A Prospective Randomized Evaluation of Rotator Cuff Healing Using a Nanofiber Scaffold in Patients Greater than 55 Years

Study Title: A Prospective Randomized Evaluation of Rotator Cuff Healing Using a Nanofiber Scaffold in Patients Greater than 55 Years

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1. INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to United States standards of Good Clinical Practice in accordance with applicable Federal regulations and institutional research policies and procedures.

Despite numerous advancements in surgical techniques and over 250,000 procedures currently performed annually in the United States, failure of tendon healing following rotator cuff surgery occurs frequently with reports as high as 94%.[1-23] Nonhealing can lead to persistent pain, poor outcomes and a significant economic burden to society when revision surgery is required.[1,24,25] Several factors have been associated with poor tendon healing with age greater than 60 years shown to be a significant risk factor due to diminishing vascularity at the bone tendon interface where the tear typically originates.[3,4,10,25-32] While numerous techniques have been devised to improve fixation over the past several decades, very few have been developed to address or enhance the biology at the repair site. Rotium nanofiber is a recent FDA approved scaffold that has been shown to improve tendon healing to bone in animal studies. It works to mimic the extracellular matrix and helps concentrates and bind cells at the repair site providing a better organizational structure of the healing tissue. The purpose of the current study is to assess if use of the scaffold significantly improves rotator cuff healing and enhances strength in patients at higher risk of perioperative failure of the repair.

2. BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

Rotator cuff tears are a frequent cause of shoulder pain and disability in the elderly population.[33] Typically, when conservative measures fail, surgery is often advised. A successful clinical outcome is felt to be heavily predicated on healing of the tendon to the bone. Despite numerous surgical and technical advancements over the past two decades not all repairs heal with re-tear or failure to heal remaining the number one complication associated with rotator cuff surgery.[4-32] This in turn creates a hefty economic burden on society whereupon surgeries are being performed with poor eventual outcomes and ultimately wasted resources.[1]

While reasons for failure are multifactorial, a strong correlation has been associated with advancing age.[3,13,27-30,32] In an observational study on the natural history of rotator cuff disease, patients younger than 50 years old rarely had rotator cuff tears whereas those greater than 60 had a statistically significant greater incidence of unilateral and bilateral tears.[25] Advancing age is believed to alter and change the intrinsic properties of the tendon leading to stiffness, hypovascularity and overall impairment of the biology of tendon healing. Furthermore, when repairs fail, they typically do so within the first four months of surgery.[34][35] Means, therefore, to enhance the zone of the repair by increasing the cellularity immediately following surgery may improve the overall healing and lessen failures.

Recently, nanofiber scaffolds have demonstrated the ability to mimic the extracellular matrix and help structure, organize and proliferate cellular material.[35-37] They do so by working in essence like a sponge when incorporated into the repair site and help to bind, organize, and promote cell migration. This in effect, creates a less haphazard arrangement and induces better organization of healing tissue at the cellular level. Rotium, is an FDA approved nonwoven microfiber matrix composed of PLCL (poly L-lactide-co-caprolactone) and PGL (polyglycolide) that is indicated for use in rotator cuff repair to enhance healing at the bone tendon interface. The implant is inserted under the rotator cuff tendon and placed on top of
the greater tuberosity at the time of surgery and typically positioned over a suture. In a recent animal study performed at Colorado State University, a nearly 75% increased strength of repair was demonstrated at twelve weeks in those tendons treated with the graft. This will be the first prospective randomized clinical study in humans assessing for a difference in healing and strength in a population of patients considered at high risk for postoperative failure of the repair.

3. STUDY OBJECTIVES

Utilizing a prospective randomized controlled trial, this study seeks to evaluate if there is a difference in post-operative healing, strength, and functional outcomes in patients older than 55 years with rotator cuff tears treated with and without the nanofiber scaffold.

A. Primary Aims & Objective

Aim 1: To determine if the use of the nanofiber scaffold reduces the occurrence of postoperative rotator cuff repair (RCR) failure in patients older than 55 years

Hypothesis: There will be a minimum of a 50% reduction in failure among patients treated with the nanofiber scaffold, as compared to the control group (standard repair without nanofiber scaffold).

Objective: Utilizing a prospective randomized controlled trial, patients treated with and without the nanofiber scaffold will be followed clinically for 24 months postoperatively. An MRI will be obtained on all patients at 6 months postoperatively to assess the repair integrity.

B. Secondary Aims & Objectives

Aim 2: To determine if the use of the nanofiber scaffold improves postoperative isometric muscle strength following RCR.

Hypothesis: Patients treated with the nanofiber scaffold will demonstrate greater isometric muscle strength as measured objectively with a muscle dynamometer (Lafayette Manual Muscle Tester) at 3, 6, 12, and 24 month postoperative visits, as compared to those patients treated without the nanofiber scaffold.

Objective: Utilizing a prospective randomized controlled trial, isometric strength will be measured in abduction with 90 of elevation with the arm in the plane of the scapula as well as external and internal rotation measure at zero degrees of elevation. Measurements will be obtained preoperatively on all patients and then postoperatively at 3, 6, and 12 months postoperatively. Measurements of the contralateral shoulder will be obtained for comparison with ultrasound confirmation of an intact rotator cuff on contralateral side.

Aim 3: To determine if there is a difference in clinical and functional outcomes of patients with rotator cuff tears treated with and without the nanofiber scaffold.
Hypothesis: Patients treated with the nanofiber scaffold will demonstrate greater improvement in clinical and functional outcomes than those patients not treated with the nanofiber scaffold during RCR surgery.

Objective: Utilizing a prospective randomized controlled trial, patients will complete ASES (American Shoulder and Elbow), SANE, VR-12, VAS (Visual Analogue Scale) Pain, and range of motion (ROM) evaluations preoperatively and postoperatively at 3, 6, 12 and 24 months. Comparisons between patients treated with and without the nanofiber scaffold will be performed.

4. STUDY DESIGN

The study design is a single-blinded randomized controlled trial.

A. Research Design

Patients undergoing RCR surgery will be randomly assigned to one of two groups: control or intervention. The intervention group will include the insertion of a nanofiber scaffold during RCR surgery whereas the control group will undergo RCR surgery but will not receive the nanofiber scaffold. Patients greater than 55 years old that have failed conservative management for a rotator cuff tear will be approached for enrollment and consent to be included in the study. This is a multicenter study. Six fellowship trained orthopedic surgeons skilled at in office ultrasound will conduct the study at six separate sites. Each clinician will enroll a total of 40 patients. For each site, half the patients (20) will be delegated to the control group and the other half (20) will be assigned to the treatment group. 40 envelopes for each location will be created and randomly assorted with half containing the treatment grouping and the other half indicating control grouping. A total of 240 patients will be enrolled at all six sites: 120 control group and 120 treatment group. At the time of surgical scheduling, an independent person (surgical scheduler) will pick one envelope and assign that sealed envelope to the patient. This envelope will be brought the day of surgery by the treating clinician and will be opened at the beginning of surgery. No patient information will be in the envelope and just the designation of “control” or “intervention” group. Patients will be blinded to the designated treatment group. Unfortunately, it would not be feasible to blind the surgeon to the treatment group.

Data Collection will occur preoperatively and postoperatively. Patient outcome measures will be collected using the REDCap clinical research system. This is a HIPAA Compliant text and email-based system that alerts and prompts patients for data collection preoperatively and at routine intervals postoperatively. Data collection postoperatively will occur at 2 weeks, 6 weeks, 3 months, 6 months, 12 months and 24 months. Data collected will include VAS Pain, VR-12, ASES and SANE scores, and ROM. Strength measurements will be collected postoperatively at 3, 6, 12 and 24 postoperatively using a Lafayette Manual Muscle Dynamometer. Isometric measurements will be taken with the arm abducted in the scapular plane at 90 degrees and then with the arm in neutral position to measure internal and external rotation. The contralateral shoulder will be measured and assessed for comparison and an ultrasound screen will be performed to verify an intact cuff for assessment purposes of contralateral shoulder. MRI scan consisting of T2 sagittal and coronal will be obtained on all subjects at 6 months. All images will be independently interpreted by a musculoskeletal radiologist for healing and...
integrity. Ultrasound will be obtained at 12 and 24 months postoperatively to assess the repair. Video clips of the repair in both short and long axis will be saved and archived. Clips will be independently evaluated for review to determine healing or failure.

B. **Data Management**

Indiana University's REDCap clinical research system (https://redcap.uits.iu.edu/) will be utilized for data collection by all treating physicians. REDCap is a password protected, HIPAA-compliant, web-based system. Patients upon enrollment will be assigned a separate clinical trial ID to allow for data tracking within the application. Primary data will be collected via the web-based system and stored electronically and encrypted under password protection. Each investigator will upload their respective patient's data. REDCap maintains an audit trail of access and edits. The REDCap system will capture Patient Reported Outcomes from each patient at the designated intervals. The principal investigator only will have access to the full database. At the conclusion of the study, the data will be exported to a password-protected encrypted Excel file on a password-protected computer. Once the data have been checked for accuracy and prior to statistical analysis, patient identifiers will be removed from the data set. The de-identified password-protected Excel spreadsheet will be provided to a statistician who will import the file into SPSS for analysis.

C. **Study Agent, Device, and/or Intervention Description**

The nanofiber scaffold that will be used during the RCR surgery is the intervention in this study. This nanofiber scaffold is inserted at the time of surgery by placing over a suture and shuttling it down the arthroscopic canula. It is positioned below the tendon and above the bone. The graft size is 2cm x 2 cm. This nanofiber scaffold has received FDA approval for the use outlined in this study. The use of the nanofiber scaffold is the only difference between the control and the intervention groups.

<table>
<thead>
<tr>
<th>Control Group</th>
<th>Intervention Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCR surgery without nanofiber scaffold</td>
<td>RCR surgery with nanofiber scaffold</td>
</tr>
</tbody>
</table>

D. **Sample Size**

RCR surgery among patients over the age of 55 years has a failure rate of approximately 25%. With the use of the nanofiber scaffold, it is estimated the RCR failure will be 10% (a decrease of 60% compared to the controls). Thus, to compare the proportion of failure between the control and intervention groups, a sample size of 200 (100 patients per group) would be required, assuming 80% power and a two-tailed alpha level of 0.05. However, to account for an attrition rate of approximately 20%, a total of 240 patients (120 patients per group) will be enrolled.

E. **Subject Selection**

Patients who meet the following criteria will be included in the study:

**Inclusion Criteria**

1. Age 55 and older
2. Primary diagnosis of rotator cuff tear
3. Able to provide informed consent

Patients who meet the following conditions will be excluded from participation:

**Exclusion Criteria**

1. Revision rotator cuff surgery
2. Partial thickness rotator cuff tears
3. Massive (greater than 5cm) rotator cuff tears
4. Patients with current tobacco history

**F. Study Outcome Measures (Endpoints)**

**Primary Endpoint:** RCR failure as diagnosed postoperatively by ultrasound at 6 months, 12 months and 24 months.
   Patients will obtain an ultrasound imaging to assess for rotator cuff repair failure. Ultrasound exams will be interpreted by 2 independent examiners blinded to the patient’s treatment group.

**Secondary Endpoint:** Isometric strength as measured by dynamometer at 3, 6, 12 and 24 months postoperatively.
   Patient strength will be assessed with a manual muscle dynamometer to assess for objective differences in strength.

**Tertiary Endpoint:** Clinical and functional outcomes including ASES, SANE, VR-12, VAS Pain, and ROM measured preoperatively and postoperatively at 2 weeks, 6 week, 3 months, 6 months, 12 months and 24 months.
   Patients will complete ASES, SANE, VR-12, and VAS Pain measures while the treating physician will evaluate ROM preoperatively and at each postoperative visit at 2 weeks, 6 week, 3 months, 6 months, 12 months and 24 months.

**5. STUDY PROCEDURES**

**A. Subject Recruitment and Screening**

Participants will be recruited from the clinical practice of the six co-investigators. Patients who present for an office visit and are diagnosed with a rotator cuff tear requiring outpatient surgical intervention will screened for eligibility for participation in the study. If a patient is eligible for the study, each treating clinician will discuss the study with the patient and obtain informed consent during the routine office visit.

**B. Randomization**

This is a single-blinded study; thus, the patient will not be informed if the nanofiber scaffold was included into the repair. A total of 240 envelopes will be created: 120 envelopes will be designated as controls and 120 envelopes will designated as nanofiber scaffold (intervention group). The control group will be managed with routine and standard arthroscopic rotator cuff repair technique with no additional augmentation. At the time of surgical scheduling, the surgical scheduler will
draw one envelope from the stack and include this into the surgical information that is brought by the treating surgeon the day of surgery. At the time of surgery and at the start of the procedure, the operating staff will open the envelope and announce the group. Once the clinician is notified, the name of the patient will be added to the envelope along with the assigned treatment group, and the envelope will be sealed. The treatment group and name of patient will be kept confidential until completion of the study. Patients will remain blinded to the intervention. Envelopes will be opened at end of study for data collection and analysis purposes with patient information deidentified. They will be stored in a locked container at the surgery center only accessible by the chief of staff.

C. **Study Visits/ Study Duration**

Participants enrolled in this study will be followed for a period of 2 years post-operatively. Data collected and time points are as below:

<table>
<thead>
<tr>
<th>Data Collection Visit</th>
<th>Data to be Collected</th>
<th>Imaging Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preoperative Visit</td>
<td>AGE</td>
<td>MRI or Ultrasound</td>
</tr>
<tr>
<td></td>
<td>BMI</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hand Dominance</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Operative Side</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Comorbidities</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VAS Pain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>SANE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VR-12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range of Motion (FF/Abd/ER)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Isometric Strength (Bilateral)</td>
<td></td>
</tr>
<tr>
<td>2 Week Postoperative Visit</td>
<td>VAS Pain</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>SANE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>VR-12</td>
<td></td>
</tr>
<tr>
<td>6 Week Postoperative Visit</td>
<td>VAS Pain</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>SANE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASES</td>
<td></td>
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<tr>
<td></td>
<td>VR-12</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range of Motion (FF/Abd/ER)</td>
<td></td>
</tr>
<tr>
<td>3 Months Postoperative Visit</td>
<td>VAS Pain</td>
<td>none</td>
</tr>
<tr>
<td></td>
<td>SANE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASES</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range of Motion (FF/Abd/ER)</td>
<td></td>
</tr>
<tr>
<td>6 Months Postoperative Visit</td>
<td>VAS Pain</td>
<td>MRI</td>
</tr>
<tr>
<td></td>
<td>SANE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASES</td>
<td></td>
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<tr>
<td></td>
<td>VR-12</td>
<td></td>
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<tr>
<td></td>
<td>Isometric Strength</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Range of Motion (FF/Abd/ER)</td>
<td></td>
</tr>
<tr>
<td>12 Months Postoperative Visit</td>
<td>VAS Pain</td>
<td>US</td>
</tr>
<tr>
<td></td>
<td>SANE</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ASES</td>
<td></td>
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<tr>
<td></td>
<td>VR-12</td>
<td></td>
</tr>
<tr>
<td>24 Months Postoperative Visit</td>
<td>Isometric Strength Range of Motion (FF/Abd/ER)</td>
<td>US</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------------------------</td>
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</tr>
<tr>
<td>VAS Pain</td>
<td>SANE</td>
<td></td>
</tr>
<tr>
<td>ASES</td>
<td>VR-12</td>
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</tr>
<tr>
<td>Isometric Strength</td>
<td>Range of Motion (FF/Abd/ER)</td>
<td></td>
</tr>
</tbody>
</table>

The enrollment period for study participation is anticipated to last for 24 months only for data analysis.

D. **Specimen Collection, Preparation, Handling and Shipping**

N/A

E. **Statistical Analysis Plan**

After data checking and validation are completed, the analysis of the data will begin with examination of the distribution of each of the study variables. Data will be analyzed by an independent statistician. In this process, outliers will be identified and evaluated for inclusion in the final study database. Appropriate summary statistics will be calculated. Means and standard deviations will be reported for normally distributed continuous variables, a median and range will be tabulated for continuous variable that are not normally distributed, and frequencies and percentages will be provided for categorical variables. The remainder of the analysis will correspond to the specific aims provided above.

**Specific Aim 1:** To determine if the use of the nanofiber scaffold reduces the occurrence of postoperative RCR failure in patients older than 55 years on ultrasound postoperatively.

A chi-square test will be used to compare the proportion of failures between the intervention and control groups at each timepoint that imaging is obtained.

**Specific Aim 2:** To determine if the use of the nanofiber scaffold improves isometric muscle strength following RCR.

If data are normally distributed, independent t-tests will be used to compare isometric strength measurements between the control and intervention groups at each preoperative and postoperative timepoint. If data are not normally distributed, then Mann-Whitney U tests will be performed.

**Specific Aim 3:** To determine if there is a difference in clinical and functional outcomes of patients with rotator cuff tears treated with the nanofiber scaffold compared to those treated without.

If data are normally distributed, independent t-tests will be used to compare VAS Pain, SANE, V-12, ASES, and ROM measures between the control and intervention groups at each preoperative and postoperative timepoint. If data are not normally distributed, then Mann-Whitney U tests will be performed.
6. POTENTIAL RISKS AND BENEFITS

A. Potential Risks

This research is collecting data on patients treated with and without a nanofiber scaffold. It is FDA approved. The following risks can be related to the procedure and study analysis.

1. **Risk of rotator cuff surgery with nanofiber scaffold:** The main risk of rotator cuff surgery is the risk of nonhealing of the repaired tendon. Other risks can include the low probability of infection. Possible risks of using the nanofiber scaffold include allergic reactions, stiffness, graft disassociation and/or dislodgement from the repair site. To date, no allergic reactions have been reported.

2. **Risk of text alerts:** A HIPPA compliant and password protected database called Surgical Outcome Scores is the application that will help gather and collect the data. Texting is not a secure form of communication and there is a risk of loss of privacy by entering the data. Measures to lessen these risks include using a password protected database and all personal information will be deidentified with your name removed. In addition, the only information you will provide will be regarding pain level and number of pain pills taken. Your phone number will be kept confidential and not shared with any outside party.

B. Potential Benefits

This novel study seeks to determine if the nanofiber scaffold may offer a potential benefit to RCR patients by decreasing the incidence of failure after surgery, increasing early postoperative muscle strength, and improving clinical and functional outcomes. If the use of the nanofiber scaffold translates to improved patient outcomes, then future patients undergoing RCR will benefit from the use of the nanofiber scaffold.

7. ADVERSE EVENTS

A. Recording of Adverse Events

At each contact with the subject, the investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events should be recorded immediately. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document.

B. Notification of Adverse Events

All adverse events will be reported according to IRB guidelines.

8. ETHICAL CONSIDERATIONS

The Principle Investigator holds equity interest in Paragen, the parent holding company of Atreon Orthopedics, RenovoDerm, Vascular Genesis, and Tarian Medical. Paragen is a holding company formed by parent companies Nanofiber Solutions and Ikove Capital.
9. FUNDING SOURCE
The project Sponsor and manufacturer of ROTIUM Bioresorable Wick, Atreon Orthopedics (a Paragen company), is funding costs that exceed standard of care, to include the MRI performed 6-months post-operative per subject.

10. SUBJECT STIPENDS OR PAYMENTS
None.

11. PUBLICATION PLAN
The paper will be submitted for publication in the Journal of Shoulder and Elbow Surgery or the Journal of Bone and Joint Surgery upon completion.
REFERENCES

16. Koh KH, Kang KC, Lim TK, Shon MS, Yoo JC. Prospective randomized clinical trial of single- versus double-row suture anchor repair in 2- to 4-em rotator cuff tears: clinical


March 11, 2019

Nanofiber Solutions, LLC
Ronald L. Bracken
Chief Operating Officer
4389 Weaver Court North
Hilliard, Ohio 43026

Re: K183236
Trade/Device Name: ROTIUM Bioresorbable Wick
Regulation Number: 21 CFR 888.3030
Regulation Name: Single/multiple component metallic bone fixation appliances and accessories
Regulatory Class: Class II
Product Code: MAI
Dated: February 7, 2019
Received: February 8, 2019

Dear Mr. Bracken,

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. Although this letter refers to your product as a device, please be aware that some cleared products may instead be combination products. The 510(k) Premarket Notification Database located at https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/CFPMN.cfm identifies combination product submissions. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration. Please note: CDRH does not evaluate information related to contract liability warranties. We remind you, however, that device labeling must be truthful and not misleading.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to additional controls. Existing major regulations affecting your device can be found in the Code of Federal Regulations, Title 21, Parts 800 to 898. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA’s issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act’s requirements, including, but not limited to registration and listing (21 CFR Part 807); labeling (21 CFR Part 801); medical device reporting (reporting of medical device-related adverse events) (21 CFR 803) for

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov