Non-Surgical Treatment for Rotator-Cuff Tears using Platelet-Rich-Plasma

Study Protocol

NCT02246530

Breanna Willeford, DO, Principal Investigator

University of Alabama at Birmingham

Birmingham, AL 35294

Non-Surgical Treatment for Rotator-Cuff Tears using Platelet-Rich-Plasma

Principal Investigator: Breanna Willeford, DO

Sponsor: UAB

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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 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 documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial subjects. 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 subject materials will be submitted to the local Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any subject 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 subjects who provided consent, using a previously approved consent form.

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Title:	Non-Surgical Treatment for Rotator-Cuff Tears using Platelet-Rich-Plasma
Study Description:	The purpose of the study was to compare the effects of an injection of "Platelet-Rich Plasma" (PRP) versus a combination of steroid/anesthetic in patients with partial tears of the supraspinatus muscle. Platelet rich plasma is a concentration of blood cells called platelets in a suspension of the liquid plasma portion of blood.
Objectives:	*To identify the utility of* Platelet-Rich Plasma (PRP) in the treatment of partial thickness tears of the rotator cuff.
Endpoints:	Six-month observation period.
Study Population:	Males and females age 18 - 65 years old.
Phase:	1
Description of Study Intervention:	• Treatment arm: PRP injection via ultrasound guidance • Control arm: Corticosteroid + anesthetic agent via ultrasound guidance
Study Duration:	July 2014 – March 2021
Subject Duration:	Six months

1.2 SCHEDULE OF ACTIVITIES (SOA)

2 INTRODUCTION

2.1 STUDY RATIONALE

This research study will test a medical procedure's ability to assist in the healing process of Partial-Thickness Rotator Cuff Tears (PTRCT). The procedure uses an isolation of growth factors and platelets called "Platelet-Rich Plasma" (PRP) isolated from your own blood and re-injected to the site of damage, under ultrasound guidance. This procedure is currently being done across the United States and world-wide and has been demonstrated as a safe procedure. Limited research on this procedure has been done in the United States involving the PTRCT. This is an investigational research study on the procedure's effectiveness. Currently standard of care at UAB is a stepwise progression. First physical therapy is prescribed anywhere from 2-6 weeks for 1-2 times per week. If physical therapy fails to improve symptoms, then shoulder injections of a combination of steroids and numbing agents are used. If this fails, then surgical procedures are considered. People who enter into the study will be randomly picked (like the flip of a coin) by a computer into 1 of 2 groups: 1) injected with PRP produced from their own blood or 2) combination steroid / anesthetic (current standard of care treatment). This study will enroll 20 participants from the Birmingham area with goal of 10 participants in each group.

2.2 BACKGROUND

Rotator cuff pathology and specifically Partial-Thickness Rotator Cuff Tears (PTRCT) remain a leading cause of shoulder pain in adult patients. Rotator cuff disease is the most common cause of disability related to shoulder pain. Typically tears develop in the supraspinatus tendon and progress gradually because of intrinsic degenerative demands. An association of cuff tears with increasing age has also been demonstrated, with 50% of individuals in their 80s having either symptomatic and/or asymptomatic RCT. There does seem to be a correlation between the presence of pain and progression of tear size indicating that the symptom of pain should warrant close monitoring.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

The most common risks include pain at the injection site, infection at the injection site, no relief of symptoms, worsening of symptoms, deep vein thrombosis, damage to neurovascular structures, bruising, allergic reaction, local toxicity, scar tissue formation, or intravascular infection.

2.3.2 KNOWN POTENTIAL BENEFITS

You may or may not benefit from the procedure. Benefits may include reduction of pain and improved function and strength.

3 STUDY DESIGN

3.1 OVERALL DESIGN

Subjects were randomized into one of two groups (treatment group vs. control group). During the first in-office visit, we obtained an initial assessment and a diagnostic ultrasound with a radiologist. If the subject was in the treatment group, we collected about 10-12 mL of autologous blood from the subject. We used this blood to isolate the PRP and inject it to the treatment area. If the subject was in the control group, an injection combination of steroid and anesthetic (1ml betamethasone + 4.5 ml bupivacaine + 4.5 ml lidocaine) was injected to the treatment area. The subject completed three phone surveys at 3 weeks, 6 weeks, and 6 months. Each subject also completed repeat ultrasound of the shoulder at a visit at 6 months post procedure.

3.2 END OF STUDY DEFINITION

This study was terminated prematurely secondary to lack of successful largely secondary to the COVID pandemic.

4 STUDY POPULATION

4.1 INCLUSION CRITERIA

- Males and females ages 18- 65
- Diagnosed with a partial thickness tear of the supraspinatus tendon via diagnostic MSK ultrasound

4.2 EXCLUSION CRITERIA

- Corticosteroid injections within the past 6 months
- Anti- inflammatory medications 2 weeks prior to the procedure
- Anticoagulation medications 5 days prior to the procedure
- Pregnancy

4.3 SCREEN FAILURES

Subjects enrolled in the study that had a negative diagnostic ultrasounds, showing lack of a tear of the rotator cuff tendon were excluded from the study.

4.4 STRATEGIES FOR RECRUITMENT AND RETENTION

Subjects were recruited from an outpatient Physical Medicine and Rehabilitation clinic at the University of Alabama. Each subject was given information regarding the study requirements and follow up obligations prior to enrollment and signed to complete based on their confidentiality agreement form.

5 STUDY INTERVENTION

5.1 STUDY INTERVENTION(S) ADMINISTRATION

5.1.1 STUDY INTERVENTION DESCRIPTION

Experimental Group

Withdraw 10-12 mL of blood from your arm.
Process blood to isolate the PRP.
Skin will be cleaned to sterilize the surface.
Ultrasound machine with sterile gel will be used to visualize injection target.
Inject the PRP into the targeted area for the actual treatment.

Control Group

Skin will be cleaned to sterilize the surface.
Ultrasound machine with sterile gel will be used to visualize injection target.
Inject combination (steroid and anesthetic) 1ml betamethasone + 4.5ml bupivacaine + 4.5ml lidocaine.

5.2 MEASURES TO MINIMIZE BIAS: RANDOMIZATION

The study was originally intended for 20 subjects. Subjects number 1 through number 20 were randomized via a randomization calculator prior to starting into the treatment or control groups. As enrollment began, subjects were numbered in the study on a rolling basis an divided into their respective group based on the predetermined randomization.

5.3 STUDY INTERVENTION COMPLIANCE

Overall, there was poor compliance in this study. We had 14 patients enroll originally. Three patients had a negative diagnostic ultrasound thus were excluded from the study. Two patients were randomized into the Control Group, and both completed all study requirements. Nine patients were randomized into the Treatment group; of these 9 patients, 4 did not complete all follow up questioners and 2 did not complete the 6 month follow up ultrasound.

5.4 CONCOMITANT THERAPY

Subjects were asked to avoid use of NSAIDs, including Advil, Aleve, Ibuprofen, Naproxen, Voltaren, Aspirin, for six weeks after the injection, as it will interfere with the beneficial effects of the PRP treatment. Tylenol (acetaminophen), ice and heat were allowed as needed for pain relief.
Activity: Normal day to day activity was permitted. Subjects were asked to refrain from any significant activity involving the injected site for first 3 days after procedure. Gradually increase activity over the next 6-12 weeks as tolerated.

6 STUDY INTERVENTION DISCONTINUATION AND SUBJECT DISCONTINUATION/WITHDRAWAL

6.1 DISCONTINUATION OF STUDY INTERVENTION

Study intervention was a one- time injection. No discontinuation was required in the study.

6.2 SUBJECT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Subjects are free to withdraw from participation in the study at any time upon request.
An investigator may discontinue or withdraw a subject from the study for the following reasons:

- 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 subject

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.

6.3 LOST TO FOLLOW-UP

A subject 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 subject fails to be available for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain if the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator or designee will make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record or study file.
- Should the subject 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 STUDY ASSESSMENTS AND PROCEDURES

7.1 STUDY ASSESSMENTS

Subjects were required to complete 3 telephone interviews to repeat questionnaire (SPADI) at week 3, week 6 and 6 months.
At 6 months after initial procedure subjects were schedule for repeat diagnostic MSK ultrasound which was the end of the study.

7.2 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

7.2.1 DEFINITION OF ADVERSE EVENTS (AE)

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related (21 CFR 312.32 (a)).

7.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

An adverse event (AE) is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event (of note, the term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event, rather than to an event which hypothetically might have caused death if it were more severe)
- inpatient hospitalization or prolongation of existing hospitalization
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- or a congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

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 to describe severity:

- **Mild** – Events require minimal or no treatment and do not interfere with the subject'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 subject'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 subject 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 Principal 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 subject 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 subject is screened will be considered as baseline and not reported as an AE. However, if the study subject'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 Study Coordinator 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 Study Coordinator 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 AND SERIOUS ADVERSE EVENT REPORTING

All serious adverse events must be reported to the IRB according to regulatory requirements. The Principal Investigator will immediately report to the sponsor any serious adverse event, whether or not considered study intervention related, including those listed in the protocol or package insert 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 Principal Investigator deems the event to be chronic or the subject is stable. Other supporting documentation of the event may be requested 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 subjects 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 subject 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 subjects 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). 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.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UPs that are serious adverse events (SAEs) will be reported to the IRB within 10 working days of the investigator becoming aware of the event.
- Any other UP will be reported to the IRB within 10 working days of the investigator becoming aware of the problem.

8 STATISTICAL CONSIDERATIONS

A statistical analysis was not completed for this study. This was due to the fact that this study was terminated early with lack of comprehensive results to analyze. At termination, we had 11 subjects in total enrolled: 9 treatment group subjects and 2 control group subjects. Five of the 11 subjects in this

study had incomplete data, being lost to follow up at some point during the 6-month observation period for various reasons. Due to the small sample size, early termination of the study, and lack of full data sets for our enrolled participants, there was inconclusive data to run statistical analysis.

9 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

9.1.1 INFORMED CONSENT PROCESS

9.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO SUBJECTS

Consent forms describing in detail the study intervention, study procedures, and risks are given to the subject and written documentation of informed consent is required prior to conducting study screening procedures. A separate screening consent form will not be used.

9.1.1.2 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 subject will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research subjects. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects 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 subjects 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 subject undergoes any study-specific procedures. The rights and welfare of the subjects 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.

9.1.2 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 to regulatory authorities. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study subjects and the Institutional Review Board (IRB), will provide the reason(s) for the termination or suspension. Study subjects 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 subjects
- 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 IRB.

9.1.3 CONFIDENTIALITY AND PRIVACY

Subject confidentiality and privacy is strictly held in trust by the participating investigators and their staff. 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 Principal Investigator.

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

Representatives of the Institutional Review Board (IRB) 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 subjects in this study. The clinical study site will permit access to such records.

The study subject'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 and/or Institutional policies.

Study subject research data, which is for purposes of statistical analysis and scientific reporting, will be stored at the UAB Department of Otolaryngology research office. This will not include the subject's contact or identifying information. Rather, individual subjects and their research data will be identified by a unique study identification number. The study data entry and study management systems used by research staff will be secured and password protected.

9.1.4 QUALITY ASSURANCE AND QUALITY CONTROL

The site will perform internal quality management of study conduct, data collection, documentation and completion. Quality control (QC) procedures will be completed by the Data Manager during data entry into the appropriate CRF. Any missing data or data anomalies will be communicated to the Study Coordinator for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements.

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

9.1.5 DATA HANDLING AND RECORD KEEPING

9.1.5.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal 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.

Hard copies of source document worksheets will be used for recording data for each subject enrolled in the study. Data recorded in the case report form (CRF) derived from source documents should be consistent with the data recorded on the source documents.

9.1.5.2 STUDY RECORDS RETENTION

Study documents should be retained for a minimum of 3 years after the completion of the study. These documents should be retained for a longer period, however, if required by local regulations.

9.1.6 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol requirements. The noncompliance may be either on the part of the subject, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.20 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the Principal Investigator to use continuous vigilance to identify and report deviations within 10 working days of identification of the protocol deviation. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The Principal Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

9.1.7 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial.

9.2 ABBREVIATIONS

AE	Adverse Event
ANCOVA	Analysis of Covariance
CFR	Code of Federal Regulations
CONSORT	Consolidated Standards of Reporting Trials
CRF	Case Report Form
DHHS	Department of Health and Human Services
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonisation
ICMJE	International Committee of Medical Journal Editors
IRB	Institutional Review Board
LSMEANS	Least-squares Means
NCT	National Clinical Trial
NIH	National Institutes of Health
OHRP	Office for Human Research Protections
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOA	Schedule of Activities
SOP	Standard Operating Procedure
UP	Unanticipated Problem
US	United States
PRP	Platelet-Rich-Plasma
PTRCT	Partial Thickness Rotator Cuff Tear

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