violations, and inclusion/exclusion criteria.

Future Use and Sharing of Research Data

If the results of this study will be used by members of the research team or shared with other researchers for future studies, please address the following:

- list the biological specimens and/or information that will be kept
- briefly describe the types, categories and/or purposes of the future research
- describe any risks of the additional use
- describe privacy/confidentiality protections that will be put into place
- describe the period of time specimens/information may be used
- describe procedures for sharing specimens/information with secondary researchers
- describe the process for, and limitations to, withdrawal of specimens/data

We will store, use, and share participant health information and imaging collected as part of this study and leftover blood, urine, and knee fluid samples and for future research in accordance with the ICF language used in this study. All data from the study is stored in the UK REDCap database outside of the study regulatory binders which will be retained for the required 6 years. Blood, urine, and knee fluid samples are labeled by the participants' ID number and stored/archived in the University of Kentucky Orthopaedic Biomarker Freezer (located in UK’s Charles T. Wethington Building, Room 443). No genetic testing will be performed on these stored biological samples. Having information and samples from many people helps researchers identify trends and discover better ways to diagnose, prevent, and treat many conditions. Researchers can use the stored information and samples to learn more about knee injuries or research additional scientific questions

Are you recruiting or expect to enroll **Non-English Speaking Subjects or Subjects from a Foreign Culture**? (does not include short form use for incidentally encountered non-English subjects)

○ Yes ◉ No

Non-English Speaking Subjects or Subjects from a Foreign Culture

Recruitment and Consent:

Describe how information about the study will be communicated to potential subjects appropriate for their culture, and if necessary, how new information about the research may be relayed to subjects during the study.
When recruiting Non-English-speaking subjects, provide a consent document in the subject's primary language. After saving this section, attach both the English and translated consent documents in the "Informed Consent" section.

Cultural and Language Consultants:

The PI is required to identify someone who is willing to serve as the cultural consultant to the IRB.

- This person should be familiar with the culture of the subject population and/or be able to verify that translated documents are the equivalent of the English version of documents submitted.
- The consultant should not be involved with the study or have any interest in its IRB approval.
- Please include the name, address, telephone number, and email of the person who agrees to be the cultural consultant for your study.
- ORI staff will facilitate the review process with your consultant. Please do not ask them to review your protocol separately.

For more details, see the IRB Application Instructions on Research Involving Non-English Speaking Subjects or Subjects from a Foreign Culture.

Local Requirements:

If you will conduct research at an international location, identify and describe:

- relevant local regulations
- data privacy regulations
- applicable laws
- ethics review requirements for human subject protection

Please provide links or sources where possible. If the project has been or will be reviewed by a local ethics review board, attach a copy in the "Additional Information/Materials" section. You may also consult the current edition of the International Compilation of Human Research Standards

53136
CLOSED

Does your study involve **HIV/AIDS research and/or screening for other reportable diseases (e.g., Hepatitis**

○ Yes ◉ No

HIV/AIDS Research

If you have questions about what constitutes a reportable disease and/or condition in the state of Kentucky, see ORI's summary sheet: "Reporting Requirements for Diseases and Conditions in Kentucky" [PDF].

HIV/AIDS Research: There are additional IRB requirements for designing and implementing the research and for obtaining informed consent. Describe additional safeguards to minimize risk to subjects in the space provided below.

For additional information, visit the online IRB Survival Handbook to download a copy of the "Medical IRB's requirements for Protection of Human Subjects in Research Involving HIV Testing" [D65.0000] [PDF], and visit the Office for Human Research Protections web site for statements on AIDS research, or contact the Office of Research Integrity at 859-257-9428.

PI-Sponsored FDA-Regulated Research

Is this an investigator-initiated study that:

Back to Top

1) involves testing a Nonsignificant Risk (NSR) Device, or
2) is being conducted under an investigator-held Investigational New Drug (IND) or Investigational Device Exemption (IDE)?

○ Yes ◉ No

PI-Sponsored FDA-Regulated Research

If the answer above is yes, then the investigator assumes the regulatory responsibilities of both the investigator and sponsor. The Office of Research Integrity provides a summary list of sponsor IND regulatory requirements for drug trials [PDF], IDE regulatory requirements for SR device trials [PDF], and abbreviated regulatory requirements for NSR device trials [PDF]. For detailed descriptions see FDA Responsibilities for Device Study Sponsors or FDA Responsibilities for IND Drug Study Sponsor-Investigators.

- Describe the experience/knowledge/training (if any) of the investigator serving as a sponsor (e.g., previously held an IND/IDE); and
- Indicate if any sponsor obligations have been transferred to a commercial sponsor, contract research organization (CRO), contract monitor, or other entity (provide details or attach FDA 1571).

IRB policy requires mandatory training for all investigators who are also FDA-regulated sponsors (see Sponsor-Investigator FAQs). A sponsor-investigator must complete the applicable Office of Research Integrity web based training, (drug or device) before final IRB approval is granted.

Has the sponsor-investigator completed the mandatory PI-sponsor training prior to this submission?

○ Yes ○ No

If the sponsor-investigator has completed equivalent sponsor-investigator training, submit documentation of the content for the IRB's consideration.

Attachments

53136
CLOSED

53136
CLOSED

HIPAA

0 unresolved comment(s)

Is HIPAA applicable? ◉ Yes ○ No

(Visit ORI's Health Insurance Portability and Accountability Act (HIPAA) web page to determine if your research falls under the HIPAA Privacy Regulation.)

If yes, check below all that apply and attach the applicable document(s):

☐ HIPAA De-identification Certification Form
☐ HIPAA Waiver of Authorization

Attachments

53136
CLOSED

STUDY DRUG INFORMATION

0 unresolved comment(s)

The term drug may include:

- FDA approved drugs,
- unapproved use of approved drugs,
- investigational drugs or biologics,
- other compounds or products intended to affect structure or function of the body, and/or
- complementary and alternative medicine products such as dietary supplements, substances generally recognized as safe (GRAS) when used to diagnose, cure mitigate, treat or prevent disease, or clinical studies of e-cigarettes examining a potential therapeutic purpose.

Does this protocol involve a drug including an FDA approved drug; unapproved use of an FDA approved drug; and/or an investigational drug?

◉ Yes ○ No

If yes, complete the questions below. Additional study drug guidance.

LIST EACH DRUG INVOLVED IN STUDY IN THE SPACE BELOW

Drug Name:

Zilretta (triamcinolone acetonide extended-release injectable suspension)

Note: Inpatient studies are required by Hospital Policy to utilize Investigational Drug Service (IDS) pharmacies (Oncology or Non-Oncology). Use of IDS is highly recommended, but optional for outpatient studies. Outpatient studies not using IDS services are subject to periodic inspection by the IDS for compliance with drug accountability good clinical practices.

Indicate where study drug(s) will be housed and managed:

☐ Investigational Drug Service (IDS) UK Hospital

Other Location:

UK Healthcare Orthopaedic and Sports Medicine Center

Is the study being conducted under a valid Investigational New Drug (IND) application?

◉ Yes ○ No

If Yes, list IND #(s) and complete the following:

Pending

IND Submitted/Held by:

Sponsor: ☐		Held By:	
Investigator: ☑		Held By:	Austin Stone, MD
Other: ☐		Held By:	

☐ Checkmark if the study is being conducted under FDA's Expanded Access Program (e.g., Treatment IND) or if this is an Individual Patient Expanded Access IND (FDA Form 3926).

FDA's Expanded Access Program Information for Individual Patient Expanded Access INDs, and attach the following:

- FDA Form 3926;
- FDA expanded access approval or correspondence;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Expanded Access

SOP.

Complete and attach the required Study Drug Form picking "Study Drug Form" for the document type. Any applicable drug documentation (e.g., Investigator Brochure; approved labeling; publication; FDA correspondence, etc.) should be attached using "Other Drug Documentation" for the document type.

Attachments

Attach Type	File Name
Study Drug Form	FDA IND Exempt Ltr.pdf
Study Drug Form	Study Drug Form.pdf
Study Drug Form	Zilretta PI (2020).pdf

53136
CLOSED

STUDY DEVICE INFORMATION

0 unresolved comment(s)

A DEVICE may be a:

- component, part, accessory;
- assay, reagent, or in-vitro diagnostic device;
- software, digital health, or mobile medical app;
- other instrument if intended to affect the structure or function of the body, diagnose, cure, mitigate, treat or prevent disease; or
- a homemade device developed by an investigator or other non-commercial entity and not approved for marketing by FDA.

For additional information, helpful resources, and definitions, see ORI's Use of Any Device Being Tested in Research web page.

Does this protocol involve testing (collecting safety or efficacy data) of a medical device including an FDA approved device, unapproved use of an approved device, humanitarian use device, and/or an investigational device?

○ Yes ◉ No

[Note: If a marketed device(s) is only being used to elicit or measure a physiologic response or clinical outcome, AND, NO data will be collected on or about the device itself, you may answer "no" above, save and exit this section, (Examples: a chemo drug study uses an MRI to measure tumor growth but does NOT assess how effective the MRI is at making the measurement; an exercise study uses a heart monitor to measure athletic performance but no safety or efficacy information will be collected about the device itself, nor will the data collected be used for comparative purposes against any other similar device).]

If you answered yes above, please complete the following questions.

LIST EACH DEVICE BEING TESTED IN STUDY IN THE SPACE BELOW

Device Name:

Is the study being conducted under a valid Investigational Device Exemption (IDE), Humanitarian Device Exemption (HDE) or Compassionate Use?

○ Yes ○ No

If Yes, complete the following:
IDE or HDE #(s)

IDE/HDE Submitted/Held by:

Sponsor: ☐ Held By:

Investigator: ☐ Held By:

Other: ☐ Held By:

☐ Check if this is a Treatment IDE or Compassionate Use under the Food and Drug Administration (FDA) Expanded Access program.

For Individual or Small Group Expanded Access, see FDA's Early Expanded Access Program Information, and attach the following:

- FDA expanded access approval or sponsor's authorization;
- An independent assessment from an uninvolved physician, if available;
- Confirmation of agreement from manufacturer or entity authorized to provide access to the product.

For guidance and reporting requirements at the conclusion of treatment see the Medical Device SOP.

Does the intended use of any research device being tested (not clinically observed) in this study meet the regulatory definition of Significant Risk (SR) device?

- Yes. Device(s) as used in this study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.
- No. All devices, as used in this study do not present a potential for serious risk to the health, safety, or welfare of subjects/participants.

Complete and attach the required Study Device Form, picking the "Study Device Form" for the document type. Any applicable device documentation (e.g., Manufacturer information; patient information packet; approved labeling; FDA correspondence, etc.) should be attached using "Other Device Documentation" for the document type.

Attachments

RESEARCH SITES

0 unresolved comment(s)

To complete this section, ensure the responses are accurate then click "SAVE".

A) Check all the applicable sites listed below at which the research will be conducted. If none apply, you do not need to check any boxes.

UK Sites

- ☐ UK Classroom(s)/Lab(s)
- ☑ UK Clinics in Lexington
- ☐ UK Clinics outside of Lexington
- ☐ UK Healthcare Good Samaritan Hospital
- ☑ UK Hospital

Schools/Education Institutions

- ☐ Fayette Co. School Systems *
- ☐ Other State/Regional School Systems
- ☐ Institutions of Higher Education (other than UK)

***Fayette Co. School systems, as well as other non-UK sites, have additional requirements that must be addressed. See ORI's IRB Application Instructions - Off-site Research web page for details.**

Other Medical Facilities

- ☐ Bluegrass Regional Mental Health Retardation Board
- ☐ Cardinal Hill Hospital
- ☐ Eastern State Hospital
- ☐ Norton Healthcare
- ☐ Nursing Homes
- ☐ Shriner's Children's Hospital
- ☐ Veterans Affairs Medical Center
- ☐ Other Hospitals and Med. Centers

- ☐ Correctional Facilities
- ☐ Home Health Agencies
- ☐ International Sites

Research activities conducted at performance sites that are not owned or operated by the University of Kentucky, at sites that are geographically separate from UK, or at sites that do not fall under the UK IRB's authority, are subject to special procedures for coordination of research review. Additional information is required (see IRB Application Instructions - Off-Site Research web page), including:

- A letter of support and local context is required from non-UK sites. See *Letters of Support and Local Context* on the IRB Application Instructions - Off-Site Research web page for more information.
- Supportive documentation, including letters of support, can be attached below.
- NOTE: If the non-UK sites or non-UK personnel are engaged in the research, there are additional federal and university requirements which need to be completed for their participation. For instance, the other site(s) may need to complete their own IRB review, or a cooperative review arrangement may need to be established with non-UK

sites.
- Questions about the participation of non-UK sites/personnel should be discussed with the ORI staff at (859) 257-9428.

List all other non-UK owned/operated locations where the research will be conducted:

Describe the role of any non-UK site(s) or non-UK personnel who will be participating in your research.

Attachments

B) Is this a multi-site study for which **you are the lead investigator or UK is the lead site**? ○ Yes ◉ No

If YES, describe the plan for the management of reporting unanticipated problems, noncompliance, and submission of protocol modifications and interim results from the non-UK sites:

C) If your research involves collaboration with any sites and/or personnel outside the University of Kentucky, then it is considered multisite research and IRB reliance issues will need to be addressed. This may include national multi-center trials as well local studies involving sites/personnel external to UK. If you would like to request that the University of Kentucky IRB (UK IRB) serve as the lead IRB for your study, or if you would like the UK IRB to defer review to another IRB, please contact the IRBReliance@uky.edu.

53136
CLOSED

RESEARCH ATTRIBUTES

0 unresolved comment(s)

Indicate the items below that apply to your research. Depending on the items applicable to your research, you may be required to complete additional forms or meet additional requirements. Contact the ORI (859-257-9428) if you have questions about additional requirements.

☐ Not applicable

Check All That Apply

	For additional requirements and information:
☐ Academic Degree/Required Research	• Cancer Research (MCC PRMC) • Certificate of Confidentiality (look up "Confidentiality/Privacy...") • CCTS (Center for Clinical and Translational Science)
☐ Alcohol/Drug/Substance Abuse Research	• Clinical Research (look up "What is the definition of....)
☐ Biological Specimen Bank Creation (for sharing)	• Clinical Trial
☐ Cancer Research	• Collection of Biological Specimens for Banking (look up "Specimen/Tissue Collection...")
☑ CCTS-Center for Clinical & Translational Science	• Collection of Biological Specimens (look up "Specimen/Tissue Collection...")
☐ Certificate of Confidentiality	• Community-Based Participatory Research (look up "Community-Engaged...")
☑ Clinical Research	• Data & Safety Monitoring Board (DSMB) *For Medical IRB: Service Request Form for CCTS DSMB
☐ Clinical Trial - Phase 1	
☑ Clinical Trial	• Data & Safety Monitoring Plan
☐ Collection of Biological Specimens for internal banking and use (not sharing)	• Deception* *For deception research, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Community-Based Participatory Research	
☐ Deception	
☐ Educational/Student Records (e.g., GPA, test scores)	
☐ Emergency Use (Single Patient)	• Emergency Use (Single Patient) [attach Emergency Use Checklist] (PDF)
☐ Gene Transfer	• Genetic Research (look up "Specimen/Tissue Collection...")
☐ Genetic Research	• Gene Transfer
☐ GWAS (Genome-Wide Association Study) or NIH Genomic Data Sharing (GDS)	• HIV/AIDS Research (look up "Reportable Diseases/Conditions") • Screening for Reportable Diseases [E2.0000] (PDF)
☐ Human Cells, Tissues, and Cellular and Tissue Based Products	• International Research (look up "International & Non-English Speaking")
☐ Individual Expanded Access or Compassionate Use	• NIH Genomic Data Sharing (GDS) Policy (PDF)
☐ International Research	• Planned Emergency Research Involving Waiver of Informed Consent* *For Planned Emergency Research Involving Waiver of Informed Consent, also go to the E-IRB Application Informed Consent section, checkmark and complete "Request for Waiver of Informed Consent Process"
☐ Planned Emergency Research Involving Exception from Informed Consent	
☐ Recombinant DNA	
☐ Registry or data repository creation	
☐ Stem Cell Research	
☐ Suicide Ideation or Behavior Research	
☐ Survey Research	
☐ Transplants	
☐ Use, storage and disposal of radioactive material and radiation producing devices	• Use, storage and disposal of radioactive material and radiation producing devices
☐ Vaccine Trials	

53136
CLOSED

53136
CLOSED

FUNDING/SUPPORT

0 unresolved comment(s)

If the research is being submitted to, supported by, or conducted in cooperation with an external or internal agency or funding program, indicate below all the categories that apply.

☐ Not applicable

Check All That Apply

- ☐ Grant application pending
- ☐ (HHS) Dept. of Health & Human Services
  - ☐ (NIH) National Institutes of Health
  - ☐ (CDC) Centers for Disease Control & Prevention
  - ☐ (HRSA) Health Resources and Services Administration
  - ☐ (SAMHSA) Substance Abuse and Mental Health Services Administration
- ☐ (DoJ) Department of Justice or Bureau of Prisons
- ☐ (DoE) Department of Energy
- ☐ (EPA) Environmental Protection Agency
- ☐ Federal Agencies Other Than Those Listed Here
- ☐ Industry (Other than Pharmaceutical Companies)
- ☐ Internal Grant Program w/ proposal
- ☐ Internal Grant Program w/o proposal
- ☐ National Science Foundation
- ☐ Other Institutions of Higher Education
- ☑ Pharmaceutical Company
- ☐ Private Foundation/Association
- ☐ U.S. Department of Education
- ☐ State

Other:

Click applicable listing(s) for additional requirements and information:

- (HHS) Dept. of Health & Human Services
- (NIH) National Institutes of Health
- (CDC) Centers for Disease Control & Prevention
- (HRSA) Health Resources & Services Administration
- (SAMHSA) Substance Abuse & Mental Health Services Administration
- Industry (Other than Pharmaceutical Companies) [IRB Fee Info]
- National Science Foundation
- (DoEd) U.S. Department of Education
- (DoJ) Department of Justice or Bureau of Prisons
- (DoE) Department of Energy Summary and Department of Energy Identifiable Information Compliance Checklist
- (EPA) Environmental Protection Agency

Specify the funding source and/or cooperating organization(s) (e.g., National Cancer Institute, Ford Foundation, Eli Lilly & Company, South Western Oncology Group, Bureau of Prisons, etc.):

Flexion Therapeutics

Add Related Grants

If applicable, please search for and select the OSPA Account number or Electronic Internal Approval Form (eIAF) # (notif #) associated with this IRB application using the "Add Related Grants" button.
If required by your funding agency, upload your grant using the "Grant/Contract Attachments" button.

Add Related Grants

Grant/Contract Attachments

53136
CLOSED

The research involves use of Department of Defense (DoD) funding, military personnel, DoD facilities, or other
(See DoD SOP and DoD Summary for details)

○ Yes ◉ No

Using the “attachments” button (below), attach applicable materials addressing the specific processes described in the DoD SOP.

DOD SOP Attachments

Additional Certification: (If your project is federally funded, your funding agency may request an Assurance/ Certification/Declaration of Exemption form.) Check the following if needed:

☐ Protection of Human Subjects Assurance/Certification/Declaration of Exemption (Formerly Optional Form – 310)

Assurance/Certification Attachments

53136
CLOSED

OTHER REVIEW COMMITTEES

0 unresolved comment(s)

If you check any of the below committees, additional materials may be required with your application submission.

Does your research fall under the purview of any of the other review committees listed below? [*If yes, check all that apply and attach applicable materials using the attachment button at the bottom of your screen.*]

○ Yes ◉ No

Additional Information

- ☐ Institutional Biosafety Committee
- ☐ Radiation Safety Committee
- ☐ Radioactive Drug Research Committee
- ☐ Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)
- ☐ Graduate Medical Education Committee (GME)
- ☐ Office of Medical Education (OME)

- Institutional Biosafety Committee (IBC) - Attach required IBC materials
- Radiation Safety Committee (RSC) - For applicability, see instructions and attach form
- Radioactive Drug Research Committee (RDRC)
- Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC)** - Attach MCC PRMC materials, if any, per instructions.
- Office of Medical Education (OME)
- Graduate Medical Education Committee (GME)

Attachments

**** If your study involves cancer research, be sure to select "Cancer Research" in the "Research Attributes" section.** ORI will send your research protocol to the Markey Cancer Center (MCC) Protocol Review and Monitoring Committee (PRMC). The MCC PRMC is responsible for determining whether the study meets the National Cancer Institute (NCI) definition of a clinical trial and for issuing documentation to you (the investigator) which confirms either that PRMC approval has been obtained or that PRMC review is not required. Your IRB application will be processed and reviewed independently from the PRMC review.

53136 Statistical Analysis Plan:

Primary objective will be assessed using two-tailed independent t-tests for comparison between timepoints. Similarly, all secondary measures will be assessed using two-tailed independent t-tests.