USE OF PRP AFTER ARTHROSCOPIC DEBRIDEMENT FOR TFCC TEARS

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Summary of Changes from Previous Version:

Affected Section(s)	Summary of Revisions Made	Rationale
6.1.2, 6.1.3, 6.2	Medical photography added	Per MCA review
9.6 and throughout	Sample size per justification	Per Biostats Review

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the sponsor and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the 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. 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 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title of the Study: Use of Platelet Rich Plasma after Arthroscopic Debridement for Triangular Fibrocartilage Complex Tears

Number of Subjects: 48

Objective: The objective of this study is to determine if treatment with platelet rich plasma (PRP) after arthroscopic debridement of triangular fibrocartilage complex (TFCC) tears improves patient outcomes when compared to those who were not treated with PRP after arthroscopic debridement.

Methodology: 48 subjects with TFCC tears will be randomized to treatment with PRP versus placebo (normal saline). Subjects and medical staff outside of the operating room will be blinded to treatment group throughout the study. Outcome measures will include pain scale scores, grip strength, wrist range of motion, Patient-rated Wrist Evaluation (PRWE) scores, and Modified Mayo Wrist scores.

Visit Schedule: Pre-operative visit, post-operative visits at month 1, month 3, month 6 and year 1.

Diagnosis and Main Inclusion Criteria for Inclusion/Exclusion: Subjects with TFCC tears.

Inclusion Criteria:

- Male or Female >18 years of age
- TFCC tear requiring surgical intervention
- Be willing to undergo arthroscopic debridement and injection with PRP
- Be in good health other than the TFCC tear
- Have realistic expectations of surgical results
- Understand and be willing to follow all aspects of the study protocol and have signed and dated the IRB-approved Informed Consent Form and the Authorization for Use and Release of Health and Research Study Information (HIPAA) form prior to any study-related procedures being performed

Exclusion Criteria: To be eligible for enrollment, the subject must not:

- Have collagen-vascular, connective tissue, or bleeding disorders
- Be a smoker or have smoked in last 2 months
- Have any disease, including uncontrolled diabetes, which is clinically known to impact wound healing ability
- Have regional sympathetic dystrophy
- Be pregnant, lactating or expecting to be within the next 24 months
- Currently have an alcohol/substance abuse problem or have had a relapse within one year to screening visit
- Have an abscess or infection at the time of surgery
- Have a condition or be in a situation that, in the Investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study

Duration of the Study: Subjects will be followed for 12 months post arthroscopic debridement.

Criteria for Evaluation: The primary outcome measure is the difference in improvement between preoperative and post-operative outcomes as measured by pain scale scores, grip strength, wrist range of motion, Patient-rated Wrist Evaluation (PRWE) scores, and Modified Mayo Wrist scores between patients treated with PRP and patients not treated with PRP after arthroscopic debridement. Pain scale scores, grip strength, wrist range of motion, PRWE scores, and the Modified Mayo Wrist Score will be measured at the pre-operative visit, and post-operatively at month 1, month 3, month 6, and year 1.

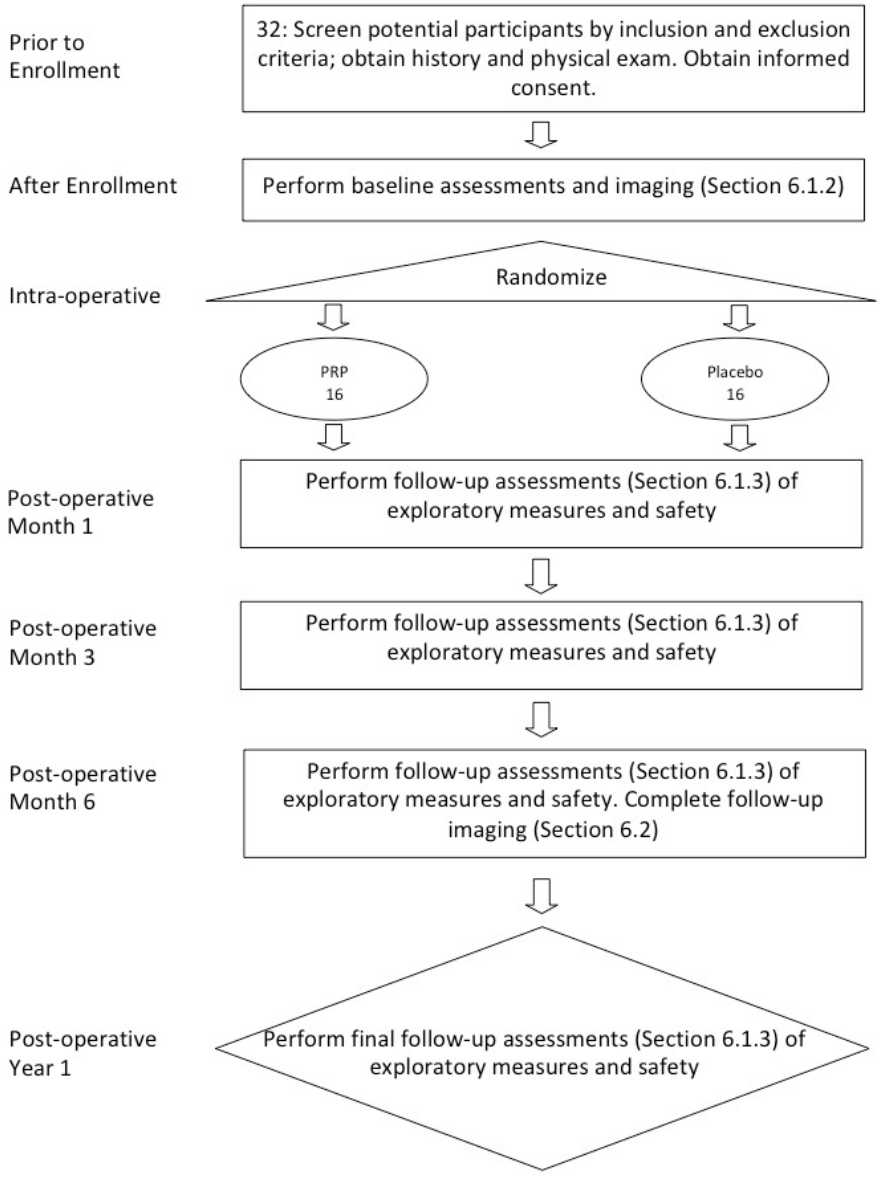
Statistical Methods:

A sample size of 48 subjects (24 in the treatment group and 24 in the control group) will provide sufficient information to produce descriptive summaries of study outcome endpoints and to perform exploratory analyses.

The purpose of this study is to explore surgical outcomes after treatment with platelet rich plasma (PRP) in patients undergoing arthroscopic debridement for triangular fibrocartilage complex (TFCC) tears. We hypothesize that use of PRP after arthroscopic debridement will result in a clinically significant reduction in pain and improved functional outcomes compared to arthroscopic debridement alone, as measured by pain scale scores, grip strength, wrist range of motion, Patient-rated Wrist Evaluation (PRWE) scores, and the Modified Mayo Wrist Score.

Schedule of Visits and Procedures: As depicted in Section 1.2.

1.2 SCHEMA



2 INTRODUCTION

2.1 ABBREVIATIONS AND TERMS:

PRP Platelet Rich Plasma
TFCC Triangular Fibrocartilage Complex
PRWE Patient-rated Wrist Evaluation

2.2 BACKGROUND AND CLINICAL RATIONALE FOR DATA REVIEW

Tears of the triangular fibrocartilage complex (TFCC) often result in ulnar sided wrist pain, decreased grip strength, and functional impairment[1]. Treatment options include conservative management with immobilization, open repair, and arthroscopic repair versus debridement with or without ulnar shortening[2]. The reported success rates after treatment, regardless of technique, are mixed.[2,3] indicating the need for new treatment modalities.

New studies have emerged that support the use of platelet rich plasma (PRP) in the treatment of cartilage injuries and joint inflammation[4,5,6]. Randomized controlled trials demonstrate that the use of PRP in patients with hip and knee osteoarthritis decreases pain and improves function[5]. A pilot study by Loibl et al. showed similar results in basilar joint arthritis[7]. Molecular studies reveal that PRP significantly increases the proliferation of chondrocytes, anabolic factors (TGF-B1) and antiinflammatory cytokines (IL-4, IL-10, IL-13) while decreasing inflammatory enzymes (COX-2) and proteinases (MMP3, MMP13, ADAMTS-5, IL-6)[4]. As such, PRP may be beneficial in the treatment of patient's with TFCC tears.

3 STUDY OBJECTIVES

The objective of this study is to compare outcomes and functionality measures of subjects treated with platelet rich plasma (PRP) after arthroscopic debridement of triangular fibrocartilage complex (TFCC) tears to subjects treated with arthroscopic debridement alone.

4 STUDY DESIGN

4.1 OVERALL DESIGN

Forty-eight (48) subjects with TFCC tears will be randomized to treatment with PRP versus placebo (normal saline). Subjects and medical staff outside of the operating room will be blinded to treatment group throughout the duration of the study. Outcome measures will include pain scale scores, grip strength, wrist range of motion, Patient-rated Wrist Evaluation (PRWE) scores, and Modified Mayo Wrist scores.

4.2 STUDY STRUCTURE

This is a randomized controlled trial, blinded to the subjects and medical support staff.

4.3 DURATION

Subjects will be followed for 12 months post arthroscopic debridement. Their postoperative pain scale scores, grip strength, wrist range of motion, Patient-rated Wrist Evaluation (PRWE) scores, and Modified Mayo Wrist scores (measured at month 1, month 3, month 6, and year 1 postoperatively) will be compared to their preoperative scores. And the difference in improvement of the outcomes will be compared between treatment and control subjects. Study visits will coincide with standard clinical course visits including: pre-operative visits and follow-up visits at month 1, month 3, month 6 and year 1 post-operatively.

4.4 STUDY QUESTIONNAIRES/ASSESSMENT

The patients of Dr. Kulber eligible to participate in the study will proceed with outcomes data collection once study consents have been signed and the patient has been enrolled in the study.

4.5 VISITS & PROCEDURES

Enrolled subjects will undergo baseline questionnaires/assessments and baseline imaging during their pre-operative visit. Once arthroscopic debridement is complete, patients will be randomized intraoperatively to treatment with PRP versus placebo (normal saline). Subjects and medical staff outside of the operating room will be blinded to treatment group throughout the study. Questionnaires/assessments will then be administered and performed at month 1, month 3, month 6 and year 1 post-operative visits. Follow-up imaging will be performed at 6 month post-operative visit.

5 STUDY POPULATION CHARACTERISTICS

5.1 NUMBER OF SUBJECTS

Forty-eight (48) subjects undergoing arthroscopic debridement for TFCC tears will be randomized intraoperatively to treatment with PRP (24 subjects) versus treatment with normal saline (24 subjects).

5.2 STUDY POPULATION CHARACTERISTICS

Subjects who meet the inclusion/exclusion criteria detailed below will be enrolled into the study.

5.3 INCLUSION CRITERIA

- Male or Female >18 years of age
- TFCC tear requiring surgical intervention
- Be willing to undergo arthroscopic debridement and injection with PRP
- Be in good health other than the TFCC tear
- Have realistic expectations of surgical results
- Understand and be willing to follow all aspects of the study protocol and have signed and dated the IRB-approved Informed Consent Form and the Authorization for Use and Release of Health and Research Study Information (HIPAA) form prior to any study-related procedures being performed

5.4 EXCLUSION CRITERIA PROCEDURES

- Have collagen-vascular, connective tissue, or bleeding disorders
- Be a smoker or have smoked in last 2 months
- Have any disease, including uncontrolled diabetes, which is clinically known to impact wound healing ability
- Have regional sympathetic dystrophy
- Be pregnant, lactating or expecting to be within the next 24 months
- Currently have an alcohol/substance abuse problem or have had a relapse within one year to screening visit
- Have an abscess or infection at the time of surgery
- Have a condition or be in a situation that, in the Investigator's opinion, may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study

6 VISITS & PROCEDURES

6.1 PRE-SCREENING & VISITS

The physician's appointment calendar will be pre-screened of potential study candidates who would be eligible for arthroscopic debridement. No study related data will be collected/administered until patient has signed consent and HIPAA.

6.1.1 PROCEDURES FOR FINAL STUDY ENTRY

A subject is considered "enrolled" when he/she has signed the IRB-approved consent form and HIPAA authorization in the presence of the Investigator, who will then collect and record the subject's demographic information and medical history.

6.1.2 PRE-OPERATIVE VISITS

The subject will be screened in accordance with the inclusion/exclusion criteria and medical history collected. Pre-operative visual pain analogue score measurements, grip strength and wrist range of motion measurements, and Patient-rated Wrist Evaluation (PRWE) scores and Modified Mayo Wrist scores will be collected. Subject health information (e.g., demographics, general health), physical examination, medical photography, and hand imaging (see section 6.2) will be performed at screening.

6.1.3 FOLLOW-UP VISITS

Subjects will be required to attend post-operative visits at month 1, month 3, month 6 and at year 1. Review of medical records, physical examination, and medical photography will be conducted at all post-operative visits. At month 1, month 3, month 6, and year 1 visual pain analogue score measurements, grip strength and wrist range of motion measurements, and Patient-rated Wrist Evaluation (PRWE) scores and Modified Mayo Wrist scores will be collected. Medical imaging (Section 6.2) will be performed at month 6 post-operatively.

6.2 STANDARD OPERATIVE PROCEDURES

Standard Imaging: PA, lateral, and oblique X-ray views of the wrist and MR Arthrogram will be obtained pre-operatively and 6 months post-operatively. Medical photographs of the hand and wrist will be taken at each visit and on the day of the procedure.

Standard Surgical Procedure: The affected wrist is placed in a traction tower and arthroscopy is performed in standard fashion. A blunt trocar is placed through the 3/4 portal and a probe is used through the 4/5 portal. The wrist is then inspected for evidence of injury including the central and peripheral portions of the TFCC. An ArthroCare device is then inserted into the 4/5 portal, and the frayed TFCC is coblated.

6.3 RESEARCH RELATED PROCEDURES

Research Related Procedures: Once the arthroscopic debridement is complete, the patient is randomized to receive wrist injections of normal saline (placebo) or PRP (treatment group). The PRP is then obtained from patients assigned to the treatment arm (~9 cc of venous blood) and processed using the CASCADE Autologous Platelet System, a product made commercially available by the Musculoskeletal Transplant Foundation (MTF). Once processed, the PRP is injected into the debrided wrist.

6.4 MEDICAL IMAGING (STANDARD OF CARE)

A copy of any medical imaging results (e.g., hand radiology) collected during the study duration will be included in the study file. Imaging of the hand will consist of 3 X-ray views including PA, lateral and oblique views and an MR Arthrogram. Imaging will be completed pre-operatively and post-operatively at month 6.

6.5 INSTRUCTIONS FOR THE SUBJECTS

There are no special instructions for the subjects beyond those typically provided for hand surgery and in the informed consent. Subjects will be asked to complete research related questionnaires and assessments as indicated in section 6.1.3.

6.6 UNSCHEDULED VISITS

Each time the subject returns to the study site the Investigator will solicit and record information about any concurrent procedures or AEs as applicable though not anticipated.

7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 EARLY DISCONTINUATION OF SUBJECTS

Each subject reserves the right to withdraw from the study at any time without jeopardy to her future medical care. All follow-up assessments and procedures

should be performed at the final study visit. For any subject who discontinues from the study, the date and reason for discontinuation will be recorded.

If a subject fails to return for one or more scheduled study visits, the Investigator will attempt to contact the subject to determine and document the reason the subject has failed to return and to encourage compliance with the study visit schedule.

A subject may be discontinued from the study for the following reasons:

- Subject did not undergo arthroscopic debridement as it was deemed not warranted by the Investigator
- Since enrollment in the study, subject has had alternative treatment that would otherwise affect the study questionnaire/outcomes data
- Subject does not complete scheduled follow-up visits per protocol
- Subject has died

8 OUTCOME MEASURES AND SUMMARY OF METHODS OF DATA COLLECTION

8.1 OUTCOME MEASURES

8.1.1 PRIMARY OUTCOME MEASURE

The primary outcome measure is the difference in improvement between preoperative and post-operative pain scale scores, grip strength, wrist range of motion, Patient-rated Wrist Evaluation (PRWE) scores, and Modified Mayo Wrist scores between patients treated with PRP and patients not treated with PRP after arthroscopic debridement.

8.1.2 SECONDARY OUT COME MEASURES

Not applicable

8.1.3 EXPLORATORY MEASURES

- Pain scale score assessment
- Grip strength
- Wrist range of motion assessed by Investigator
- PRWE score assessment
- Modified Mayo Wrist Score assessment

8.2 SAFETY MEASURES

The incidence and severity of AEs related to the study will be captured. Investigators will inquire about the occurrence of any AEs at all study visits and unscheduled visits. Subjects will also be asked to self- report AEs throughout the duration of the study. Adverse events will be recorded.

8.3 SUMMARY OF METHODS OF DATA COLLECTION

Paper documents will be used to collect standardized assessments for PRWE scores, Modified Mayo Wrist scores, and pain assessment. Study-specific information, such as Investigator reviews and assessments will be recorded directly in the subject's medical record.

Grip strength and wrist range of motion will be recorded by the Investigator in the subjects' medical record.

9 STATISTICAL PROCEDURES

Every attempt will be made to collect complete data and limit the occurrence of missing data. Due to the descriptive nature of all analyses, no imputation of missing data will be performed. Descriptive summaries will be based on all observations available within each of the relevant analysis populations.

Descriptive statistics will be presented for key outcome measures.

9.1 POPULATIONS FOR ANALYSES

All subjects will be included in the full analysis population. The per protocol population is defined as subjects who have not had any major protocol deviations throughout the study (Section 9.8) and will be analyzed as the primary study group. Other subgroups may be analyzed as detailed in the subgroup analyses section. Subjects that have been discontinued will be excluded from data analysis.

9.2 COLLECTION AND DERIVATION OF PRIMARY AND SECONDARY OUTCOME MEASURES

9.2.1 PRIMARY OUTCOME MEASURES

The primary outcome measure is the difference in improvement between preoperative and post-operative pain scale scores, grip strength, wrist range of motion, Patient-rated Wrist Evaluation (PRWE) scores, and Modified Mayo Wrist scores between patients treated with PRP and patients not treated with PRP after arthroscopic debridement.

9.2.2 SECONDARY OUTCOME MEASURES

Not applicable

9.2.3 EXPLORATORY MEASURES

All exploratory variables will be analyzed as reported, without further derivation, except for the calculation of change from baseline, or change from prior time-points.

9.3 HYPOTHESIS AND METHODS OF ANALYSIS

We hypothesize that use of PRP after arthroscopic debridement will result in greater pain reduction and improved functional outcomes when compared to arthroscopic debridement alone, as measured by pain scale scores, grip strength, wrist range of motion, Patient-rated Wrist Evaluation (PRWE) scores, and the Modified Mayo Wrist Score.

9.3.1 PRIMARY OUTCOME MEASURE ANALYSIS

The primary outcome measure is the difference in improvement between preoperative and post-operative pain scale scores, grip strength, wrist range of motion, Patient-rated Wrist Evaluation (PRWE) scores, and Modified Mayo Wrist scores between patients treated with PRP and patients not treated with PRP after arthroscopic debridement.

Preoperative and postoperative outcome measures will be analyzed using descriptive statistics, including n, mean, standard deviation, median, minimum, maximum, and skewness.

9.3.2 SECONDARY OUTCOME MEASURE ANALYSIS

Not applicable.

9.3.3 EXPLORATORY MEASURES ANALYSIS

All exploratory variables will be summarized with descriptive statistics appropriate to the scale of measurement for each variable.

9.3.4 SAFETY ANALYSIS

Safety analyses will include the incidence and severity of adverse events observed over the study assessment period. These will be tabulated and presented overall and by relatedness, severity, and preferred term.

9.4 SUBGROUP ANALYSIS

Subgroup analyses will be performed to explore their relationship to key study outcomes.

9.5 EXPLORATORY ANALYSES

The difference in preoperative versus postoperative outcomes within groups (treatment versus placebo) will be tested for significance using paired t-tests. The significance of differences in preoperative versus postoperative outcomes between groups (treatment and placebo group) will be analyzed using 2-sample t-tests. Additional analyses of possible relationships between outcomes may also be performed using appropriate inferential tests.

9.6 SAMPLE SIZE CALCULATION

The trial will be powered to detect a difference in post-treatment PRWE scores between groups of 15, deemed to be clinically significant by the investigators. The standard deviations for PRWE scores previously published after treatment for TFCC tears ranges from 6.6 to 20.5. To detect a mean difference in post-treatment PRWE score of 15 points (SD = 18) with a two-sided significance level of 5% and power of 80% with equal allocation to two arms would require 24 patients in each arm of the trial.

Subjects will be assessed per standard of care of their clinical requirement and qualification for surgery and upon subject's decision to participate in the study. The difference in preoperative and postoperative outcomes will be analyzed to

determine which group has the most improvement based on the following outcomes: pain scale scores, wrist range of motion, PRWE scores, and Modified Mayo Wrist scores.

9.7 INTERIM ANALYSES

Not applicable.

9.8 PROTOCOL DEVIATIONS

Protocol deviations may include:

- Deviations from the protocol, contrary to protocol specifications (i.e., deviations from the protocol, eligibility, visit windows, etc.).
- Deviations affecting the endpoint outcome not previously specified in the protocol (i.e., deviation that had not been previously considered in the protocol or eligibility criteria, however having a clear impact on the primary outcome measure)

All protocol deviations will be reviewed and categorized as major (i.e., those that affect measurement or interpretation of the primary endpoint) or minor (those not affecting the primary endpoint).

10 STUDY ADMINISTRATION PROCEDURES

10.1 SUBJECT ENTRY PROCEDURES

10.1.1 OVERVIEW OF ENTRY PROCEDURES

Prospective subjects as defined by the criteria in Section 5.3 and 5.4 (inclusion/exclusion criteria) will be considered for entry into this study.

10.1.2 INFORMED CONSENT AND SUBJECT PRIVACY

The purpose, procedures, risks, benefits, and alternatives to study participation will be discussed with each potential subject. Prior to any study-related procedures or change in treatment, subjects wishing to participate must give their written informed consent (IC). The subject must also give Authorization for Use and Release of Health and Research Study Information (HIPAA) and other written documentation in accordance with the relevant country and local privacy

requirements (where applicable) prior to any study-related assessments/questionnaires. Subjects will be consented to provide a copy of all medical imaging (e.g. radiology) collected as standard-of-care or research during the study duration for inclusion in the study file. The Investigator will conduct the IC discussion and will document in the subject's medical records the process for acquiring IC and the subject's agreement or refusal to notify her primary care physician about the study. The subject should personally sign and date the IC form. The Investigator will retain the original copy of the signed IC form, and the subject will also receive a copy. Upon signing the IC form, the subject will receive a subject number that will be used on all documentation for the subject throughout the study. Subject numbers should be assigned in ascending order, and numbers should not be omitted or reused. The subject number is a unique identification for each subject.

10.2 COMPLIANCE WITH PROTOCOL

All eligible subjects to be treated by Dr. David Kulber will be counseled on the procedure as well as the possibility of treatment with PRP, as dictated by their randomization to treatment with PRP versus normal saline. Eligible patients enrolled into each treatment arm will be asked to complete research questionnaires and post-operative assessments as indicated within the schedule or procedures. The Investigator is responsible for the overall conduct of the study and compliance with the protocol including subject recruitment, IC, screening evaluations, eligibility, assessment/procedure, study evaluations, and any study-related medical care. The Investigator may choose to delegate some of these tasks to suitably trained research staff personnel, but the Investigator is ultimately responsible for these activities.

10.3 STUDY TERMINATION

If conditions arise during the study that indicate that the study should be terminated, the Investigator, Monitor, IRB, and/or regulatory agencies will discuss the situation and take appropriate action after consultation. Conditions that may warrant termination of the study or site include, but are not limited to:

- Discovery of an unexpected, serious, or unacceptable risk to subjects enrolled in the study
- Failure of the Investigator to comply with pertinent national or state regulations, IRBimposed conditions, or protocol requirements
- Submission of knowingly false information from the Investigator to IRB, or any regulatory agency

11 ADVERSE EVENTS

Throughout the course of the study, AEs will be monitored and reported on an AE CRF, including seriousness, severity, relationship to device, and action taken. If AEs occur, the first concern will be the safety of the study participants. The Investigator and the research staff will monitor each subject closely, and record any complications that may arise, though not anticipated. Study clinician will use his/her medical judgment to do whatever is necessary to help treat the problem. Potential risks and/or side effects include:

Foreseeable Risk

- Discomfort
- Pain
- Redness
- Swelling
- Local or systemic infection
- Dehiscence and/or necrosis due to poor revascularization
- Specific or nonspecific immune response to some component of PRP treatment

11.1 DEFINITIONS

11.1.1 ADVERSE EVENT

An adverse event (AE) is any untoward medical occurrence in a subject that does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or temporal disease, whether or not related to the study assessment(s)/questionnaire(s).

Pre-existing disease or symptoms thereof prior to study enrollment are not considered AEs unless the condition recurs after the subject has recovered from the pre-existing condition, or the condition worsens in intensity or frequency during the study. Normal post-operative sequelae will not be recorded as adverse events. Specifically, normal post-operative pain, swelling, tenderness, loss of skin sensation and ecchymosis within the first two weeks postoperative, requiring normal levels of medication will not be recorded; all abnormal intensity or duration will be recorded and considered an adverse event as well as following the two-week post-operative period.
Adverse events will be monitored throughout the study. At each post-baseline visit, the Investigator will begin querying for adverse events by asking each subject a general, nondirected question such as “Have you had any changes to your condition since your last visit?” Previous adverse events and changes in therapy/concomitant medications should be updated. Directed questioning and examination will then be done as appropriate. All reported adverse events will be documented.

11.1.2 SERIOUS ADVERSE EVENT

A serious adverse event (SAE) is defined as 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
- is a congenital anomaly/birth defect

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

11.2 PROCEDURES FOR REPORTING ADVERSE EVENTS

Adverse events should be reported to governing IRB per governing IRB reporting requirements.

11.3 REPORTING AN SAE

Any SAE occurring during the study period and for at least 30 days after the last study visit should be immediately reported (within 24 hours) and recorded. The Investigator should supply the Sponsor and the IRB with any additional requested information (e.g., hospital discharge summary, autopsy report, pathology report, operative report, terminal medical report, etc.).

12 ADMINISTRATIVE ISSUES

This protocol is to be conducted in accordance with the applicable Good Clinical Practice regulations and guidelines, e.g., the International Conference on Harmonisation (ICH) Guideline on Good Clinical Practice (GCP).

12.1 PROTECTION OF HUMAN SUBJECTS

12.1.1 COMPLIANCE WITH INFORMED CONSENT REGULATIONS

Written informed consent is to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative. The process for obtaining informed consent must also be documented in the subject's medical record.

12.1.2 COMPLIANCE WITH IRB REGULATIONS

This study is to be conducted in accordance with applicable IRB regulations. The Investigator must obtain approval from a properly constituted IRB prior to initiating the study and re-approval or review at least annually.

12.1.3 COMPLIANCE WITH GOOD CLINICAL PRACTICE

This protocol is to be conducted in accordance with the applicable GCP regulations and guidelines.

12.2 SUBJECT CONFIDENTIALITY AND PRIVACY

A report of the results of this study may be published, but the subject's name will not be disclosed in these documents. The subject's name may be disclosed to the study Sponsor, the governing health authorities or the Food and Drug Administration (FDA), if they inspect the study records. Appropriate precautions will be taken to maintain confidentiality of medical records and personal information.

Written Authorization and other documentation in accordance with the relevant country and local privacy requirements (where applicable) are to be obtained from each subject prior to enrollment into the study, and/or from the subject's legally authorized representative in accordance with the applicable privacy requirements (e.g., HIPAA).

12.3 DOCUMENTATION

12.3.1 SOURCE DOCUMENTS

Source documents may include a subject's original (or certified copy) medical records, hospital charts, clinic charts, the Investigator's subject study files, as well as the results of diagnostic tests such as X-rays and MR Arthrograms.

The following information should be entered into the subject's medical record:

- Subject's name
- Subject's contact information
- Date that the subject entered the study and subject number
- The study title and/or the protocol number
- A statement that informed consent was obtained and the process for obtaining consent, including the date. A statement that HIPAA Authorization or other country and local subject privacy required documentation for this study has been obtained, including the date.
- Dates of all subject visits
- All concomitant procedures
- Subject standardized radiology as specified in the outcome metrics
- Occurrence, treatment for, and status of any adverse events
- Date the subject exited the study, and a notation as to whether the subject completed the study or reason for discontinuation.
- Protocol deviations, as applicable

12.3.2 DOCUMENT COMPLETION

Source documents must meet the criteria to be acceptable in assessing the quality and integrity of the data during inspection or review of that data: attributable, legible, contemporaneous, original, accurate and available upon request. The Investigator is responsible for ensuring that data is properly recorded on each subject's record.

12.3.3 RETENTION OF DOCUMENTATION

All study related correspondence, subject records, consent forms, subject privacy documentation, records of the distribution and use of device, and copies of documentation should be maintained on file. Documents should be retained and available for audit by regulatory authorities until at least 2 years after the latest among the following scenarios: completion or termination of the study, the last approval of a marketing application, no pending or contemplated marketing applications, or formal discontinuation of clinical development of the device. These documents should be retained for a longer period, however, if mandated by the applicable regulatory requirements, by conditions imposed by the IRB.

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