Double Blinded Prospective Pilot Study to Determine the Safety and Effectiveness of a Connective Tissue Allograft (Active Matrix®) vs. Standard of Care in Adhesive Capsulitis of the Shoulder

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Short Title: Study of Active Matrix in Adhesive Capsulitis of the Shoulder

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Sponsor: **Skye Biologics Holdings, LLC**
[redacted]

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STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP). The protocol, informed consent form(s), and all participant materials will be submitted to the Advarra Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

1 INTRODUCTION

1.1 BACKGROUND

Introduction

Patients often present with pain and progressive limitation of active and passive shoulder motion due a variety of intrinsic and extrinsic pathologies, including adhesive capsulitis[1]. The term "frozen shoulder", as first used by Codman[2], is often used to refer to a painful stiff shoulder though this diagnosis does not denote a specific pathology. Rather, it encompasses what Codman described as "many conditions which cause spasm of the short rotators or adhesions about the joint or bursae." To quote Nevaiser and Nevaiser[1]," Adhesive capsulitis is a specific pathologic entity in which chronic inflammation of the capsule sub synovial layer produces capsular thickening, fibrosis, and adherence of the capsule to itself and to the anatomic neck of the humerus[3] The contracted, adherent capsule causes pain, especially when it is stretched suddenly, and produces a mechanical restraint to motion. The natural history of adhesive capsulitis is a matter of controversy. Some have suggested that adhesive capsulitis is self-limiting and need not be treated. Management of true capsular restriction of motion (ie, true adhesive capsulitis) begins with gentle, progressive stretching exercises. Most patients improve with nonsurgical treatment. Uncertainty regarding the ultimate progression of adhesive capsulitis hampers efforts to measure the effectiveness of new treatments. Given the prolonged disability these patients face, interventions should be focused on hastening recovery of motion and diminishing pain."

There are many extracellular matrix (ECM) products currently being used for regenerative purposes in the repair of musculoskeletal injuries[3]. Placental-tissue derived matrices have recently become an area of increasing interest due to source tissue availability and the abundance of bioactive molecules in the tissue[4]. These bioactive molecules are known to promote tissue repair by regulating the inflammatory response and recruiting cells to the site of injury[5]. Past studies have shown that placental-based ECMs have helped treat other orthopedic connective tissue injuries, suggesting that such a matrix may have novel utility as a therapeutic for adhesive capsulitis [6-10].

ActiveMatrix®

ActiveMatrix® (AM) is a human placental allograft currently regulated by the FDA as a human cell, tissue, or cellular or tissue-based product (HCT/P) under Section 361 of the Public Health Service Act and regulations in 21 CFR Part 1271. AM is sterile with a primary function to supplement injured connective tissue where applied.

Safety: There is low risk associated with the sterile AM graft other than injection site pain or discomfort, however, the patient will be under general anesthesia at the time of application. AM and other Skye grafts have been implanted in over 250,000 applications to date. Donors are screened and tissues are tested extensively per 21 CFR Part 1271 to ensure there is no risk of disease transmission.

AM is a natural allograft derived from human placenta confirmed to contain high levels of various growth factors and structural proteins: PDGF-AA/-BB, bFGF, EGF, KGF, PIGF, IL-4, TGF-β3, TIMP-1/-2, hyaluronic acid, and collagen.[4] Additional growth factors found in placental tissue are likely to be similarly preserved in AM as well, but remain to be differentially tested.[4]

1.2 RISK/BENEFIT ASSESSMENT

1.2.1 KNOWN POTENTIAL RISKS

There is low risk associated with the sterile AM graft other than injection site pain or discomfort. AM is a commercially available, human placenta-derived tissue graft that is regulated by the FDA as a human cell, tissue, or cellular or tissue-based product (HCT/P) under Section 361 of the Public Health Service Act and regulations in 21 CFR Part 1271; AM and other Skye grafts have been implanted in over 250,000 applications to date. Donors are screened and tissues are tested extensively per federal guidelines to ensure there is minimal risk of disease transmission.

1.2.2 KNOWN POTENTIAL BENEFITS

Numerous medical treatments through commercial use and scientific studies have investigated the role of placental grafts in the repair of soft tissue defects and shown numerous benefits/ enhancements; however, the exact mechanism of action of AM in response to injury, and regulation of physiologic and regenerative processes are unknown. The potential benefit from participating in this study is that the participants may achieve reduced pain and increased function of the effected shoulder.

2 HYPOTHESIS

In patients with adhesive capsulitis, shoulder function at 4 weeks, 12 weeks, and 6 months after administration of ActiveMatrix® connective tissue allograft will be equivalent to treatment with corticosteroid injections.

3 STUDY DESIGN

3.1 OVERALL DESIGN

This prospective randomized control trial will include two intervention groups, each allocated an equal number of patients. We will not include a 'control' group of patients due to ethical considerations of withholding treatment. One intervention group will receive an intra-articular corticosteroid injection (Group 1) and the other will receive a human placental connective tissue derived allograft injection (Group 2; ActiveMatrix, Skye Biologics, Inc.). Assuming an attrition rate of 20%, the number of patients required for the study was calculated to be 25 in each group. The intervention period will be over a period of months until we reach this target sample size of 50. Patients will be assessed at 4 weeks, 12 weeks, and 6 months after administration of therapy. The patients will be recruited from the city of Houston and neighboring municipalities by referral from UT Houston orthopedic surgeons.

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all the following criteria:

1. Provision of signed and dated informed consent form
2. Stated willingness to comply with all study procedures and availability for the duration of the

study

3. Male or female, ≥ 18 years of age to ≤ 75 years of age
4. Have a clinical diagnosis of adhesive capsulitis, defined as:
   i. pain along the C5 dermatome
   ii. limitations of passive range of motion of more than 20 degrees in at least one or more of the PROM measurements compared to the contralateral side. The planes of motion measured are abduction internal rotation, abduction external rotation, forward elevation, abduction, neutral external rotation, neutral internal rotation.
5. Have no contraindications or allergies to the treatment administered
6. Have experienced shoulder pain for more than 6 weeks and less than 1 year (to ensure the patient is in the "freezing" stage of adhesive capsulitis).
7. Have current imaging studies (plain radiographs and MRI exams) of the shoulder to rule out other etiologic diagnoses.
8. Negative pregnancy test for patients who are of childbearing age
   i. Female patients who are postmenopausal do not need a pregnancy test
   ii. Female patients who are surgically sterile do not need a pregnancy test

4.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Any prior treatment for this episode of shoulder pain, such as prior intra-articular injection
2. Evidence, based on MRI or plain radiographs, of any pathology within the shoulder other than adhesive capsulitis (e.g. glenohumeral osteoarthritis, full thickness tears of the labrum or rotator cuff, , calcific tendonitis)
3. A history of significant trauma to the shoulder
4. Poorly controlled diabetes mellitus, as defined by HbA1c > 8 mmol/L and glucose > 200 mg/dL. For diabetic participants HbA1c and glucose levels will be measured prior to intervention and documented for later analysis. For non-diabetic participants, previous labs will be utilized. All other medical diseases will be documented for later analysis.
5. History of Cardiovascular Accident (CVA) such as stroke or Transient Ischemic Attack (TIA)
6. Blood dyscrasias
7. Prior shoulder surgery
8. Any one of child-bearing age who has a positive pregnancy test

There is no intended distribution or restriction of subjects by racial and ethnic origin. No vulnerable subjects are included in this protocol.

4.3 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical trial but are not subsequently randomly assigned to the study intervention or entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants, to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse event (SAE).

Individuals who do not meet the criteria for participation in this trial (screen failure) because of a systemic or local infection may be rescreened. Rescreened participants should be assigned the same participant number as for the initial screening.

4.4 BLINDED GROUP ASSIGNMENT

Eligible patients who consented to the study will be randomly assigned to one of two treatment groups according to a serial number on a closed envelope. Investigators and patients will be "blinded" to each

5 STUDY INTERVENTION

patients group assignment for the duration of the trial.

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

Both the corticosteroid and the AM treatment will be administered via intra-articular injections. This procedure will be performed by an interventional radiologist via a posterior approach using ultrasound guidance. (Prior studies indicate that injection performed without fluoroscopic guidance are inaccurate in as many as 60% of cases[11].) The same interventional radiologist will complete all of the injections for the trial to eliminate any bias.

5.1.2 TREATMENT GROUP 1

Patients in Group 1 will receive a corticosteroid injection consisting of Triamcinolone 20 mg (1cc) with Lidocaine 10 mg/ml (5 cc).

5.1.3 TREATMENT GROUP 2

Patients in Group 2 will receive an injection consisting of ActiveMatrix (1cc; Skye Biologics, Inc.) with Lidocaine 10 mg/ml (5cc). ActiveMatrix is a human tissue derived allograft intended for homologous use to supplement or replace inadequate connective tissue (Skye Biologics, Inc). The allograft has been registered with the U.S. FDA and commercially available since 2014 as a human cell, tissue, or cellular or tissue-based product (HCT/P; Skye Biologics, Inc). All participants will begin physical therapy 1-week post-injection. In total, 8-12 sessions of physical therapy.

5.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

5.2.1 ACQUISITION AND ACCOUNTABILITY

Distribution of AM for this study will be handled by Skye Biologics. The product will be shipped to the study site and received by the investigator. Recipient records must be maintained for the purpose of tracking tissue post-transplant per The Joint Commission and FDA requirements. Supplemental labels, which indicate the Tissue ID number, are contained in the package to aid in the tracking process. The allograft ID number must be recorded in the operative record. The Allograft Tracking Record must be completed and returned to Skye Biologics, Inc.

5.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

Donor eligibility determined & tissues processed by: Human Regenerative Technologies, LLC
Distributed by: Skye Biologics, Inc.
[redacted]

Tissue Origin: Tissue is obtained aseptically at Cesarean birth delivery, which is performed by a licensed OB/GYN physician in a hospital operating room environment.

Processing: The HCT/Ps are processed in a controlled environment using methods designed to prevent contamination of the tissues. Tissues are exposed to antibiotics at an initial processing step and subsequently subjected to multiple rinse steps using sterile saline. Final products are sized and packaged according to approved specifications and procedures and are terminally sterilized by E-Beam irradiation technology in accordance with ANSI/AAMI/ISO11137.

Donor/Tissue Screening: The donor of the Donated Human Tissue has been deemed free from risk factors for, and clinical evidence of, infection due to relevant communicable diseases and other exclusionary disease conditions through the review of the donor's medical records, including medical/behavior risk assessment and a recent physical examination. The donor is deemed eligible for tissue donation by the tissue bank's Medical Director and the enclosed Donated Human Tissue has been determined to be acceptable for transplantation use through a stringent quality assurance review process. Additionally, testing of a qualified blood sample indicates that the donor is negative or nonreactive for the following communicable disease markers:

- Human Immunodeficiency Virus (HIV)
    - HIV-1/2 Antibodies
    - Nucleic Acid Test for HIV-1 RNA
- Hepatitis B Virus (HBV)
    - HBV Surface Antigen
    - HBV Core Antibody (Total)
    - Nucleic Acid Test for HBV DNA
- Hepatitis C Virus (HCV)
    - HCV Antibody
    - Nucleic Acid Test for HCV RNA
- Human T Cell Lymphotrophic Virus I/II
    - HTLV-I/II Antibody
- Syphilis
    - Rapid Plasma Reagin Screen*, or
    - Treponemal Specific Test
- West Nile Virus (WNV)
    - Nucleic Acid Test for WNV RNA**

* A donor whose blood specimen is unsuitable for the nontreponemal screening assay, such as the RPR test, or with a reactive result from the non-treponemal screening assay, is deemed eligible for tissue donation only when the result from the treponemal-specific (confirmatory) assay is nonreactive.

** Starting June 2017, blood samples from donors acquired during the seasonal time period (from June 1 - October 31 every year), will be tested with the WNV NAT assay.

The non-required screening test for exposure to the virus listed below may have been performed on the donor. A negative / nonreactive result is not required for this test; however, all donors are evaluated on a case-by-case basis by the Medical Director.

- Cytomegalovirus (CMV)
    - CMV Antibody (Total)

All laboratories performing these tests are registered with FDA and certified to perform testing on human specimens in accordance with the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and 42 CFR part 493, or equivalent requirements. Test kits used are approved and cleared (for screening blood specimens collected from living donors) by the FDA. A copy of the medical records can be obtained upon request.

Adverse Reactions: No adverse clinical reactions to this tissue product have been reported. Adverse reactions or outcomes that potentially involve the use of this tissue product must be reported immediately to Skye Biologics, Inc.

5.2.3 PRODUCT STORAGE AND STABILITY

The product can be stored at ambient temperature (50-86°F / 10-30°C) until use. The product is for single

patient, one time use only. Once opened, the AM must be used immediately or disposed of appropriately. Do not re-sterilize. Dispose of any unused product. Do not use if the integrity of the packaging has been violated, opened or damaged, or if mishandling has caused possible damage or contamination. Do not use if the seal has been broken or compromised.

5.2.4 PREPARATION

The tissue in its vial packaging is terminally sterilized via irradiation and may be placed directly onto the sterile field.

1. Open product package & remove the peel-pack containing the vial.
2. Using aseptic technique, peel open pouch and present vial into sterile field.
3. Shake the vial to mix completely.
4. Open vial and draw into a syringe containing the predetermined amount of saline using an 18G needle.
5. Mix thoroughly in the syringe.
6. Replace 18G needle with a 21G needle prior to injection.

5.3 CONCOMITANT THERAPY

For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Case Report Form (CRF) are concomitant prescription medications, over-the-counter medications and supplements.

6 STUDY PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Participants are free to withdraw from participation in the study at any time upon request.

An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study intervention non-compliance
- If any clinical adverse event (AE), laboratory abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant

The reason for participant discontinuation or withdrawal from the study will be recorded on the Case Report Form (CRF). Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

6.2 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if he or she fails to return for 2 scheduled visits and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 5 days of the missed visit and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods).

These contact attempts should be documented in the participant's medical record or study file.

- Should the participant continue to be unreachable, he or she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

7 OUTCOME MEASURES

The primary outcome measure for this study will be the Shoulder Pain and Disability Index (SPADI). SPADI is a self-administered questionnaire that measures a combination of pain and functional disability. SPADI is scored from 0 to 100 with a high score representing more pain and disability. SPADI score will be recorded at inclusion and at 4 weeks, 12 weeks, and 6 months following injection.

We will use SPADI as the primary outcome measure. The minimal clinically important difference (MCID) for SPADI in the literature has been primarily cited as between 8 and 13, however values as high 23 have been cited12-16. Prior trials have considered a change of 14 to be clinically significant1,17. For our MCID we will use a value of 13. In previous studies where SPADI was the primary outcome measure, the variance in SPADI was 15. Given = 0.05, a sample size of 21 per group is required to provide 80% power in detecting a 13 point difference in mean SPADI score of the 2 treatment groups. Assuming an attrition rate of 20%, the number of patients required for the study was calculated to be 25 in each group.

The Visual Analogue Scale (VAS), The American Shoulder and Elbow Surgeons Shoulder Score (ASES), and Passive range of motion (PROM) will be secondary outcome measures. VAS is a questionnaire scored on a 100mm horizontal scale that represents the patients pain intensity. A higher score corresponds to increased pain intensity. ASES is a standardized shoulder assessment form and is offered as a baseline measure of shoulder function. Score ranges from 0 to 100, with a score of 0 indicating a worse shoulder condition and a score of 100 indicating a better shoulder condition. A goniometer will be the measuring instrument for PROM. In addition, photographs will be taken to document each joint position. PROM will be measured in the following planes: abduction internal rotation, abduction external rotation, forward elevation, abduction, extension and neutral internal rotation. PROM will be measured on both sides and compared at inclusion and at each follow-up visit. The endpoint for PROM is when the patient either cannot move their arm any further or the pain becomes unbearable.1 PROM will be measured by UTHealth MD shoulder specialists who are "blinded" to which group the patient was randomized to.

7.1 DATA COLLECTED

Demographics (DOB/age, sex, involved shoulder, race, PMedHx, PSurgHx, Allergies, smoking Hx, medications), PROM measurements (abduction internal rotation, abduction external rotation, forward elevation, abduction, extension and neutral internal rotation), vascular/neuro status of the involved limb, pain levels (VAS), and SPADI index. Patient will be assessed at the time of initial injection as well as 4 weeks, 12 weeks, and 6 months after administration of therapy. Adverse and Serious Adverse Events will be collected and reported as defined below.

7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

7.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

7.2.3 CLASSIFICATION OF AN ADVERSE EVENT

7.2.3.1 SEVERITY OF EVENT

For adverse events (AEs), the following guidelines will be used by the investigator to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate** – Events result in a low level of inconvenience or concern with the therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe** – Events interrupt a participant's usual daily activity and may require systemic drug therapy or other treatment. Severe events are usually potentially life-threatening or incapacitating. Of note, the term "severe" does not necessarily equate to "serious".

7.2.3.2 RELATIONSHIP TO STUDY INTERVENTION

All adverse events (AEs) must have their relationship to study intervention assessed by the clinician who examines and evaluates the participant based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below. In a clinical trial, the study product must always be suspect.

- **Related** – The AE is known to occur with the study intervention, there is a reasonable possibility that the study intervention caused the AE, or there is a temporal relationship between the study intervention and event. Reasonable possibility means that there is evidence to suggest a causal relationship between the study intervention and the AE.
- **Not Related** – There is not a reasonable possibility that the administration of the study intervention caused the event, there is no temporal relationship between the study intervention and event onset, or an alternate etiology has been established.

7.2.3.3 EXPECTEDNESS

The investigator will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention.

7.2.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW -UP

The occurrence of an adverse event (AE) or serious adverse event (SAE) may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor.

All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate case report form (CRF). Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution.

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AEs characterized as intermittent require documentation of onset and duration of each episode.

The investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 7 (for non-serious AEs) or 30 days (for SAEs) after the last day of study participation. At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

7.2.5 ADVERSE EVENT REPORTING

The investigator must record nonserious adverse events and report them to the sponsor within 30 days.

7.2.6 SERIOUS ADVERSE EVENT REPORTING

The study clinician will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or investigator brochure and must include an assessment of whether there is a reasonable possibility that the study intervention caused the event. Study endpoints that are serious adverse events (e.g., all-cause mortality) must be reported in accordance with the protocol unless there is evidence suggesting a causal relationship between the study intervention and the event (e.g., death from anaphylaxis). In that case, the investigator must immediately report the event to the sponsor.

All serious adverse events (SAEs) will be followed until satisfactory resolution or until the site investigator deems the event to be chronic or the participant is stable. Other supporting documentation of the event may be requested by the study sponsor and should be provided as soon as possible.

7.3 UNANTICIPATED PROBLEMS

7.3.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

The Office for Human Research Protections (OHRP) considers unanticipated problems involving risks to participants or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the Institutional Review Board (IRB)-approved research protocol and informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.3.2 UNANTICIPATED PROBLEM REPORTING

The investigator will report unanticipated problems (UPs) to the reviewing Institutional Review Board (IRB) and to the Sponsor within 24 hours. The UP report will include the following information:

- Protocol identifying information: protocol title and number, PI's name, and the IRB project number;
- A detailed description of the event, incident, experience, or outcome;
- An explanation of the basis for determining that the event, incident, experience, or outcome represents an UP;
- A description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

8 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

8.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

8.1.1 INFORMED CONSENT PROCESS

8.1.1.1 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.

8.1.1.2 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.

8.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor and IRB.

8.1.3 CONFIDENTIALITY AND PRIVACY

Participant confidentiality and privacy is strictly held in trust by the investigator, their staff, and the sponsor and their interventions. This confidentiality is extended to cover testing of biological samples 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 study monitor, 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 the 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 by the sponsor. 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 sponsor 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 sponsor facility.

8.1.4 QUALITY ASSURANCE AND QUALITY CONTROL

The clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be clarified/resolved.

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

8.1.5 DATA HANDLING AND RECORD KEEPING

8.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

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. Data recorded in the electronic case report form (eCRF) derived from source documents should be consistent with the data recorded on the source documents.

8.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP). The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

9 REFERENCES

1. Neviaser AS, Neviaser RJ. Adhesive capsulitis of the shoulder. JAAOS-Journal of the American Academy of Orthopaedic Surgeons. 2011 Sep 1;19(9):536-42.

2. Sharma SP, Bærheim A, Moe-Nilssen R, Kvåle A. Adhesive capsulitis of the shoulder, treatment with corticosteroid, corticosteroid with distension or treatment-as-usual; a randomised controlled trial in primary care. *BMC Musculoskelet Disord*. 2016;17(1):232. doi:10.1186/s12891-016-1081-0

3. Badylak SF. The extracellular matrix as a scaffold for tissue reconstruction. *Semin Cell Dev Biol*. 2002;13(5):377-383. doi:10.1016/s1084952102000940

4. Irvin J, Danchik C, Rall J, et al. Bioactivity and composition of a preserved connective tissue matrix derived from human placental tissue. *J Biomed Mater Res B Appl Biomater*. 2018;106(8):2731-2740. doi:10.1002/jbm.b.34054

5. Diegelmann R F. Wound healing: an overview of acute, fibrotic and delayed healing. *Front Biosci*. 2004;9(1-3):283. doi:10.2741/1184

6. Werber B, Martin E. A Prospective Study of 20 Foot and Ankle Wounds Treated with Cryopreserved Amniotic Membrane and Fluid Allograft. *J Foot Ankle Surg*. 2013;52(5):615-621. doi:10.1053/j.jfas.2013.03.024

7. Zelen CM, Poka A, Andrews J. Prospective, randomized, blinded, comparative study ofinjectable micronized dehydrated amniotic/chorionic membrane allograft for plantar fasciitis--a feasibility study. *Foot Ankle Int*. 2013;34(10):1332-1339. doi:10.1177/1071100713502179

8. Lullove E. A Flowable Placental Tissue Matrix Allograft in Lower Extremity Injuries: A Pilot Study. *Cureus*. 7(6). doi:10.7759/cureus.275

9. Huddleston HP, Cohn MR, Haunschild ED, Wong SE, Farr J, Yanke AB. Amniotic Product Treatments: Clinical and Basic Science Evidence. *Curr Rev Musculoskelet Med*. 2020;13(2):148-154. doi:10.1007/s12178-020-09614-2

10. McIntyre JA, Jones IA, Danilkovich A, Vangsness CT. The Placenta: Applications in Orthopaedic Sports Medicine. *Am J Sports Med*. 2018;46(1):234-247. doi:10.1177/0363546517697682

11. Carette S, Moffet H, Tardif J, et al. Intraarticular corticosteroids, supervised physiotherapy, or a combination of the two in the treatment of adhesive capsulitis of the shoulder: A placebo-controlled trial. *Arthritis Rheum*. 2003;48(3):829-838. doi:10.1002/art.10954

12. Schmitt JS, Di Fabio RP. Reliable change and minimum important difference (MID) proportions facilitated group responsiveness comparisons using individual threshold criteria. *J Clin Epidemiol*. 2004;57(10):1008-1018. doi:10.1016/j.jclinepi.2004.02.007

13. Roy J-S, MacDermid JC, Woodhouse LJ. Measuring shoulder function: A systematic review of four questionnaires. *Arthritis Care Res*. 2009;61(5):623-632. doi:10.1002/art.24396

14. Laslett M, Steele M, Hing W, McNair P, Cadogan A. Shoulder pain patients in primary care--part 1: Clinical outcomes over 12 months following standardized diagnostic workup, corticosteroid injections, and community-based care. *J Rehabil Med*. 2014;46(9):898-907. doi:10.2340/16501977-1860

15. Starkey C, Brown SD. *Examination of Orthopedic & Athletic Injuries*. F.A. Davis; 2015.

16. Graaf M, Scholten-Peeters G, Duijn E, et al. The Responsiveness and Interpretability of the Shoulder Pain and Disability Index. *J Orthop Sports Phys Ther*. 2017;47:1-21. doi:10.2519/jospt.2017.7079

17. Paruthikunnan SM, Shastry PN, Kadavigere R, Pandey V, Karegowda LH. Intra-articular steroid for adhesive capsulitis: does hydrodilatation give any additional benefit? A randomized control trial. *Skeletal Radiol*. 2020;49(5):795-803. doi:10.1007/s00256-019-03316-8