Cover Page

Study Protocol and Statistical Analysis Plan

Official Title: Extracellular matrix scaffold graft augmentation in rotator cuff repair: a prospective, randomized, controlled trial

NCT Number: NCT03551509

Document Date: 28 February 2023

Title: Extracellular matrix scaffold graft augmentation in rotator cuff repair: a prospective, randomized, controlled trial

Protocol No: FLA 18-008

Principal Investigator: Gregory Gilot, MD
Co-Investigator: Streubel Philipp, MD

Organization: Cleveland Clinic Florida
Levitetz Department of Orthopedic Surgery
2950 Cleveland Clinic Blvd.
Weston, FL 33331

Summary of Changes from Previous Version:

Affected Section(s)	**Summary of Revisions Made**	**Rationale**
1; 5	Increase to 70 patients	Increased due to large drop-out rates
1; 2A	Including 2.5-5 cm tears	Large screen failure rate due to tear size specifications
1; inclusion criteria; 2B	Clarifying imaging needed for diagnosis	Imaging is only needed for diagnostic purposes, not all is needed
2D	Removal of Dr. Vani Sabesan	No longer a surgeon at Cleveland Clinic
3C	Added in time points for ultrasounds	IRB approved previously – updating protocol to reflect this
3C	Updated the US physician	All sports medicine physicians at Cleveland Clinic can perform the US
10	Included verbiage for adding/removing study personnel	Was not in the original protocol and needed guidance

Contact Information

Role	Name	Number and Email
Research Director:	Carlos Higuera, MD	higuerc@ccf.org (216) 401-1385
Principal Investigator:	Gregory Gilot, MD	gilotg@ccf.org (954) 659-5430
Co-Investigator:	Philipp Streubel, MD	streubp@ccf.org (954) 659-5000
Research Manager:	Alison Klika	klikaa@ccf.org (216) 444-4954
Research Coordinator(s):	Ashley Valdes	valdesa4@ccf.org (561) 923-5830

Synopsis

Title:	Extracellular matrix scaffold graft augmentation in rotator cuff repair: a prospective, randomized, controlled trial
Study Description:	This is a prospective, randomized, controlled, multi-center clinical trial to evaluate the effectiveness of an ECM scaffold graft to augment repair of a large/massive rotator cuff tear. The study will involve 70 patients. 35 patients will be randomly assigned to each arm of the study. A-FLEX graft will be used in those patients randomly assigned to the treatment group who are undergoing an arthroscopic large (defined as 2.5-5 cm) or massive (defined as >5 cm) rotator cuff repair. Patients randomly assigned into the control group will undergo open or arthroscopic rotator cuff repair using the surgeon's standard technique.
Objectives:	The purpose of this study is to evaluate the efficacy of using the Arthroflex (A-FLEX) graft to augment large to massive arthroscopic rotator cuff repairs *in vivo* and decrease repair failures in a prospective, randomized, controlled trial. By undergoing serial US examinations at follow-ups, we also intend to evaluate when during the postoperative period the failure of the repair occurs.
Indication/Target:	The population target is all subjects 18 years or older undergoing primary arthroscopic rotator cuff surgery (please see Inclusion/Exclusion criteria).
Endpoints:	The primary clinical outcomes to be measured and subsequently evaluated will be the following: a. Success as defined by tendon healing after rotator cuff repair, as indicated based on MRI at 1year. b. Comparison of tendon healing will be assessed using US imaging modalities versus MRI at 1 year time point. c. Progress of tendon healing based on US will be used as predictive data for 1 year success (based on primary outcome). The secondary clinical outcomes to be measured and subsequently evaluated will be the patient satisfaction, quality of life, and shoulder function, to be determined with the following outcome measures: a. The Veterans Rand 12-item Health Survey (VR-12). b. The American Shoulder and Elbow Surgeons Shoulder (ASES) c. The Western Ontario Rotator Cuff Index (WORC). d. Shoulder activity level as per Brophy et al. [15].

	e. Subjective Shoulder Value (SSV) f. Constant Shoulder Score (Constant)
Study Population:	Approximately 70 subjects is needed to assess the primary outcome, measured as the percentage of repairs that heal and remain intact after 1 year. All statistical comparisons will be made using the Statistical Package for Social Science (SPSS) version 16.0 software. Inclusion Criteria: 1. Patients with a large (2.5-5 cm) to massive (>5 cm) rotator cuff tear who will be undergoing open or arthroscopic repair. The cuff tear size will be determined on either pre-operative magnetic resonance imaging (MRI), or ultrasound (US), or intra-operative measurements, or computerized tomography (CT). 2. Patients who are willing and able to provide written informed consent for their involvement in the study. 3. Patients who meet criteria for RCR surgery. 4. Patients older than 18 years of age. Exclusion criteria: 1. Those with a known sensitivity to materials of porcine origin. 2. Patients with addiction to illegal drugs, solvents or alcohol who are actively using or have previously attempted and failed a treatment program. 3. Patients with bacteremia, a systemic infection, or infection of the surgical site. 4. All those who are prisoners. 5. Patients who are pregnant or nursing. 6. All those with a condition that may limit a patient's ability to finalize the study or that may cause an undue risk to the patient's health and well-being.
Description of Site/Facilities Enrolling Participants:	Levitetz Department of Orthopedic Surgery Department of Anesthesiology Locations: Cleveland Clinic Florida – Weston 2950 Cleveland Clinic Blvd Weston, FL 33331 Cleveland Clinic Florida – Coral Springs 5701 N University Dr Coral Springs, FL 33067
Study Duration:	Subjects will be followed for 1 year.
Data Collection:	Electronic (REDCap and EPIC) database (please see Data Handling and Record Keeping).

Statistical Reporting:	Statistical analysis will be performed by a biostatistician at Cleveland Clinic.

Schedule of Activities (SoA)

	Visit 1	Visit 2	Visit 3	Visit 4	Visit 6	Visit 5
Assessment	**Screening (Pre-Op)**	**6 weeks Post-op**	**3 mo. Post-op**	**6 mo. Post-op**	**9 mo. Post-op**	**1 year Post-op**
Eligibility	X					
Informed Consent	X					
Medical History and Physical Exam	X					
MRI						X
US		X	X	X	X	X
Shoulder Outcome Surveys	X	X	X	X	X	X

Time and Events Schedule: Summary Table

Introduction

Despite advances in surgical technology, repairs of large (3-5 cm) and massive (>5 cm) rotator cuff tears (RCT) fail from 20-90% [1]. Due to their size and increased structural involvement, large or massive RCT present a substantial challenge to orthopaedic surgeons. [16] The repairs tend to fail at the suture-tendon junction, which is due to several factors, including tension at the repair and quality of the tendon [1-2,5]. Full thickness tears are uncommon in younger patients, especially those less than forty years old and are usually traumatic in etiology. Younger patients also typically fair better following arthroscopic rotator cuff repair with fewer failures and more successful return to pre-injury level of function [16]. One strategy to augment repair of large to massive rotator cuff tears has been the development of biological scaffold materials, which are composed of extracellular matrix (ECM). The ECM composing the scaffolds are made from a number of tissues, including, but not limited to, small intestinal submucosa (SIS), dermis, and pericardium [3]. Studies to date include both prospective and retrospective in animal and human models, and include Restore, a porcine-derived SIS by DePuy Orthopaedics, GraftJacket, a human-derived, non-cross-linked dermis graft by Wright Medical Technology, and Zimmer Collagen Repair, a cross-linked porcine derived dermal graft made by Zimmer. Restore studies have shown no benefit and some even an increase in repair failure with recommendations not to use to augment repair [1, 4-8]. GraftJacket studies have shown a reduction in graft failure [1, 9-11]; however, several of the Restore and GraftJacket studies are limited by a lack of a control cohort. The Zimmer graft studies have conflicting results with both an improvement and no improvement in failure rates of repair [1,12,13]. The prior studies listed are all *in vivo*; however, the majority are not randomized trials and thus do not have a control with which to compare data. In addition, some trials include open repairs. A lack of prospective, randomized, controlled, *in vivo* trials exist that evaluate the ability of the ECM scaffold graft augmentation in large to massive arthroscopic rotator cuff repairs to decrease the failure rate.

The purpose of this study is to evaluate the efficacy of using the Arthroflex (A-FLEX) graft to augment large to massive arthroscopic rotator cuff repairs *in vivo* and decrease repair failures in a prospective, randomized, controlled trial. By undergoing serial US examinations at follow-ups, we also intend to evaluate when during the postoperative period the failure of the repair occurs.

1. Study Design

Methods

This is a prospective, randomized, controlled, multi-center clinical trial to evaluate the effectiveness of an ECM scaffold graft to augment repair of a large/massive rotator cuff tear. The study will involve 70 patients. 35 patients will be randomly assigned to each arm of the study.

A-FLEX graft will be used in those patients randomly assigned to the treatment group who are undergoing an arthroscopic large (defined as 2.5-5 cm) or massive (defined as >5 cm) rotator cuff repair. Patients randomly assigned into the control group will undergo open or arthroscopic rotator cuff repair using the surgeon's standard technique.

A. Inclusion Criteria
The following patients will be found eligible for inclusion into the study sample:

1. Patients with a large (2.5-5 cm) to massive (>5 cm) rotator cuff tear who will be undergoing open or arthroscopic repair. The cuff tear size will be determined on either pre-operative magnetic resonance imaging (MRI), or ultrasound (US), or intra-operative measurements, or computerized tomography (CT).
2. Patients who are willing and able to provide written informed consent for their involvement in the study.
3. Patients who meet criteria for RCR surgery.
4. Patients older than 18 years of age.

B. Exclusion Criteria
The following patients will not be found eligible for inclusion into the study sample.

1. Those with a known sensitivity to materials of porcine origin.
2. Patients with addiction to illegal drugs, solvents or alcohol who are actively using or have previously attempted and failed a treatment program.
3. Patients with bacteremia, a systemic infection, or infection of the surgical site.
4. All those who are prisoners.
5. Patients who are pregnant or nursing.
6. All those with a condition that may limit a patient's ability to finalize the study or that may cause an undue risk to the patient's health and well-being.

2. Research Procedures

Treatment Plan

A. Preoperative Screening

Patients scheduled for an open or arthroscopic repair of a rotator cuff tear ≥ 2.5 cm will be identified during clinical visits or through EPIC. If the patient meets the eligibility inclusion/exclusion criteria for the study, he or she will be asked to participate in the study the following way:

During a patient's pre-operative clinical visit, the researcher will describe in detail the study at hand including, but not limited to, study benefits, potential risks, and alternative treatment modalities. He/she will hand a copy of the Informed Consent to the patient for review. If the patient agrees to participate in the study, the written informed consent will be completed and filed. The patient will be told explicitly that if he or she declines participation, his or her care will not be affected.

If patient is unavailable during pre-operative clinical visit, patient will be contacted via phone call. Any information regarding the study including IRB approved consent and brochure will be emailed and/or mailed to the patient for review. There will be documentation in the patient's chart when this patient was contacted via phone. Patient will be consented in-person on same-day as surgery, only if the above is completed and documented.

B. Enrolled Patients

After enrollment, all indicated preoperative assessments will be performed and recorded.

C. Randomization

All patients that meet the criteria will be randomized the day the informed consent is signed. If the patient is randomized into the control group, the surgery will continue as planned with no ECM scaffold graft to augment the repair. However, if the patient falls within the treatment group, an FDA-approved ECM scaffold graft will be used to augment the repair. The post-operative care will be as per standard care following a rotator cuff repair. There is no expectation that the patient should require a longer hospital stay.

D. Surgical Treatment

All surgical procedures will be performed by Board Certified and Fellowship trained Orthopedic Surgeons from Cleveland Clinic, Dr. Gregory Gilot or as appointed by the PI. A standardized surgical repair technique will be used by the participating surgeon.

1. Control Treatment Group

Patients randomly assigned into the control group will undergo open or arthroscopic rotator cuff repair using the surgeon's standard practice. No ECM graft will be used.

2. Treatment Group

Patients randomly assigned into the treatment group will undergo open or arthroscopic rotator cuff repair with A-FLEX graft to augment the repair. ECM scaffold grafts are indicated for the reinforcement of soft tissues repaired by sutures or suture anchors during tendon repair surgery, including rotator cuff.

3. Alternative Treatment Group

Patients who meet pre-op inclusion criteria where a repair cannot be accomplished due to intraoperative findings will remain in the study. This group will be analyzed separately and still follow study procedures.

E. Surgical Methods

Prior to repair

Tendon qualities and measurements will quantified and recorded:

- Tear size, retraction, quality of tissue

Arthroscopic Primary Rotator Cuff Repair
All patients will undergo arthroscopic primary repair using a suture bridge technique. An acromioplasty, distal clavicle excision and biceps tenodesis or tenotomy may be performed by routine techniques as clinically indicated. The tendon tear will be identified and mobilized, as indicated, such that the tendon can be approximated over the greater tuberosity. Standard double row suture bridge fixation technique will be used for all repairs

Mini-open/ Arthroscopic Graft Augmentation
In patients receiving a graft, thru mini open technique the lateral portal incision will be extended vertically approximately 5-6 cm. A standard, deltoid-splitting, mini-open approach will then be performed, leaving the deltoid attachment to the acromion intact. For arthroscopic technique same method of fixation will be used below. The dermis graft will be sized and cut so as to cover the entire repair site in both medial-lateral and anterior-posterior dimensions. The medial sutures previously placed in the tendon at the time of arthroscopic repair will then be passed in a mattress technique through the medial side of the graft. At least two

mattress sutures will be used, bringing the graft medial to the medial sutures used for the primary tendon repair. The graft will then be tensioned and secured in the anterior-posterior direction using at least two sutures on each side, passed through intact rotator cuff tissue. The suture limbs retained from the laterally placed suture bridge repair anchors will be placed as mattress sutures into the graft, and the graft will be tensioned to a position distal to the repair footprint.

Data for RCR will be recorded:

- Number of anchors
- Quality of repair
- Footprint coverage

3. Assessments

Eligible patients will be evaluated according to the pre-, intra- and post- operative assessment plans, delineated below, as well as the time and events schedule. All clinical results will be assessed during the period of hospital stay.

A. Preoperative Assessments

The following assessments/tests will be taken prior to patient operative treatment.

- Eligibility criteria, including informed consent.
- Age, gender, height, weight, BMI
- Primary diagnosis
- Medical History
- Physical Exam
- Current medications
- American Society of Anesthesiologists (ASA) risk
- Smoking status
- Imaging of shoulder
- Shoulder outcome surveys (SSV, ASES, Constant, VR12, WORC)

B. Operative Assessments

The following medical information will be collected from the Operative and Anesthesia records.

- Tear size, retraction, quality of tissue
- Length of surgery
- Possible intraoperative arthroscopic photographs

- Implants used
- Quality of repair

C. Postoperative Assessments

The following information will be collected after surgery: standard clinical follow-up PE and history, medications and serial US exams at 6 weeks, 3 months, 6 months, 9 months and 1 year postop, and MRI exam at 1 year postop. All US examinations will be performed by one Board Certified and Fellowship trained Sports Medicine physician in the office and coordinated with scheduled follow-up appointments. Shoulder outcome forms will also be collected at each follow up visit (listed below):

4. Data Collection and Analysis

The primary clinical outcomes to be measured and subsequently evaluated will be the following:

d. Success as defined by tendon healing after rotator cuff repair, as indicated based on MRI at 1year.
e. Comparison of tendon healing will be assessed using US imaging modalities versus MRI at 1 year time point.
f. Progress of tendon healing based on US will be used as predictive data for 1 year success (based on primary outcome).

The secondary clinical outcomes to be measured and subsequently evaluated will be the patient satisfaction, quality of life, and shoulder function, to be determined with the following outcome measures:

g. The Veterans Rand 12-item Health Survey (VR-12).
h. The American Shoulder and Elbow Surgeons Shoulder (ASES)
i. The Western Ontario Rotator Cuff Index (WORC).
j. Shoulder activity level as per Brophy et al. [15].
k. Subjective Shoulder Value (SSV)
l. Constant Shoulder Score (Constant)

5. Sample Size Justification and Statistical Analysis

Approximately 70 subjects are needed to assess the primary outcome, measured as the percentage of repairs that heal and remain intact after 1 year. A re-tear rate of 40% is expected in patients who have undergone rotator cuff repair for large and massive rotator cuff tears, based on the current literature (reference ted below). We anticipate that in this study, the percentage of re-tears in the augmented group will be reduced by

approximately half (~20%), while the control group would experience rates of re-tear comparable to what is reported in the current literature (~40%). Reducing this rate by half would be clinically meaningful. An SD of 15% within groups was allowed. Power analysis indicated that 20 patients in each group would provide sufficient power to identify statistical significance in healing rates between the control and augmented groups. With the assumption that the control group will have a failure rate of approximately 40% and the augmented group will have a failure rate of approximately 20%, at least 34 should be randomized in the control group and 26 in the augmented group. It is estimated that an overall fewer percentage of subjects initially randomized to the control group will complete the trial as augmentation may be required due to tear severity and other procedure variables. Those patients randomized to the control arm and withdrawn for repair by augmentation may be followed for safety.

A power analysis was also considered for shoulder function, a secondary clinical outcome. It demonstrated that at least thirty-four cases must complete the study (seventeen cases in each arm- augmented and control) in order to assess the difference between each group. This sample size was statistically derived by an ASES score power analysis, using a power of 0.8, an effect size d of 0.9, an alpha error probability of 0.05, and an allocation ratio of 1. This is assuming an ASES score of 84 at 12 months postsurgical repair in the augmented group (standard deviation of 16) and 72 (standard deviation of 12) for the control group. The ASES data used was derived from a recently completed ArthroFlex rotator cuff repair study for which data is on file at LifeNet Health. Again, with the assumption that the control group will have a failure rate of approximately 40% and the augmented group will have a failure rate of approximately 20%, at least 30 should be randomized in the control group and 22 in the augmented group to assess a difference in shoulder function.

Once data is acquired for 15 subjects in each group, a post-hoc power analysis will be conducted to confirm that alpha and beta error probabilities are still under the accepted limits.

The primary analysis will be conducted on both the intent to treat and the per protocol populations. The intent to treat population will be comprised of all subjects that have completed rotator cuff repair surgery. The per protocol population will be comprised of all subjects that have completed all study visits and did not have any major protocol violations (e.g., missed visits, noncompliance with postsurgical instructions, etc.). Standard adjustments to analyses for pre-specified or baseline-suggested clinical covariates will be made; these covariate-adjusted analyses will be considered secondary analyses. Primary analysis results will be declared statistically significant if the two-sided p-value is less than 0.05.

Safety analyses will be performed on the intent to treat population and will include the incidence of treatment-emergent AEs and clinically significant changes in vital signs and

physical examinations. Impact of treatment on infection rate, treatment emergent AEs, and changes in vital signs and physical examination will all be assessed.

Safety data will be summarized with descriptive statistics by treatment group and also by visit, where applicable. AE data will be listed individually and summarized by system organ class and preferred terms within a system organ class for each treatment group.

All statistical comparisons will be made using the Statistical Package for Social Science (SPSS) version 16.0 software. Results will be reported as an aggregate.
Statistical analysis will be performed by the orthopaedic research fellows in conjunction with Cleveland Clinic-Main biostatistician.

6. Study Product Description

ArthroFlex (A-FLEX) is not considered investigational and is currently available. The material is classified as a human and cellular tissue product under Food and Drug Administration (FDA) regulations and thus is not subject to any clinical evaluations before use. LifeNet Health uses several steps to ensure that allograft tissue is safe for use with patients. Extensive donor screening is performed to prevent risk of disease transmissions. There is a medical and social history taken from every donor, and questionable donors are refused. Blood is drawn from each donor for testing to rule out diseases such as HIV, hepatitis, and syphilis. Each section of recovered tissue is tested for any bacteria. In addition, tissue used to make A-FLEX is treated with antibiotic to inactivate bacteria. The tissue is also cleaned thoroughly with detergent, enzymes, and solvent to remove cells from tissue. This MATRACELL™ technology also effectively removes donor DNA from the ADM ensuring a biocompatible scaffold to facilitate repair. All these screenings, tests, and treatments are designed to eliminate the risk of disease transmission. The remaining intact acellular framework contains native growth factors, proteoglycans, hyaluronic acid, collagen, fibronectin, and elastin, therefore promoting wound healing.
A-FLEX is terminally sterilized with low dose gamma irradiation to provide a medical-device grade Sterility Assurance Level (SAL) of 10^{-6}.

Labeling

Since this will be an open-label study, study product will be identified. The Instructions for Use for A-FLEX will be provided in the site study binders.

Storage and Handling of Investigational Product

A-FLEX is provided in a sealed and sterile pouch and is stored at room temperature (between 15ºC and 30ºC). A-FLEX should not be frozen or refrigerated. It should be stored in its original cardboard sleeve. There should be minimal excessive exposure to light and A-FLEX should be protected from excessive heat. The product should not be used past the expiration date indicated

on the label. A-FLEX should not be used if it is damaged, if the packaging integrity is compromised, if the color of the product is other than white, or if the temperature dot on the package is not present. Rinsing is not required prior to application; however, it may improve handling.

Accountability Procedures for the Study Products

Investigation product records must include the following:

- Receipt, date and quantity, and batch or lot number
- Disposition dates and quantity administered to each subject
- Inventory records
- All correspondence related to the study product

All product records should be stored in the study binder with product instructions for use.

7. Confidentiality of Data

The only patient identifying information to be used will be the medical record number in order to facilitate collection and organization of data and ensure that serial US and shoulder surveys are attributed to the same patient. All data will be recorded in a password-protected REDCap database. The principal investigator, orthopaedic research fellows, research coordinators, and the study's preceptors will be the only individuals allowed access to this information.

8. Adverse Events and Data Monitoring Committee

All adverse events (AE) will be recorded. Details to be documented include the nature, onset, duration, severity, relationship to the device, relationship to the operative procedure and outcome of each event.

Most likely adverse events:

- Infection
- Injury to nerves and blood vessels
- Chronic pain or Complex regional pain syndrome

Note: The above-mentioned AE are not related to the use of ECM scaffold graft. They are potential complications associated with rotator cuff repair.

Potential serious adverse events related to ECM scaffold graft use:

- Anaphylactoid or anaphylactic reaction to ECM allograft.

If an unanticipated (in nature, severity or frequency) or serious (fatal, life-threatening or permanently disabling) adverse event arises, the study will be halted and the IRB

notified. The situation will be discussed among surgical faculty, and if there is a prudent solution, it will be presented to the IRB for approval. If there are no effective solutions, the investigators will have no choice but to discontinue the study.

Data will be reviewed by the PI and physicians conducting the study. The ECM scaffold grafts have not been linked to potentially serious or life-threatening complications. Our research will limit the potential for complications even further by screening and excluding patients with a known allergy to materials of porcine origin. Lastly, the ECM grafts are FDA-approved scaffold material that is indicated for reinforcement or augmentation of soft tissue repairs. In view of this, we will not be deviating from the standard of care by using the ECM allograft and the investigators do not anticipate having to discontinue the study or having to alter the protocol based on interim results. For these reasons, an independent data monitoring committee will not be needed or used.

9. Consent

In a private, outpatient setting, the PI or one of the research coordinators involved in the study will describe in detail the characteristics of the research study. Understandable language will be used. The process of pre-operative assessment, randomization, treatment, data collection and analysis along with the potential risks/benefits of the study are to be described in detail. Furthermore, the methods of maintaining data security and confidentiality will be outlined. The patient is to be explicitly told that he or she does not have to participate in the study and that regardless of his/her decision, will receive the best care this hospital can provide.

The informed consent process will take place during the patient's pre-operative clinical visit. The original consent form will be kept with study records by the principal investigator in a secure location, and a copy of the consent will be given to the subject. The subject's decision to participate will be documented in his or hers electronic record. A copy of the consent may be placed in the hospital record.

10. Principal Investigators

Principal Investigators (PIs) and Co-Investigators (Co-Is) and any other study personnel will added and removed through Cleveland Clinic's IRB. Any changes to this will be communicated with the sponsor via e-mail, and the regulatory binder will be updated accordingly. It is not necessary to amend this protocol with the changes of PIs, Co-Is, and other study personnel.

Adding and removing PIs will also be updated in regards to the legal agreements.

References

1. Derwin KA, Badylak SF, Steinmann SP, Ianotti JP. Extracellular matrix scaffold devices for rotator cuff repair. *J Shoulder Elbow Surg* 2010;19:467-476.

2. Schlegel TF, Hawkins RJ, Lewis CW, Motta T, Turner AS. The effects of augmentation with swine small intestine submucosa on tendon healing under tension: histologic and mechanical evaluations in sheep. *Am J Sports Med* 2006;34:275-280.

3. Badylak SF, Freytes DO, Gilbert TW. Extracellular matrix as a biological scaffold material: Structure and function. *Acta Biomaterialia* 2009;1:1-13.

4. Metcalf MH, Savioe FH, Kellum B. Surgical technique for xenograft (SIS) augmentation of rotator-cuff repair. *Oper Tech Orthop* 2002;12:204-8.

5. Sclamberg SG, Tibone JE, Itamura JM, Kasraeian S. Six-month magnetic resonance imaging follow-up of large and massive rotator cuff repairs reinforced with porcine small intestinal submucosa. *J Shoulder Elbow Surg* 2004;13:538-41.

6. Ianotti JP, Codsi MJ, Kwon YW, Derwin K, Ciccone J, Brems JJ. Porcine small intestine submucosa augmentation of surgical repair of chronic two-tendon rotator cuff tears. A randomized, controlled trial. *J Bone Joint Surg Am* 2006;88:1238-44.

7. Walton JR, Bowman NK, Khatib Y, Linklater J, Murrell GA. Restore orthobiologic implant: not recommended for augmentation of rotator cuff repairs. *J Bone Joint Surg Am* 2007;89:786-91.

8. Zheng MH, Chen J, Kirilak Y, Willers C, Xu J, Wood D. Porcine small intestine submucosa (SIS) is not an acellular collagenous matrix and contains porcine DNA: possible implications in human implantation. *J Biomed Mater Res B Appl Biomater* 2005;73:61-7.

9. Dopirak R, Bond JL, Snyder SJ. Arthroscopic total rotator cuff replacement with an acellular human dermal allograft matrix. *Int J Shoulder Surg* 2007;1:7-15.

10. Burkhead WZ, Schiffern SC, Krishnan SG. Use of Graft Jacket as an augmentation for massive rotator cuff tears. *Semin Arthroplasty* 2007;18:11-8.

11. Bond JL, Dopirak RM, Higgins J, Burns J, Snyder SJ. Arthroscopic replacement of massive, irrecparable rotator cuff tears using GraftJacket allograft: technique and preliminary results. *Arthroscopy* 2008;24:403-9.

12. Badhe SP, Lawrence TM, Smith FD, Lunn PG. An assessment of porcine dermal xenograft as an augmentation graft in the treatment of extensive rotator cuff tears. *J Shoulder Elbow Surg* 2008;17:35S-9.

13. Soler JA, Gidwani S, Curtis MJ. Early complications from the use of porcine dermal collagen implants (Permacol) as bridging constructs in the repair of massive rotator cuff tears. A report of 4 cases. *Acta Orthop Belg* 2007;73:432-6.

14. Brophy RH, Beauvais RL, Jones EC, Cordasco FA, and Marx RG. Measurement of shoulder activity level. *Clin Orthop Relat Res* 2005;439:101-108.

15. Krishnan SG, Harkins DC, Schiffern SC, Pennington SD, Burkhead WZ. Arthroscopic repair of full-thickness tears of the rotator cuff in patients younger than 40 years. *Arthroscopy: J of Arthro and Rel Surg* 2008;24(3):324-328.

16. Chung SW, Kim JY, Kim MH, Kim SH, Oh JH. Arthroscopic repair of massive rotator cuff tears: outcome and analysis of factors associated with healing failure or poor postoperative function. *The American journal of sports medicine.* 2013;41(7):1674-1683. doi:10.1177/0363546513485719.
17. Greenspoon JA, Petri M, Warth RJ, Millett PJ. Massive rotator cuff tears: pathomechanics, current treatment options, and clinical outcomes. *Journal of shoulder and elbow surgery / American Shoulder and Elbow Surgeons ... [et al.].* 2015;24(9):1493-1505. doi:10.1016/j.jse.2015.04.005.
18. Gerber C, Fuchs B, Hodler J. The results of repair of massive tears of the rotator cuff. *Journal of Bone and Joint Surgery - Series A.* 2000;82(4):505-515.