A Randomized, Post-market Study Evaluating Dermal Allograft Augmentation of Large and Massive Rotator Cuff Tears

Sponsor Protocol Number: AIRR-0094

Version Number: 1.0

Protocol Date: May 3, 2023

Protocol Revision History:

Version Number	Version Date	Summary of Revisions Made:
1.0	05.03.2023	Original version

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the Clinical Trial Agreement, fundamental principles set forth in the Declaration of Helsinki and ISO 14155, far as relevant, and local regulations.

The study should not begin at a site until the required Institutional Review Board (IRB) or Ethics Committee (EC) approval has been obtained. Any additional requirements imposed by an IRB/EC shall be followed.

Arthrex, Inc. or Arthrex, GmbH will reimburse study sites for trial expenses that are beyond the standard of medical care and within fair market value.

INVESTIGATOR SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the Clinical Trial Agreement, and protocol, including all statements regarding confidentiality, Fundamental principles of the Declaration of Helsinki, ISO 14155, as far as relevant, local regulatory requirements and applicable international standards.

Signed: _____ Date: _____

Printed Name:_____

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PROTOCOL SUMMARY

Title:	A Randomized, Post-market Study Evaluating Dermal Allograft Augmentation of Large and Massive Rotator Cuff Tears
Summary:	The purpose of this study is to compare postoperative healing of large and massive rotator cuff tears with preoperative MRI confirmed fatty infiltration stage II and higher repaired with or without dermal allograft augmentation (DAA).
Objectives and Outcome Measures:	The primary objective is to evaluate postoperative healing of rotator cuff repair with and without DAA. **Primary:** The primary outcome measure is healing evaluation in MRI • MRI Post-Operative Assessment (Goutallier Stage and Sugaya Classification) **Secondary:** The secondary outcome measures are patient-reported outcome measures from validated outcome scoring systems, including: • American Shoulder and Elbow Surgeons Score (ASES) • Single Assessment Numeric Evaluation score (SANE) • Visual Analog Scale (VAS) for pain Veterans RAND Health Survey (VR-12)
Population:	Males and females between the ages of 30 and 75 years that require surgery for large and massive rotator cuff tears
Phase:	Post market
Description of Treatment:	Rotator cuff repair with or without augmentation using decellularized human dermal allograft.

Inclusion and Exclusion Criteria

Inclusion criteria:

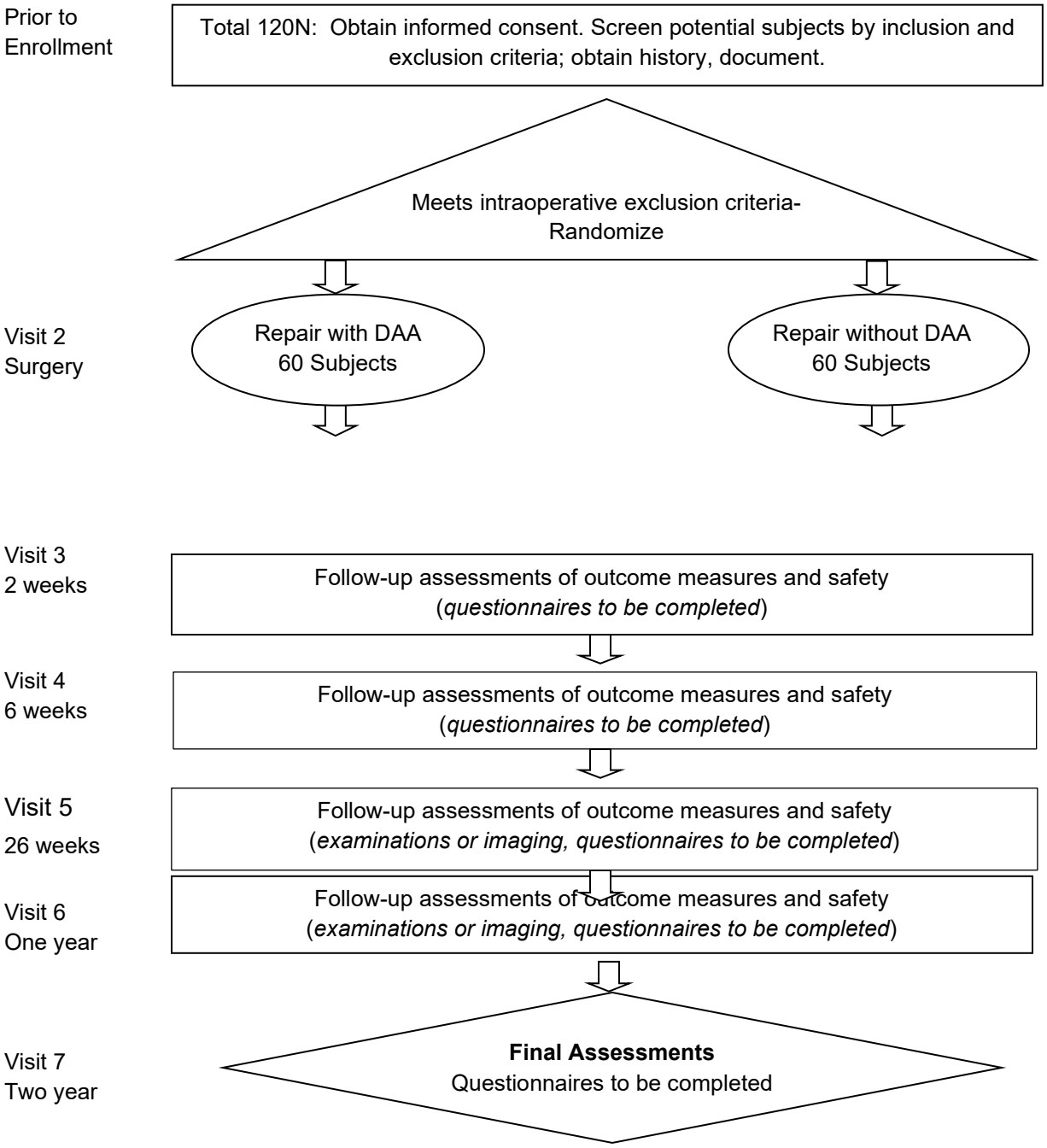
1. The subject is between the ages of 30 and 75 years.
2. Subject is planning to undergo arthroscopic surgery for full-thickness rotator cuff tear (RCT)
3. Two complete RCTs or tear size equal to or greater than 3 cm in either the anterior-posterior or medial-lateral dimension
4. Primary rotator cuff repair
5. Stage II fatty infiltration or higher of the supraspinatus or infraspinatus muscle based on preoperative MRI6. Subject has a dual x-ray absorptiometry (DXA) or anterior posterior x-ray view of the target shoulder

Exclusion criteria:

1. The Subject is unable or unwilling to sign the patient informed consent, approved by the Institutional Review Board.
2. The subject objects to the use of allograft
3. Stage I or lower fatty infiltration of the supraspinatus AND infraspinatus muscle
4. Complete full-thickness subscapularis tears of greater than the superior one third of the tendon (Lafosse grade 3 and above)
5. Less than 2 mm joint space of the glenohumeral joint on either an anteroposterior or axillary radiograph
6. Recurrent shoulder instability
7. Corticosteroid injection in the operative shoulder within one month of surgery
8. Revision rotator cuff repair
9. Subject preoperative MRI obtained more than 12 months prior to surgery
10. Pregnant or planning to become pregnant during the study period
11. Workman's compensation case
12. Subject has conditions or circumstances that would interfere with study requirements.

	Intraoperative exclusion criteria: 1. Partial rotator cuff repairs 2. Lafosse grade 3 or higher subscapularis tears
Study Duration and Subject Participation:	The enrollment period is estimated to be 12 months, with estimated subject participation of two years for a total study duration of approximately three years.

Schematic of Study Design:



1 CONTACT INFORMATION

Sponsor:

Arthrex, Inc.

Orthopedic Research Department
1370 Creekside Blvd.
Naples, FL 34108

2 BACKGROUND AND DEVICE DESCRIPTION

2.1 Background Information

Increasing tear size, increasing retraction, and fatty infiltration are the primary factors associated with decreased rates of tendon healing.[1,2] The retear rate, for example, increases by 4-fold when tear size increases from 1 to 3 cm.[2] It is well-established that the most common mode of failure in large and massive rotator cuff tears, especially those with fatty degeneration infiltration, is tendon tearing through suture.[3] Given the association between tendon healing and functional outcome[4], it is important to identify techniques that can improve tendon healing.[5,6,7]

Dermal allograft augmentation (DAA) has been shown to improve the biomechanics of rotator cuff repair, and case reports have described the capability for vascularization and neotendon formation.[8,9] One study of 42 patients suggested that DAA can improve healing. However, repairs were limited to single-row constructs, which may have lower healing than double-row constructs.

2.2 Device(s) Description

Providing an efficient, simple approach to augmenting partial- and full-thickness rotator cuff tears, the CuffMend™ augmentation technique incorporates 1mm-thick ArthroFLEX® human dermal allograft for mechanical strength and to support healing. The graft is inserted with a graft spreader and securely fixed to native tendon using FiberStitch™ RC tendon anchors for medial soft-tissue fixation and Knotless PushLock® anchors for lateral bony fixation. The primary anchors utilized will be 3.5 mm PushLock® anchors (Arthrex Inc.). If poor bone quality is encountered the surgeon may use a larger anchor if required (i.e., 4.75 or 5.5 SwiveLock®; Arthrex, Inc) and the patient will not be excluded from analysis.

Scientific literature has shown acellular dermal allografts to be a safe and effective solution for rotator cuff repair augmentation.[3,4]

Surgeons are advised to review the product-specific surgical technique prior to performing any surgery.

The devices are approved for marketing and will not be traced as required for pre-market devices. The standard traceability for all post-market medical device sales, shipments, and returns will be applied to the devices of this study.

Materials of the device(s) that come into contact with human tissue and body fluids have previously been described in United States (U.S.) marketing submissions and remain unchanged.

3 STUDY DESIGN

3.1 Study Design and Rationale

This is a prospective randomized study comparing the outcomes of patients undergoing rotator cuff repair with dermal allograft augmentation (DAA) or a control group without dermal allograft. Patient outcomes will be collected and compared between the two cohorts at two years postoperative and will include a range of subjective and functional outcomes and radiographic imaging. All patients undergoing primary rotator cuff repair surgery will be invited to be part of the study after pre-operative inclusion/exclusion criteria have been met.

Hypothesis: Patients undergoing rotator cuff repair surgery will experience improved tendon healing with the use of CuffMend™ dermal allograft augmentation.

The purpose of this study is to compare postoperative healing of large and massive rotator cuff tears with preoperative MRI confirmed fatty infiltration stage II and higher repaired with or without dermal allograft augmentation (DAA).

The outcome measures were selected based on the recommendations of the American Academy of Orthopaedic Surgeons (AAOS) and literature review.

3.2 Potential Risks and Benefits

3.2.1 Potential Risks

Potential risks from the surgery are equivalent to standard surgery and will be discussed with the patient as standard of care.

Potential risks related to the DAA include possible allergic or host reaction to the allograft. However, these risks are minimal.

Treatment risks are standard procedure risks that are discussed as part of orthopedic care. These include:

- Infections, both deep and superficial
- Allergies or other reactions to device materials
- Temporary or permanent nerve damage as a result of pressure or hematoma.
- Loosening of the implant or tissue reaction to implant
- Dislocation, subluxation, or inadequate scope of movement as a result of failure to achieve optimum positioning of the implant.
- Bone fractures as a result of one-sided overload or weakened bone structure.
- Allergic reaction to allograft or residual allograft processing reagents

3.2.2 Potential Benefits

The treatment may be obtained outside of the study and is considered standard of care. The benefit of participation in the study is furthering scientific knowledge of available treatments. There may not be a direct benefit to participation in this study. Future patients undergoing an RCR using DAA may benefit from the knowledge gained from this research.

3.3 Study Objectives and Outcome Measures

3.3.1 Study Objectives

The purpose of this study is to compare postoperative healing of large and massive rotator cuff tears with preoperative fatty infiltration stage II and higher repaired with or without DAA.

Primary Hypothesis:	Improved postoperative healing with the addition of CuffMend™ DAA, assessed with MRI Imaging
Secondary Hypothesis:	Improved Patient-Reported Outcomes and range of motion with the addition of CuffMend™ DAA

3.4 Study Outcome Measures

The primary outcome measure is the healing rate in MRI.

- MRI Post-Operative Assessment (Goutallier Stage and Sugaya Classification)

The secondary outcomes measures patient-reported outcomes from validated outcome scoring systems and range of motion objective measures.

- American Shoulder and Elbow Surgeons Score (ASES)
- Single Assessment Numeric Evaluation score (SANE)
- Visual Analog Scale (VAS) for pain
- Veterans RAND Health Survey (VR-12)
- ASES Objective Shoulder Assessment (ROM)

3.5 Subjective Outcome Measures

The subjective data will be collected as listed in the table: The American Shoulder and Elbow Surgeons Shoulder Score, (ASES score), Veterans RAND Health Survey (VR-12), Single Assessment Numerical Evaluation (SANE), and the Visual Analogue Scale (VAS pain) surveys.

3.6 Objective Outcome Measures

Shoulder range of motion (ROM) in forward flexion, external rotation at the side, external rotation at 90˚ of abduction, and internal rotation at 90° of abduction will be measured with a goniometer. Internal rotation will also be estimated to the nearest spinal level. The lead investigator or assigned research staff at each site will perform all measurements.

The MRI imaging will be collected according to standard of care pre-operatively and then at the 26 ± 8 weeks timepoint.

A standard shoulder MRI protocol utilizing a minimum of a 1.5 Tesla magnet shall be utilized. A recommendation for setting is: 5 pulse sequences, sagittal oblique T1-weighted and fast spin echo (FSE) T2-weighted with fat saturation, axial FSE proton density and FSE T2-weighted with fat saturation, and coronal oblique FSE T2-weighted with fat saturation. Post-operative cuff integrity will be classified utilizing the 5 categories described by Sugaya et al[10]: type I, sufficient thickness with homogenously low intensity; type II, sufficient thickness with partial high intensity; type III, insufficient thickness without discontinuity; type IV, presence of a minor discontinuity; type V, presence of a major discontinuity.

4 STUDY ENROLLMENT AND WITHDRAWAL

4.1 Study Population and Study Duration

This study population will include both male and female patients, with an anticipated enrollment goal of 120 subjects (n= 60 subjects per group) study-wide from the practices of all participating sites.

Subjects will be recruited from the surgeon's patient population or referrals from other physicians. The enrollment period is estimated to be 12 months. Study subjects' length of participation is 24 months. The total estimated study duration is approximately three years. Subjects will be considered enrolled at the time of treatment.

4.2 Inclusion and Exclusion Criteria

All individuals must meet all of the inclusion criteria in order to be eligible to participate in the study:

1. The subject is between the ages of 30 and 75 years.
2. Subject is planning to undergo arthroscopic surgery for full-thickness rotator cuff tear (RCT)
3. Two tendon tears or tear size equal to or greater than 3 cm in either the AP or ML dimension
4. Primary rotator cuff repair
5. Stage II fatty infiltration or higher of the supraspinatus or infraspinatus muscle based on preoperative MRI

6. Subject has a dual x-ray absorptiometry (DXA) or anterior posterior x-ray view of the target shoulder

All individuals meeting any of the exclusion criteria will be excluded from study participation:

1. The subject is unable or unwilling to sign the patient informed consent, approved by the Institutional Review Board.
2. The subject objects to the use of allograft
3. Grade 1 or lower fatty infiltration of the supraspinatus AND infraspinatus muscle
4. Complete full-thickness subscapularis tears of greater than the superior one third of the tendon (Lafosse grade 3 and above)
5. Less than 2 mm joint space of the glenohumeral joint on either an anteroposterior or axillary radiograph
6. Recurrent shoulder instability
7. Corticosteroid injection in the operative shoulder within one month of surgery
8. Revision rotator cuff repair
9. Subject preoperative MRI taken more than 12 months prior to surgery
10. Pregnant or planning to become pregnant during the study period
11. Workman's compensation case
12. Subject has conditions or circumstances that would interfere with study requirements.

All individuals who meet any of the intraoperative exclusion criteria will also be excluded from study participation:

1. Partial rotator cuff repairs
2. Lafosse grade 3 or higher subscapularis tears

4.3 Discontinuation of Subjects

Subject Screen Failure

Subject that leaves the study for any reason prior to the surgical visit will be considered a screen failure. Screen failures are not included in the subject total and will be replaced.

Subject and Investigator Withdrawal

Subjects will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The Investigator(s) may elect at any time to withdraw a subject from the study for any reason. Subjects who are withdrawn for any reason from the study after treatment will not be replaced. Subjects who withdraw consent and refuse to complete the follow-up assessment will be considered off-study at that time.

Lost to Follow-up

If the Investigator(s) reports a subject as lost to follow-up, the site will ensure that documentation is complete regarding the reason(s) this has occurred and will ensure that every attempt is made by the Investigator(s) to contact the subject or significant other persons associated with the subject to determine subject status. Appropriate documentation will consist of at least two documented attempts at contact via telephone by the site.

The primary reason for termination or discontinuation of any subject will be documented in the EDC.

4.4 Randomization Procedures

Randomization shall be performed during surgery after intra-operative inclusion/exclusion eligibility has been met, using computer-generated randomization. Patients will be randomized to have either the addition of DAA following a standard rotator cuff repair (DAA Group) or standard Rotator Cuff repair without DAA (Control group).

Intra-operative exclusion criteria:

1. Partial rotator cuff repairs
2. Lafosse grade 3 or higher subscapularis tears

4.5 Premature Termination or Suspension of Study

For any study that is prematurely terminated or suspended by the site principal investigator (PI), the PI will promptly inform the IRB/EC and Arthrex and provide the reason(s) for the termination or suspension. Arthrex reserves the right to terminate the study or a site's participation for any reason with written notification as specified in the clinical trial agreement.

5 TREATMENT AND PROCEDURES

5.1 Concomitant Treatments

There are no restrictions on medications or treatments in the study.

5.2 Study Procedures

The surgery is performed as standard of care. Surgeons are advised to review the product-specific surgical technique prior to performing any surgery. Arthrex provides detailed surgical techniques in electronic formats on the Arthrex website.

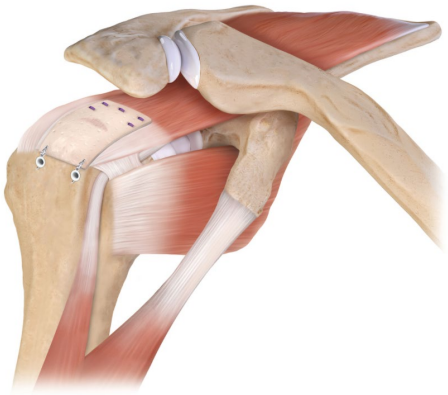
The rotator cuff will be repaired per each surgeon's preferred method, documenting the number of anchors and usage of single-row or double-row repair.

Tears with sufficient mobility to cover the greater tuberosity will be repaired with a knotless double-row technique with a minimum of 4 anchors (SpeedBridge™; Arthrex, Inc.)

In the study group, DAA will be performed with a 1 mm acellular dermal allograft (CuffMend™ graft; Arthrex Inc., Naples, FL) (Figure 1). The DAA is designed to augment the rotator cuff repair. The DAA will be inserted through a portal with a graft spreader. The graft is then secured into the medial rotator cuff tissue. The graft spreader is removed. Finally, the graft is secured into the lateral greater tuberosity with two knotless anchors (3.5 mm PushLock®; Arthrex, Inc.)

Medial graft fixation will be performed with FiberStitch™ RC (Arthrex Inc.) based on surgeon preference. In the FiberStitch™ technique a minimum of two anchors will used to secure the allograft to the medial tissue. Tears with limited tendon mobility in which only a single-row repair can be performed will be repaired with a knotless technique using inverted mattress FiberTape sutures (Arthrex, Inc) and a medial looped suture (Knotless Ripstop; Arthrex Inc.)

Postoperatively the patient will be placed in a sling for six weeks with hand, elbow, and wrist range of motion only. At six weeks, the sling will be removed, and passive range of motion will be initiated. At nine weeks, active motion will be initiated. At 12 weeks, postoperative strengthening will be allowed. Full activities will be permitted at six months postoperative.



6 STUDY SCHEDULE

Study Activity		Pre-op/Baseline	Surgery	Two week post op (± 7 days)	6 weeks post op (± 7 days)	26 weeks (± 2 weeks)	1 Year (- 8 weeks + 12 weeks)	2 Year (- 8 weeks + 12 weeks)
Signed Consent Form		X						
Review of Medical History Demographics/Diagnosis		X						
Inclusion/Exclusion Criteria form		X	X					
Randomization form			X					
Surgical details form			X					
Clinical Assessments	MRI	SOC				X		
	Rotator Cuff Assessment and Healing Index	X				X		
	Radiograph AP View or Bone Mineral Density Scan	SOC						
	ASES Range of Motion	X				X	X	
Patient Surveys	ASES	X				X	X	X
	VAS	X		X	X	X	X	X
	VR-12	X				X	X	X
	SANE	X				X	X	X
WHOOP Management*		X**		X	X	X		
Assessment of Adverse Events			As occurs					

* for selected sites only

**Whoop set up and patient instruction for use

Diagnosis and intra-operative data will be obtained and will include but not be limited to the type and size of the rotator cuff tear.

Shoulder range of motion (ROM) in forward flexion, external rotation at the side, external rotation at 90˚ of abduction, and internal rotation at 90° of abduction will be measured with a goniometer. Internal rotation will also be estimated to the nearest spinal level. The lead investigator or assigned research staff at each site will perform all measurements.

6.1 Radiograph

The MRI imaging will be collected according to standard of care pre-operatively and then at the 26 ± 2 weeks timepoint.

6.2 MRI Sequence and Outcomes

A standard shoulder MRI protocol utilizing a minimum of a 1.5 Tesla magnet shall be utilized. A recommendation for setting is: 5 pulse sequences, sagittal oblique T1-weighted and fast spin echo (FSE) T2-weighted with fat saturation, axial FSE proton density and FSE T2-weighted with fat saturation, and coronal oblique FSE T2-weighted with fat saturation. Post-operative cuff integrity will be classified utilizing the 5 categories described by Sugaya et al[10] type I, sufficient thickness with homogenously low intensity; type II, sufficient thickness with partial high intensity; type III, insufficient thickness without discontinuity; type IV, presence of a minor discontinuity; type V, presence of a major discontinuity.

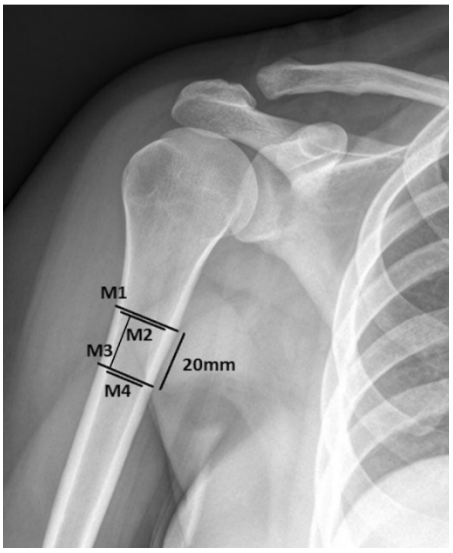
6.3 WHOOP Wearable Strap

For selected sites utilizing the WHOOP wearable strap: Continuous general health data will be recorded with a WHOOP device. The WHOOP device will be provided to each patient at select sites prior to surgery. This device is worn on the wrist continuously and provides real-time data that is transmitted wirelessly and will be worn by the patient for six months post-operatively. Data includes general health measures such as heart rate, respiratory rate, sleep, and activity levels. For example, total sleep duration and REM sleep duration will be compared between groups to assess whether or not patient sleep is improved with DAA in the postoperative period.

6.4 Rotator Cuff Healing Index

For the Rotator Cuff Healing Index score, if a DXA scan is not available for bone mineral density determination, an AP radiograph of the target shoulder will be used for evaluation and measured as follows.

The first level is the most proximal point on the humerus where the outer medial and lateral cortical borders become parallel. A perpendicular line will be drawn from the medial outer cortex of the humerus to the lateral outer cortex of the humerus and measured with a digital caliper to provide the thickness of the entire bone (M1). At the same level, a measurement of the width of the intramedullary canal will be obtained (M2). The M2 distance was then subtracted from M1 to obtain the combined cortical thickness at level 1 (C1). The second level measurements were obtained 20 mm distal to level 1. The same methods were used to calculate the combined cortical thickness at this second level (C2). The C1 and C2 values were then averaged to determine the CBT_{AVG} for each patient. Denote the parallelism of the outer proximal humerus cortex at levels 1 and 2 if the bone thickness measurements are not more than 1.0 mm different between levels.[11]



Cortical thickness average:

- If ≥ 6 mm - score = 0
- If < 6 mm - score = 2

7 MONITORING

Based on human subject risk, size, nature, and complexity this study is considered to be minimal risk. . The product has been cleared for sale and Arthrex has not identified any additional device risks during its time on the market. Therefore, the study will be monitored using a risk-based approach, including periodic monitoring calls with site staff and when necessary on-site visits. The EDC system will be reviewed periodically by the sponsor, or designee, for remote data queries, missing data, and data inconsistencies.

Sponsor will have the right, upon reasonable notice and during regular business hours, to audit the documents of the study. The Site and Investigator will cooperate with Sponsor or designee and will make all study documents including informed consent documents, HIPAA authorizations, and study data available. Sponsor will communicate findings to the Site in an exit meeting or in writing. The Site and Principal Investigator must correct or explain any deficiencies noted by the Sponsor.

The Sponsor will collect all site staff's essential documents, record of training, and delegation of authority logs. New members of the site study team may be added from time to time and should only start their assignments after receiving adequate training.

When findings indicate that retraining is required, Arthrex, or designee, must retrain site staff as soon as possible. Source verification on-site will be performed when risks are triggered by issues identified during central data review. Sites are subject to CAPA and Root Cause Analysis to address outstanding or inconsistent data and/or protocol deviations.

8 ADVERSE EVENTS

8.1 Adverse Events

An adverse event (AE) is any undesirable experience (e.g., sign, symptom, illness, clinically significant abnormal laboratory value, or other medical event) occurring in a subject during the course of the study, whether or not it is related to the study device or procedure.

Due to the minimal risk of the study, only device related adverse events or events that impact the study outcomes will be reported in the electronic data capture (EDC) system. The Sponsor is responsible for the classification for AE's and ongoing safety evaluation

for the products. All related AEs shall be classified by relatedness, event type, and serious or non-serious. The Sponsor shall review the PI's assessment of all AEs. In the case of disagreement between Sponsor and PI, the Sponsor shall communicate both opinions to medical monitor.

8.1.1 Serious Adverse Events

A serious adverse event is an adverse event that led to any of the following:

- death,
- serious deterioration in the health of a subject or user as defined by one or more of the following:
  - life-threatening illness or injury, or
  - a permanent impairment of a body structure or function
  - inpatient hospitalization or prolongation of existing hospitalization, or
  - medical or surgical intervention to prevent life-threatening illness or permanent impairment
- fetal distress, fetal death or a congenital anomaly or birth defect

All applicable serious adverse events will be reported by entering the event in the EDC as soon as possible and reported to the IRB/EC per their guidelines.

8.2 Non-reportable Events

Within the scope of this study, an AE does not include:

- Medical or surgical procedure (e.g., surgery, endoscopy, transfusion); the condition that leads to the procedure is considered an AE
- Pre-existing diseases or conditions present or detected at the start of the study that do not worsen
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalizations for cosmetic elective surgery, social and/or convenience admissions)
- The disease or disorder being studied, or sign or symptom associated with the disease or disorder, unless the disease, sign or symptom is more severe than expected based on the subject's condition and/or requires intervention.

8.3 Adverse Event Documentation

The Principal Investigator or designee will report related adverse events for the study analysis. Adverse events will be evaluated and differentiated by:

- Severity of the event defined below.
    - Mild: Awareness of signs and symptoms, but easily tolerated; are of minor irritant type, causing no loss of time from everyday activities; symptoms would not require medication or a medical evaluation; signs and symptoms are transient.
    - Moderate: Discomfort severe enough to cause interference with usual activities; requiring treatment, but not extended hospitalization or intensive care for the subject.
    - Severe: Incapacitating with the inability to do work or normal activities; signs and symptoms may be systemic in nature or require medical evaluation and treatment; requiring additional hospitalization or intensive care (prolonged hospitalization).

- The following clarifications are provided for the serious adverse events:
    - Life-threatening means that the subject was, in the view of the Investigator, at immediate risk of death from the event as it occurred. The definition does not include an event that, had it occurred in a more severe form, might have caused death.
    - Hospitalization for elective treatment of a pre-existing condition that did not worsen during the study is not considered a serious adverse event.
    - “Inpatient” hospitalization means the subject has been formally admitted to a hospital for medical reasons. This may or may not be overnight. It does not include presentation at a causality or emergency room.
    - Important medical events that may not result in death, or be life-threatening, however, based upon appropriate medical judgment, may jeopardize the subject, and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
    - Is significant for any other reason.

- Relatedness to the device or procedure, defined as:
    - Unrelated: AE is due to the underlying disease state or concomitant medication, or therapy not related to the study-specific devices or procedures.
    - Probably not Related: AE had minimum or no temporal relationship to the study-specific devices or procedures, and more likely alternative etiology exists.
    - Possibly Related: AE had a strong temporal relationship to the study-specific devices or procedures and alternative etiology is equally or less likely compared to the potential relationship to the study-specific devices or procedures.
    - Probably Related: AE had a strong temporal relationship to the study-specific devices or procedures, and another etiology is unlikely.

Unknown: Relationship of the AE to the study-specific devices or procedures and alternative etiology is unknown.

9 STATISTICAL CONSIDERATIONS

The study is a post-market clinical follow-up study. Given the observational nature of the study a sample size calculation was not performed. The total enrollment goal of 120 subjects was selected in an effort to create a generalizable sample that is large enough to provide sufficient data on safety and performance. Outcomes recorded at specific time points will be analyzed according to standard measures of descriptive statistics. The number of dropouts and withdrawals will be presented. Interim analyses may be conducted based on regulatory request. After completion of the study, a final report encompassing all study data will be generated.

9.1 Sample Size

Sample size calculations were based on a one-sided Z-test for two proportions. The study was powered to detect a difference in the proportion healed in the treatment and control groups. The healing rate on the postoperative MRI in the treatment group was assumed to be 75%, and in the control group, 40%. Further assumptions included a one-sided alpha level of 0.025 and 90% power. Under these assumptions, 40 subjects per group are required. To account for a potential dropout of up to 33%, this study will enroll 120 total subjects (60 per group).

Sample size was estimated using PASS 2021 Power Analysis and Sample Size Software (2021). NCSS, LLC. Kaysville, Utah, USA, ncss.com/software/pass.

9.2 Descriptive Statistics

Continuous data will be summarized with mean, standard deviation, median, minimum, maximum, and number of evaluable observations. Categorical data will be summarized with frequency counts and percentages. Confidence intervals may be presented, where appropriate, using the t-distribution for continuous data and normal approximation for binomial data (unless otherwise noted).

9.3 Handling of Missing Data

All attempts will be made to limit the amount of missing data. Unless otherwise specified, no attempt will be made to impute missing data. The number of subjects that contribute data to each analysis will be stated in the final report. In cases of subject withdrawal, data recorded from subjects up to the time of withdrawal will be reported and analyzed. The number of dropouts and withdrawals will be presented.

9.4 Demographics and Baseline Characteristics

Descriptive statistics will be presented for baseline demographic, medical history, and procedural data on the randomized subjects. Data will be presented by group.

9.5 Analysis of Study Outcomes

9.5.1 Primary Outcomes

The primary outcome of difference in healing rates between groups will be assessed under the following hypothesis:

H0: $\pi T - \pi C \leq 0$

Ha: $\pi T - \pi C > 0$

Where πT is the healing rate at six months in the treatment group (RCR + DAA) and πC is healing rate in the control group (non-augmented RCR) at six months. The difference in rates between groups will be summarized, along with a 95% confidence interval.

A chi-square test will be performed to obtain a p-value of the comparisons between groups. A one-sided p-value of <0.025 will be used to define success of the hypothesis (i.e., postoperative healing is improved with the addition of DAA).

9.5.2 Secondary Outcomes

The following secondary outcomes will be assessed using descriptive statistics, with results presented by group at Pre-op/Baseline and each follow-up.

- American Shoulder and Elbow Surgeons Score (ASES)
- Single Assessment Numeric Evaluation score (SANE)
- Visual Analog Scale (VAS) for pain
- Veterans RAND Health Survey (VR-12)

Changes from pre-operative values will also be summarized by group. Changes between groups may be compared using two-sample t-tests.

9.5.3 Objective Outcomes

Shoulder range of motion (ROM) in forward flexion, external and internal rotation will be summarized by group at 26 weeks and one year, along with the changes from Pre-op/Baseline to each time point.

Post-operative cuff integrity is determined through MRI and is classified into five categories, as described by Sugaya et al.[10] type I, sufficient thickness with homogenously low intensity; type II, sufficient thickness with partial high intensity; type III, insufficient thickness without discontinuity; type IV, presence of a minor discontinuity; type V, presence of a major discontinuity. Data will be summarized by group using frequency distributions.

10 ETHICS/PROTECTION OF HUMAN SUBJECTS

10.1 Ethical Standards and Guidelines

The investigator will ensure that this study is conducted in full conformity with the protocol and the fundamental principles set forth in Declaration of Helsinki and ISO 14155, as far as relevant.

10.2 Institutional Review Board/ Ethics Committee

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB/EC 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 be reviewed and approved by the IRB/EC per the IRB/EC guidelines. All written and dated approvals from the IRB/EC shall be retained by the Site and Sponsor.

10.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of the risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject.

Consent forms will be IRB/EC-approved, and the subject is given ample time to read and review the document. The investigator or designee will explain the research study to the subject and answer any questions that may arise. The investigator or designee will ensure that the subject's participation is voluntary, and no coercion to enroll in the study has occurred. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study without prejudice to their medical care. The informed consent process will be documented in the source documents. A copy of the signed and dated informed consent document will be given to subjects for their records. The subject will be updated with any new study information that may affect their willingness to participate. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

10.4 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, site staff, and the sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to subjects.

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.

The study monitor or other representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

11 DATA HANDLING AND RECORD KEEPING

11.1 Data Management Responsibilities

The investigators are 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. The investigators will maintain adequate case histories of study subjects, including accurate case report forms (CRFs), and source documentation. Site staff shall ensure any change or correction reported on a CRF shall be dated, initialed, and explained if necessary, and shall not obscure the original entry. Site staff will maintain appropriate medical and research records for this study. Site staff will permit authorized representatives of Arthrex to examine research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Data collection and accurate documentation are the responsibility of the site staff under the supervision of the investigator. All source documents must be reviewed by the study team and data entry staff, who will ensure that they are accurate and complete.

The sponsor will have procedures in place for system validation for the EDC. The sponsor shall periodically remotely review data and send queries to the site for missing or erroneous data. eCRF completion guidelines will be given to the site and are maintain separate from the protocol. If an amendment of the protocol occurs, CRFs will be updated as appropriate and applicable. The eCRFs shall be signed and dated by the Principal Investigator or authorized designee prior to site closeout.

11.2 Data Capture Methods

Data will be entered into a password protected EDC system by the site staff. The data may be collected on paper source worksheets or from the medical record. The sponsor should use an unambiguous subject identification code that allows identification of all the data reported for each Subject. The link between the code and each Subject shall be retained by the PI in a secure location. Subject questionnaires may be entered directly into the EDC by the subject. All data shall be entered into the EDC in a timely manner. De-identified images (MRIs) will be stored separately from the EDC, in a DICOM system for the study.

11.3 Study Records Retention

At the site, study records will be maintained for at least three years from date of study completion. No records will be destroyed without the written consent of the sponsor. The

Sponsor and PI shall retain all study documents and shall take action to ensure no accidental or premature destruction of these documents occurs. The PI and Sponsor may transfer custody of records to another person or party and document the transfer.

11.4 Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, ethical standards, or regulations. Investigators shall not deviate from the protocol except to protect the rights or well-being of a subject. Significant deviations will be reported to Arthrex in a timely manner and to the IRB/EC per their guidelines.

11.5 Amendments to the Protocol

Protocol amendments will be completed by Arthrex. At each protocol amendment all appendices and supporting documents will be reviewed for impact and updated as appropriate. Arthrex will notify all active sites of each protocol amendment for submission to the IRB/EC as necessary per the IRB/EC guidelines.

12 STUDY CLOSE OUT

The completion of a clinical study shall be deemed to coincide with the final database lock, whether or not the clinical study concluded according to the pre-specified study closeout activities or was terminated prematurely.

After study close out, a report of the clinical study shall be completed, even if terminated prematurely. The report shall be in written form, and include identification of the device(s), a description of the methodology and design of the clinical study, deviations from the Protocol, data analysis and statistics, and critical appraisal of the results compared to the objectives of the clinical study.

The results of the clinical study shall be entered in a publicly accessible database where the clinical study was registered, such as clinicaltrials.gov, and published whether positive, inconclusive, or negative to help guide future research device development and medical treatment.

13 PUBLICATION/DATA SHARING POLICY

The clinical study will be registered in a publicly accessible database, as appropriate to the study location guidelines.

Publication rights, criteria for authorship, conditions and time frames for publication are defined in the site clinical trial agreement.

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SUPPLEMENTAL MATERIALS

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Site Roster
- Key Sponsor Personnel
- CRF Completion Guidelines
- Case Report Forms

APPENDICES

Appendix 1: Key Study Questionnaires

Appendix 2: Consent Form Template