Prospective multi-center study comparing REGENETEN in lieu of standard arthroscopic repair of high-grade (>50%) partial-thickness tears

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Protocol Version:	Version 3.0
Study Product Name:	REGENETEN Implant
Sponsor:	Smith & Nephew, Inc. 7135 Goodlett Farms Parkway Cordova, TN 38016 US

1. SIGNATURES

1.1 PROTOCOL SIGNATURE PAGE

This page will be returned to Smith & Nephew, Inc. and a copy retained at the investigational site.

I have read the attached protocol entitled "Prospective multi-center study comparing REGENETEN in lieu of standard arthroscopic repair of high-grade (>50%) partial-thickness tears", Version 3.0, dated 10SEP2019, and agree to abide by all provisions set forth herein.
I agree to comply with the Investigator's Obligations stipulated in Section 21 of the protocol,
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the described clinical investigation without the prior written consent of Smith & Nephew, Inc.

Role	Name	Signature	Date Signed (DD-MMM-YYYY)
Principal Investigator			

1.2 SPONSOR APPROVAL

	Job title	DocuSign Stamp
Head of Global Clinical Operations	DocuSigned by: Signer Name: Shirley Mak-Parisi Signing Reason: I have reviewed this document Signing Time: 25-Sep-2019 | 17:06:52 BST 72696DE2BF3F44E4853E034C1C6E1C5D	Regional Operations Manager, Global Clinical Operations
Head of Global Clinical Strategy	DocuSigned by: Cristin Taylor Signer Name: Cristin Taylor Signing Reason: I have reviewed this document Signing Time: 26-Sep-2019 | 22:24:38 BST F24622B51EF74D0288F7B6AE43DA7EAD	Clinical Strategy Lead, GCS Sports Med and ENT
Head of Global Biostatistics	DocuSigned by: Alan Rossington Signer Name: Alan Rossington Signing Reason: I approve this document Signing Time: 24-Sep-2019 | 09:54:35 BST 556E7DBFCA8A4287A7EE3EE9B5B3ABFD	Director Biostatistics and Data Management, Global Clinical Strategy
Medical Affairs Representative	DocuSigned by: Signer Name: Luca Orlandini Signing Reason: I approve this document Signing Time: 23-Sep-2019 | 22:00:05 BST FC872951AC1C4261B85EC7A7CD09ACDC	Vice President Medical Affairs, Scientific & Medical Affairs
GRS Representative	President, Global Research Solutions	Signer Name: Mohit Bhandari Date: 02-Oct-2019

2. SYNOPSIS

Title of Study:	Prospective multi-center study comparing REGENETEN in lieu of standard arthroscopic repair of high-grade (>50%) partial-thickness tears
Study Design:	Non-blinded, multi-center
Study Type:	Prospective cohort study
Study Product:	REGENETEN™ Implant
Comparison Group:	Arthroscopic repair of the high-grade (>50%) partial-thickness tear using standard surgical techniques.
Study Purpose:	Demonstrate that REGENETEN is superior to standard repair techniques when surgically treating high-grade (>50%) partial-thickness tears because REGENETEN preserves more of the native tendon footprint resulting in less post-operative pain and faster recovery.
Primary Objective:	To determine if arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN yields statistically superior participant-rated shoulder function and reduced pain and disability at 3 months following index surgery compared to standard surgical repair techniques.
Secondary Objective:	To generate performance and health economic evidence supporting the use of REGENETEN in treating high-grade (>50%) partial-thickness rotator cuff tears.
Statistical Rationale:	Superiority hypothesis for American Shoulder and Elbow Surgeons (ASES) score at 3 months following index surgery using a minimal clinically important difference (MCID) of 11.1[1] and a drop-out rate of 15%.
Sample Size:	118 participants (59 per group)
Number of Study Sites:	Up to 12 clinical sites
Targeted Global Regions:	United States
Inclusion Criteria:	Patients will be considered qualified for enrollment if they meet the following criteria:

	1. Male or female ≥18 years 2. High-grade (>50% tendon thickness) partial-thickness tear 3. Failed conservative medical management of the tendon tear defined as: a. Four (4) to six (6) weeks of formal physical therapy or guided home exercises b. Activity modification c. Shoulder injection at the discretion of the surgeon 4. Able to comply with the post-operative physiotherapy and follow-up schedule 5. Able to speak and read English 6. Provide written informed consent
Exclusion Criteria:	Any one (1) of the following criteria will disqualify a patient from participation in the study: 1. Prior shoulder surgery on index shoulder within 12 months of enrollment 2. Failed primary rotator cuff surgery of the index shoulder 3. Systemic steroid use (oral, IV) or locally injected at the surgical site within 1 month of enrollment 4. Metastatic disease 5. Concomitant surgeries for bone defects requiring bone implantation (Latarjet procedures) or for superior labral tear from anterior to posterior (SLAP) 6. Concomitant biceps tenodesis 7. Rheumatoid arthritis 8. Advanced osteoarthritis 9. Fatty infiltration of the index shoulder rotator cuff muscle ≥ Grade 3 10. Chronic pain disorders (i.e., fibromyalgia) 11. History of insulin dependent diabetes 12. History of heavy smoking (> 1 pack per day) within 6 months of enrollment 13. Currently involved in any injury litigation or workers compensation claims 14. Hypersensitivity to bovine-derived materials 15. Medical or physical condition that, in the opinion of the Investigator, would preclude safe participation in the study
Study Duration:	18 months enrollment (estimated), 24 month follow-up (primary endpoint assessed at 3 month follow-up)
Primary endpoint:	ASES (American Shoulder and Elbow Surgeons) score at 3 months following index surgery

Secondary endpoint(s):	Performance endpoints include: - ASES score over initial 3 months following index surgery - Single Assessment Numeric Value (SANE) score over initial 3 months following index surgery - ASES Visual Analog Scale (VAS) pain score over initial 3 months following index surgery - ASES score at 6, 12, 18 and 24 months following index surgery - SANE score at 6, 12, 18 and 24 months following index surgery - ASES VAS pain score at 6, 12, 18 and 24 months following index surgery - Constant-Murley score at 3, 6, 12 and 24 months following index surgery - Cumulative opioid use to treat the index shoulder over 3 months following index surgery - Cumulative non-opioid prescription medication use to treat the index should over 3 months following index surgery - Cumulative opioid use to treat the index shoulder over 12 months following index surgery - Cumulative non-opioid prescription medication use to treat the index shoulder over 12 months following index surgery - Duration of shoulder immobilization following index surgery - Time to return to work by work type (sedentary; laborer) - Time to return to driving - Time to return to sports - Incidence of progression to full-thickness tear within 12 months following index surgery - Incidence of progression to full-thickness tear within 24 months following index surgery - MRI assessment of percent filling at 12 months following index surgery - MRI assessment of percent filling at 24 months following index surgery - Rotator cuff tendon thickness at 12 months following index surgery - Rotator cuff tendon thickness at 24 months following index surgery - Goutallier classification of rotator cuff at 12 months following index surgery - Goutallier classification of rotator cuff at 24 months following index surgery - Sugaya score of rotator cuff at 12 months following index surgery

	- Sugaya score of rotator cuff at 24 months following index surgery - Incidence of revision surgery within 24 months following index surgery (index shoulder; all causes) Economic endpoints include: - Aggregate health care utilization costs over 12 months following index surgery - Operating room time (index surgery) - Number of steroid injections over 12 months following index surgery - Number of unscheduled clinic visits over 12 months following index surgery - Number of for-cause imaging procedures over 12 months following index surgery - Number of physiotherapy sessions over 12 months following index surgery
Safety Data	All Adverse Events over 24 months

STUDY SCHEMATIC

Schedule of Events	Pre-Op (days -60 to -1)	Surgery (day 0)	3 Mo (±30 days)	6 Mo (±30 days)	12 Mo (±30 days)	18 Mo (±60 days)	24 Mo (±60 days)
Informed Consent	✓						
Inclusion/Exclusion	✓						
Demographics/ Medical History	✓						
Operative Data		✓					
ASES Score	✓		✓†	✓	✓	✓	✓
SANE	✓		✓†	✓	✓	✓	✓
Constant-Murley Score	✓		✓	✓	✓		✓
Participant Diary			✓‡	✓‡	✓‡		
Adverse Events		✓	✓	✓	✓	✓	✓
Heath Care Utilization			✓	✓	✓		
Revision Surgery			✓	✓	✓	✓	✓
Upper Extremity MRI	✓*				✓		✓

Pre-Op indicates pre-operative; Mo, month(s); SANE, Single Assessment Numeric Evaluation; ASES, American Shoulder and Elbow Surgeons Score including VAS Pain

†The ASES score and SANE will be completed every week (i.e., every 7±3 days) though 3 month follow-up.

‡Participant diaries will be used to document opioid and non-opioid prescription medication use, use of a sling, other related healthcare utilization (i.e. steroid injections, clinic visits, imaging, physiotherapy sessions, etc.) and return to work, driving, and sports. Participant diary will be updated weekly (7±3 days) through 3 month follow-up and monthly (30±7 days) thereafter until 12 months post-surgery.

*The pre-op MRI is the participant's standard of care MRI and will not follow the study MRI Image Acquisition Protocol which is used for the 12 and 24 month MRIs. The pre-op MRI must occur within 6 months of enrollment into this study. All MRIs will be submitted to the imaging vendor per the Image Transfer Protocol.

3. TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
AAROM	Active Assisted Range of Motion
ADE	Adverse Device Effect(s)
ADL	Activities of Daily Living
AE	Adverse Event(s)
AROM	Active Range of Motion
ASADE	Anticipated Serious Adverse Device Effect
ASES	American Shoulder and Elbow Surgeons
CRF	Case Report Form(s)
CRO	Contract Research Organization
CSR	Clinical Study Report
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency(ies)
DDD	Defined Daily Dosage
EDC	Electronic Data Capture
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
ICJME	International Committee of Medical Journal Editors
IFU	Instructions for Use
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
MCID	Minimal Clinically Important Difference

Abbreviation	Definition
NSAE	Non-Serious Adverse Event(s)
PEEK	Polyetheretherketone
PI	Principal Investigator
PROM	Passive Range of Motion
PRP	Platelet-rich Plasma
SANE	Single Assessment Numeric Evaluation
S&N	Smith & Nephew Inc.
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAP	Statistical Analysis Plan
SLAP	Superior Labral Tear from Anterior to Posterior
USADE	Unanticipated Serious Adverse Device Effect(s)
VAS	Visual Analog Scale

4. INTRODUCTION

4.1 BACKGROUND

Rotator cuff disease is a painful, progressive condition resulting from damage and/or injury to one or more of the tendons within the rotator cuff, often involving the upper-most (supraspinatus) tendon.[2,3] Degenerative damage is predominantly the result of continual wear and tear, while acute injury may be caused by trauma such as sudden heavy lifting or a fall onto an outstretched arm.[4] Patients with atraumatic rotator cuff disease usually report pain and weakness in the arm, leading to impaired function and mobility,[5] and are typically recommended conservative treatments to manage symptoms in the first instance.[6] However, such conservative treatments may be ineffective;[7] surgical treatment may therefore be subsequently advised to remove damaged tissue or repair the rotator cuff.[8,9,10] Tear progression may continue after conventional surgical intervention with re-tear rates as 79% for massive tears.[11,12,13]

Overall, rotator cuff disease accounts for 4.5 million physician visits each year,[14] a burden which will inevitably increase as the incidence of disease grows. The substantial burden of rotator cuff disease on healthcare resources is compounded by the additional indirect costs associated with reduced employment and income, missed workdays, and disability payments. It is evident that the disability associated with rotator cuff disease comes at a high societal cost, which is expected to grow given the increasing prevalence of rotator cuff disease.[14,15,16]

The REGENETEN™ Implant is a collagen implant that provides a layer of collagen over injured tendons. The induction of this layer of new tendinous tissue may reduce micro-strains within the tendon, resulting in an optimized mechanical environment for tendon healing.[17] Use of REGENETEN in the treatment of high-grade partial-thickness tears in lieu of completion of tear and repair, which may accelerate patient recovery and shoulder mobility while reducing post-operative pain.[18]

The objective of this study is to demonstrate arthroscopic surgical treatment of high-grade (>50%) partial-thickness tears using REGENETEN yields statistically superior patient post-operative recovery outcomes, faster return to activities of daily living, and less health care utilization versus standard surgical repair techniques.

4.2 STUDY PURPOSE

The purpose of this prospective, post-market, multi-center cohort study is to demonstrate REGENETEN is superior to standard arthroscopic repair techniques when surgically treating high-grade (>50%) partial-thickness tears because REGENETEN preserves more of the native tendon footprint resulting in less post-operative pain and faster recovery.

5. OBJECTIVES

5.1 PRIMARY OBJECTIVE

The primary objective of this study is to determine if arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN yields statistically superior participant-rated shoulder function and reduced pain and disability at 3 months following index surgery compared to standard surgical repair techniques.

5.2 SECONDARY OBJECTIVE(S)

The secondary objectives of this study are to generate performance and health economic evidence supporting the use of REGENETEN in treating high-grade (>50%) partial-thickness rotator cuff tears. Specifically, these objectives will determine whether arthroscopic surgical treatment using REGENETEN versus standard surgical repair techniques for high-grade (>50%) partial-thickness rotator cuff tears results in:

1. Early benefits related to a participant-reported composite of daily shoulder function/disability and pain (over initial 3 months following index surgery)
2. Early benefits related to participant-reported average shoulder function as a percentage of normal (over initial 3 months following index surgery)

3. Early benefits related to participant-reported shoulder pain (over initial 3 months following index surgery)
4. Improved participant-reported composite of daily shoulder function/disability and pain (over 24 months following index surgery)
5. Improved participant-reported average shoulder function as a percentage of normal (over 24 months following index surgery)
6. Decreased participant-reported shoulder pain (over 24 months following index surgery)
7. Improved participant-reported and examiner-assessed shoulder pain and function (over 24 months following index surgery)
8. Decreased opioid use to treat the index shoulder (over initial 3 months following index surgery)
9. Decreased non-opioid prescription medication use to treat the index shoulder (over initial 3 months following index surgery)
10. Decreased opioid use to treat the index shoulder (over 12 months following index surgery)
11. Decreased use of non-opioid prescription medication to treat the index shoulder (over 12 months following index surgery)
12. Decreased shoulder immobilization time following index surgery
13. Earlier return to work by work type (sedentary; laborer)
14. Earlier return to driving
15. Earlier return to sports
16. Lower incidence of progression to full-thickness tear (within 12 months following index surgery)
17. Lower incidence of progression to full-thickness tear (within 24 months following index surgery)
18. Increased percent filling of rotator cuff (at 12 months following index surgery)
19. Increased percent filling of rotator cuff (at 24 months following index surgery)
20. Improvements in rotator cuff tendon thickness (at 12 months following surgery)
21. Improvements in rotator cuff tendon thickness (at 24 months following surgery)

22. Lower fatty infiltration of the rotator cuff (at 12 months following surgery)
23. Lower fatty infiltration of the rotator cuff (at 24 months following surgery)
24. Improved rotator cuff integrity (at 12 months following surgery)
25. Improved rotator cuff integrity (at 24 months following surgery)
26. Lower incidence of revision surgery (index shoulder; all causes) (within 24 months following index surgery)
27. Lower aggregate health care utilization costs (over 12 months following index surgery)
28. Decreased operating room time (index surgery)
29. Fewer shoulder steroid injections (over 12 months following index surgery)
30. Fewer unscheduled index shoulder-related clinic visits (over 12 months following index surgery)
31. Fewer for-cause imaging procedures (over 12 months following index surgery)
32. Fewer physiotherapy sessions (over 12 months following index surgery)

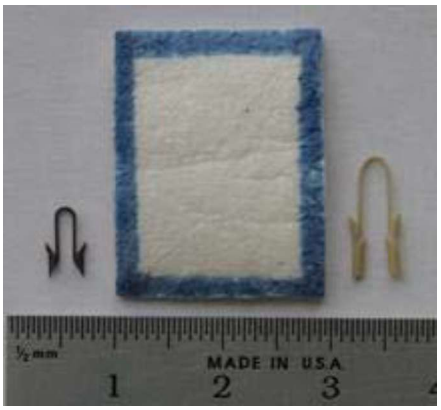
6. INVESTIGATIONAL PRODUCT(S)

6.1 IDENTIFICATION

The REGENETEN Implant system is biologic solution to a biomechanical problem and has been cleared by the Food and Drug Administration for commercial use in the United States. The REGENETEN Implant is a collagen implant that provides a layer of collagen over injured tendons. The induction of this layer of new tendinous tissue on the bursal side of the supraspinatus tendon may reduce micro-strains within the tendon. Reduction in these forces may in turn optimize the mechanical environment for tendon healing and inhibit, or arrest, tear propagation. Use of REGENETEN in the treatment of high-grade partial-thickness tears in lieu of converting the partial tear to a full-thickness tear and surgically reattaching the tendon to bone may accelerate patient recovery and shoulder mobility while reducing post-operative pain.

The REGENETEN Implant system (Figure 1) is comprised of disposable instruments, a resorbable collagen implant, and anchors to secure the scaffold to the underlying tendon and bone. The system is provided sterile, for single-use only, and in a dual sterile seal, tray-in-tray configuration. The REGENETEN Implant is indicated for the management and protection of rotator cuff tendon injuries in which there has been no substantial loss of tendon tissue.

Figure 1. Shown from left to right, tendon anchor, Implant and bone anchor



The collagen implant consists of a resorbable type I collagen matrix derived from bovine Achilles tendon. It is contraindicated for use in patients with a history of hypersensitivity to bovine-derived materials. The device is designed to completely resorb within six to 12 months.

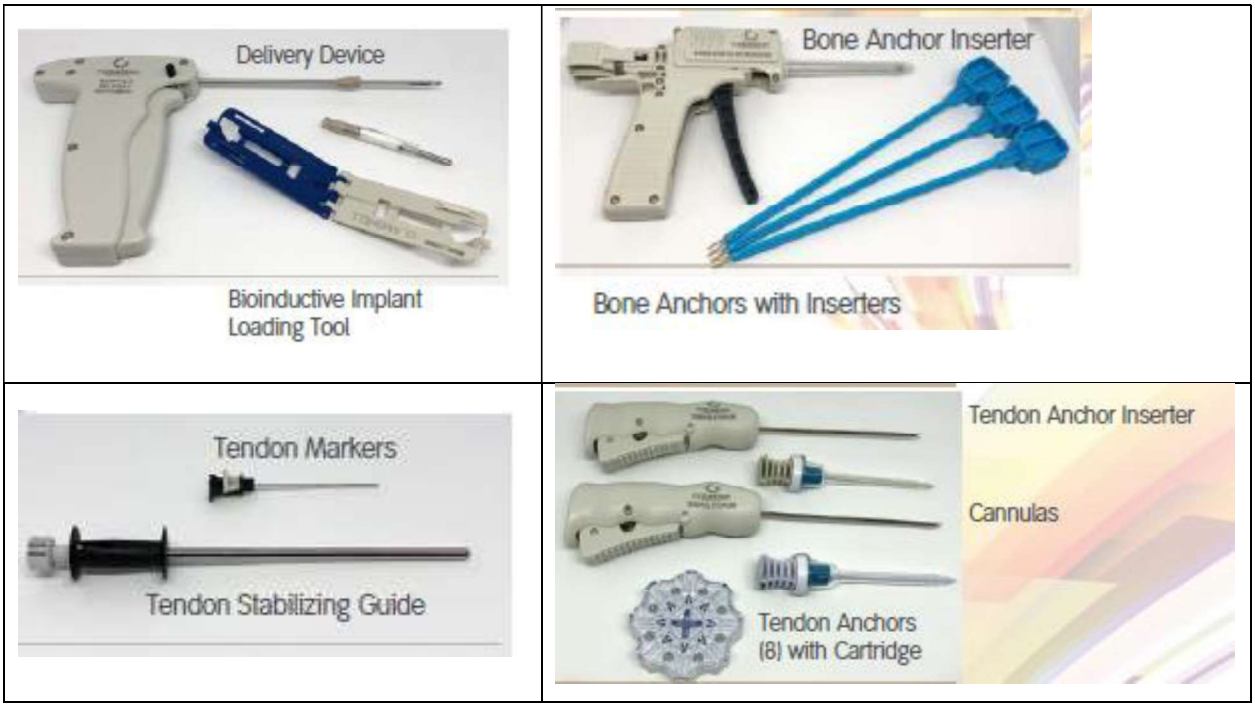
The tendon anchors are made from poly(L-lactide-co-D,L-lactide) in a molar ratio of 70% L-lactide to 30% D,L-lactide. Polylactide materials have been used in a variety of medical devices, such as bone anchors, bone pins, screws, plates, and spinal fusion cages. The tendon anchors are intended for the fixation of prosthetic material to soft tissues and designed to completely absorb within approximately 12 months.

The bone anchors are made from polyetheretherketone (PEEK), which is a common polymer used for bone anchors in orthopedic surgery. The bone anchors are intended for fixation of soft tissue grafts. The bone anchors are not resorbable.

The device does not contain, nor does it deliver, any medicinal substance, phthalates or other hazardous substances.

The disposable instrument system (Figure 2) includes the arthroscopic implant delivery instrument, tendon anchor delivery instruments, and bone anchor delivery instruments. There is also an implant loading tool and tendon stabilizing guide.

Figure 2 Disposable Instrument System



A summary of known and potential risks and benefits to humans of the REGENETEN Implant system can be found in the Instructions for Use (IFU).

6.2 PRODUCT USE

Surgical treatment of partial-thickness rotator cuff tears with the REGENETEN Implant system will be performed in accordance with its IFU.

6.3 SURGICAL PROCEDURE

All surgeries in both treatment cohorts will be performed arthroscopically unless the surgeon determines a mini-open procedure is required to protect participant health and well-being. Concomitant use of other biologics to augment the rotator cuff, including but not limited to stem cell therapy or platelet-rich plasma (PRP), are contraindicated.

7. PARTICIPANT ENROLLMENT AND WITHDRAWAL

7.1 PARTICIPANT POPULATION

One hundred eighteen (118) participants undergoing arthroscopic surgical treatment of a high-grade (>50%) partial-thickness tear, meeting the eligibility criteria, will be recruited from up to 12 sites in the United States. Participants who meet the eligibility criteria will be enrolled from the population of patients routinely seen by the Investigator.

7.2 INCLUSION CRITERIA

Patients will be considered qualified for enrollment if they meet the following criteria:

1. Male or female, ≥18 years
2. High-grade (>50% tendon thickness) partial-thickness tear
3. Failed conservative medical management of the tendon tear defined as:
    a. Four (4) to six (6) weeks of formal physical therapy or guided home exercises
    b. Activity modification
    c. Shoulder injection at the discretion of the surgeon
4. Able to comply with the post-operative physiotherapy and follow-up schedule
5. Able to read and write English
6. Provision of written informed consent

7.3 EXCLUSION CRITERIA

Any one (1) of the following criteria will disqualify a patient from enrollment in the study:

1. Prior shoulder surgery on index shoulder within 12 months of enrollment
2. Failed primary rotator cuff surgery of the index shoulder
3. Systemic steroid use (oral, IV) or locally injected at the surgical site within 1 month of enrollment
4. Metastatic disease
5. Concomitant surgeries for bone defects requiring bone implantation (Latarjet procedures) or for superior labral tear from anterior to posterior (SLAP)
6. Concomitant biceps tenodesis
7. Rheumatoid arthritis
8. Advanced osteoarthritis
9. Fatty infiltration of the index shoulder rotator cuff muscle ≥ Grade 3
10. Chronic pain disorders (i.e., fibromyalgia)
11. History of insulin dependent diabetes
12. History of heavy smoking (> 1 pack per day) within 6 months of enrollment
13. Currently involved in any injury litigation or workers compensation claims
14. Hypersensitivity to bovine-derived materials
15. Medical or physical condition that, in the opinion of the Investigator, would preclude safe participation in the study

7.3 SCREENING

All patients diagnosed with a high-grade (>50%) partial-thickness tear who are undergoing arthroscopic surgical treatment by the Investigator are to be screened for eligibility at their pre-operative visit based on medical record review and discussions with the patient and Investigator. Participating clinical sites are required to document all screened patients. If a patient is excluded from the study, the reasons for exclusion will be documented in the patient's source documents and noted in the Screening Form.

7.4 INFORMED CONSENT

Before conducting any study procedures or examinations, informed consent shall be obtained from all participants according to ISO14155 guidelines. Patients must be informed as to the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected as described in the written Informed Consent Form (ICF). The patients shall have sufficient opportunity to consider participation in the study. Patients will then be invited to read, sign and personally date the Institutional Review Board (IRB)-approved ICF, indicating their consent for enrollment. Additionally, the individual who obtains consent from the participant will sign and date the ICF. A copy of the signed informed consent documentation will be provided to the participant, and the original filed in the investigator site file (ISF).

7.5 ENROLLMENT

Enrollment in this study shall occur at the pre-operative visit after the investigator has confirmed eligibility and participant has completed the informed consent process. At this time, the participant will be assigned a Subject ID via the REDCap Cloud Electronic Data Capture (EDC) system.

7.6 LOST TO FOLLOW-UP

Once a participant is enrolled in the study, every reasonable effort will be made to follow the participant for the entire duration of the study period. A participant should not be deemed lost to follow-up until after he/she fails to complete the final 24 month visit and study personnel are unable to contact the participant.

Study personnel must make a reasonable effort to contact the participant in accordance with the site's local policies. All attempts to reach the participant should be documented and retained with the participant’s source documents.

7.7 WITHDRAWAL

Participants may be withdrawn from the study prior to 24 months post-surgery for the following reasons:

- Withdrawal of informed consent by the participant
- Determination of ineligibility by the Investigator during the index surgical procedure

Study participation is voluntary and participants may withdraw at any point without giving their reason to do so. Where participants withdraw consent, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the participant's privacy. All reasonable efforts should be made to retain participants for the full 24 month follow-up period of this study. If a participant withdraws prior to completing the study, study personnel will document the reason for withdrawal and attempt to collect any available outcome data. In cases where the participant withdraws consent, the data collected up to the point of withdrawal may be used but no additional data for that participant may be collected.

The Investigator may also withdraw a participant from the study if he/she determines during the index surgery that the rotator cuff tear does not meet the eligibility criteria based on direct arthroscopic visualization of the tear.

Participants will not be withdrawn from the study due to lack of adherence to the requirements of the study protocol (e.g., lack of compliance with physiotherapy guidelines, missed follow-up visits).

7.7.1 Replacement of Withdrawn Participants

Participants who are withdrawn by the Investigator due to ineligibility identified during the index surgery will be replaced. Any participants who withdraw their consent to participate prior to their index surgical procedure will also be replaced. Participants who withdraw their consent at any time following their index surgical procedure will not be replaced.

8. STUDY DESIGN

8.1 STUDY DESIGN

This is a prospective, non-blinded, multi-center cohort study to collect relevant clinical data and compare the REGENETEN Implant in lieu of standard arthroscopic repair in 118 participants (59 participants per group) with a high-grade (>50% tendon thickness) partial-thickness rotator cuff tear.

Up to 12 clinical sites in the United States will enroll and follow 118 participants who meet the study eligibility criteria. Follow-up clinical assessments will be performed at 3 months (±30 days), 6 months (±30 days), 12 months (±30 days), 18 months (±60 days), and 24 months (±60 days) post-operatively.

The total estimated study duration will be 42 months: 18 months enrollment (estimated) and up to 24 months follow-up (primary endpoint assessed at 3 month follow-up) post-operatively.

8.2 ALLOCATION AND BLINDING

This study is not randomized. Selection of the surgical approach (repair with REGENETEN versus standard repair techniques) will be at the discretion of the Investigator, in consultation with the participant, as appropriate.

Standard surgical repair techniques of the rotator cuff will be defined as either:

1. Debridement and a transtendinous repair, or
2. Complete takedown and repair.

To ensure an equal number of participants enrolled into each treatment group, the Sponsor and Contract Research Organization (CRO) will continuously monitor enrollment and will close enrollment into the faster enrolling cohort (REGENETEN cohort or standard repair technique

cohort) once the targeted enrollment has been reached. Enrollment into the slower enrolling cohort will continue until the study is fully enrolled.

8.3 STUDY ENDPOINTS

8.3.1 Primary Endpoint

The primary endpoint of this study is the American Shoulder and Elbow Surgeons (ASES) score at 3 months following index surgery.

8.3.2 Secondary Endpoints

The secondary endpoints of this study include performance endpoints and economic endpoints. The performance endpoints are:

1. ASES score over initial 3 months following index surgery
2. Single Assessment Numeric Evaluation (SANE) score over initial 3 months following index surgery
3. ASES Visual Analog Scale (VAS) pain score over initial 3 months following index surgery
4. ASES score at 6, 12, 18 and 24 months following index surgery
5. SANE score at 6, 12, 18 and 24 months following index surgery
6. ASES VAS pain score at 6, 12, 18 and 24 months following index surgery
7. Constant-Murley score at 3, 6, 12 and 24 months following index surgery
8. Cumulative opioid use to treat the index shoulder over 3 months following index surgery
9. Cumulative non-opioid prescription medication use to treat the index shoulder over 3 months following index surgery
10. Cumulative opioid use to treat the index shoulder over 12 months following index surgery
11. Cumulative non-opioid prescription medication use to treat the index shoulder over 12 months following index surgery
12. Duration of shoulder immobilization following index surgery
13. Time to return to work by work type (sedentary; laborer)
14. Time to return to driving

15. Time to return to sports
16. Incidence of progression to full-thickness tear within 12 months following index surgery
17. Incidence of progression to full-thickness tear within 24 months following index surgery
18. MRI assessment of percent filling at 12 months following index surgery
19. MRI assessment of percent filling at 24 months following index surgery
20. Rotator cuff tendon thickness at 12 months following index surgery
21. Rotator cuff tendon thickness at 24 months following index surgery
22. Goutallier classification of rotator cuff at 12 months following index surgery
23. Goutallier classification of rotator cuff at 24 months following index surgery
24. Sugaya score of rotator cuff at 12 months following index surgery
25. Sugaya score of rotator cuff at 24 months following index surgery
26. Incidence of revision surgery within 24 months following index surgery (index shoulder; all causes

The economic endpoints are:

27. Aggregate related health care utilization costs over 12 months following index surgery
28. Operating room time (index surgery)
29. Number of steroid injections over 12 months following index surgery
30. Number of unscheduled clinic visits over 12 months following index surgery
31. Number of for-cause imaging procedures over 12 months following index surgery
32. Number of physiotherapy sessions over 12 months following index surgery

8.4 Methods Used to Minimize Bias and Maximize Validity

The study will be conducted at up to 12 clinical sites, reducing the risk of bias inherent in a single-center study. To eliminate the potential for selection bias, Investigators will consecutively screen all patients over the age of 18 years who are candidates for arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears.

9. STUDY PROCEDURES

9.1 VISITS AND EXAMINATIONS

9.1.1 Summary

For a summary of the required procedures by visit, refer to Table 1: Study Procedures by Visit.

Table 1: Study Procedures by Visit

Schedule of Events	Pre-Op (days -60 to -1)	Surgery (day 0)	3 Mo (±30 days)	6 Mo (±30 days)	12 Mo (±30 days)	18 Mo (±60 days)	24 Mo (±60 days)
Informed Consent	✓						
Inclusion/Exclusion	✓						
Demographics/ Medical History	✓						
Operative Data		✓					
ASES Score	✓		✓†	✓	✓	✓	✓
SANE	✓		✓†	✓	✓	✓	✓
Constant-Murley Score	✓		✓	✓	✓		✓
Participant Diary			✓‡	✓‡	✓‡		
Adverse Events		✓	✓	✓	✓	✓	✓
Heath Care Utilization			✓	✓	✓		
Revision Surgery			✓	✓	✓	✓	✓
Upper Extremity MRI	✓*				✓		✓

Pre-Op indicates pre-operative; Mo, month(s); SANE, Single Assessment Numeric Evaluation; ASES, American Shoulder and Elbow Surgeons Score including VAS Pain
†The ASES score and SANE will be completed every week (i.e., every 7±3 days) though 3 month follow-up.
‡Participant diaries will be used to document opioid and non-opioid prescription medication use, use of a sling, other related healthcare utilization (i.e. steroid injections, clinic visits, imaging, physiotherapy sessions, etc.) and return to work, driving, and sports. Participant diary will be updated weekly (7±3 days) through 3 month follow-up and monthly (30±7 days) thereafter until 12 months post-surgery.
*The pre-op MRI is the participant's standard of care MRI and will not follow the study MRI Image Acquisition Protocol which is used for the 12 and 24 month MRIs. The pre-op MRI must occur within 6 months of enrollment into this study. All MRIs will be submitted to the imaging vendor per the Image Transfer Protocol.

9.1.2 Pre-operative Visit (60 days to 1 day prior to surgery)

1. Screen patient for protocol inclusion and exclusion criteria (based on medical record review and preliminary discussion of study with patient).
2. Obtain written informed consent from the participant as detailed in Section 7.4
   ----- Do not proceed until consent has been obtained -----
3. Enter screening data into REDCap Cloud EDC and obtain a Subject ID number.
4. Obtain demographic information and medical history, including information on opioid and non-opioid prescription medications used during the past 30 days.
5. Complete the ASES questionnaire, SANE questionnaire, and Constant-Murley assessment.
6. Obtain copy of the standard of care MRI of index shoulder, if available. Pre-op MRI must have occurred within 6 months of enrollment into this study.
7. Confirm date of surgery with participant.

9.1.3 Index Surgery (Day 0)

1. Confirm eligibility based on arthroscopic visualization of the tear.
2. Complete surgical procedure.
3. Record operative details as specified in Case Report Forms (CRFs)
4. If any adverse events, adverse device effects, or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 – Adverse Events and Device Deficiencies.
5. Instruct the participant on proper post-operative care/procedures, including any contraindicated treatments/medication(s).
6. Instruct the participant on follow-up procedures, including completing the weekly ASES and SANE questionnaires, completing the weekly diary, and returning for clinical follow-up at 3 months.
7. Provide participants with the cohort-specific Physiotherapy Guidelines.

9.1.4 Weekly Diary (week 1 to week 12 (±3 days))

1. Participant will complete the ASES questionnaire and SANE questionnaire.
2. Participant will document opioid and non-opioid prescription medication use, use of sling, other healthcare utilization related to the index shoulder (i.e. steroid injections, clinic visits, imaging, physiotherapy sessions, etc.) and return to work, driving, and sports in their diary.
3. Study personnel will remind each study participant to complete the questionnaires and diary weekly via telephone, email, or text.
4. Study personnel will remind participant of the importance of complying with the specified Physiotherapy Guidelines.

9.1.5 3 Month Visit (±30 days), 6 Month Visit (±30 days), 12 Month Visit (±30 days), 18 Month Visit (±60 days), and 24 Month Visit (±60 days)

1. Complete the ASES questionnaire (all visits), SANE questionnaire (all visits), and Constant-Murley assessment (3, 6, 12 and 24 month visits only).
2. Review diary entries for completeness with participant.
3. Document any health care utilization involving the index shoulder not recorded in the participant diary (3, 6, and 12 month visits).
4. Document any revision surgeries involving the index shoulder (all visits).
5. If any adverse events, adverse device effects, or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 – Adverse Events and Device Deficiencies (all visits).
6. MRI of index shoulder (12 month and 24 month visits).
7. Instruct the participant on follow-up procedures, including returning for the next clinical follow-up (except for the 24 month exit visit).

9.1.6 Post-Operative Physiotherapy Guidelines

Participants in each cohort (i.e. REGENETEN and standard surgical repair) will be provided with cohort-specific Physiotherapy Guidelines. Participants will be required to adhere strictly to the Physiotherapy Guidelines. Study personnel will remind participants of the importance of compliance, and the completion of physiotherapy sessions will be documented in the participant diary. Refer to the cohort-specific Physiotherapy Guidelines for details.

9.1.7 Concomitant Medications

Use of opioids, non-opioid prescription medications, and steroid injections to treat the index shoulder over 12 months following the index surgery will be documented in the participant diary or recorded from the participant's medical record per sections 9.1.4 and 9.1.5. Concomitant medications associated with the treatment of SAEs or ADEs will also be recorded.

9.1.8 MRI Submissions

Upper extremity MRIs for study participants will be collected pre-operatively, at 12 months post-surgery and at 24 months post-surgery. The pre-operative MRI is the participant's standard of care MRI and will not follow the study MRI Image Acquisition Protocol. The pre-op MRI must occur within 6 months of enrollment into this study.

Participants will receive an MRI of the index shoulder at 12 months and 24 months post-surgery per the Image Acquisition Protocol. The standard of care pre-operative MRI and the 12 and 24 month MRIs will be submitted to the imaging vendor per the Image Transfer Protocol. 3T MRIs are strongly preferred for submission, wherever available, but are not required.

9.1.9 Discontinued Participants

Discontinued participants are those who voluntarily discontinue participation or who are lost to follow-up after all reasonable attempts to contact them. Where possible, a final follow-up visit should be completed for all participants who discontinue the study early. Where consent is withdrawn, the date and any reason given for discontinuation should be captured, at a minimum

(Section 7.7). Finally, if appropriate, the Investigator will also advise the participant of subsequent therapy and/or procedures necessary for their medical condition.

9.1.10 Pregnancy

Women of child-bearing potential are not excluded from the study. Pregnancy is not reportable as an adverse event; however, complications related to the pregnancy may be reportable as determined on a case-by-case basis.

9.2 STUDY ENDPOINTS

9.2.1 Performance Endpoints

American Shoulder and Elbow Surgeons (ASES): The ASES instrument is composed of 2 sections containing participant self-reported and clinician assessments. The ASES score is a 0 to 100-point rating based solely on participant responses and is a combination of the participant's shoulder pain rating (VAS Pain) and self-reported ability to perform 10 different activities of daily living (ADLs).[19] ASES scores will be recorded pre-operatively, weekly from 1 week to 3 months post-surgery, and at 6,12,18 and 24 months post-surgery.

Single Assessment Numeric Evaluation (SANE): The SANE is a simple, single-question, patient-based shoulder function assessment tool: ''How would you rate your shoulder today as a percentage of normal (0% to 100% scale with 100% being normal)?'' It is popular because of its simplicity and ability to be applied to a wide variety of clinical situations. It has not been validated and no minimal clinically important difference has been reported.[20] SANE scores will be recorded pre-operatively, weekly from 1 week to 3 months post-surgery, and at 6,12,18 and 24 months post-surgery.

Participant-reported Shoulder Pain: Pain in the participant's index shoulder will be assessed using the VAS Pain rating from the ASES instrument. The VAS Pain rating will be recorded pre-

operatively, weekly from 1 week to 3 months post-surgery, and at 6, 12, 18, and 24 months post-surgery.

Constant-Murley Score: The Constant-Murley Score is a validated assessment of pain and shoulder functionality. The test is divided into four subscales: pain, activities of daily living, strength and range of motion (forward elevation, external rotation, abduction and internal rotation of the shoulder. At the end of the assessment, a score is obtained out of 100 points where higher scores indicate a higher quality of shoulder function.[21] The score is obtained through a combination of participant-reported and objective (examiner-assessed) shoulder outcome measures.[22]

Duration of Shoulder Immobilization: The duration of medically required shoulder immobilization following index surgery will be calculated based on the number of days in a sling, as reported in the participant diary.

Cumulative opioid use: Cumulative opioid use to treat the index shoulder from index surgery to 12 months will be calculated based on usage reported in the participant diary (name, dose, duration).

Cumulative Non-opioid Prescription Medication Use: Cumulative non-opioid prescription medication use to treat the index shoulder from index surgery to 12 months will be calculated based on usage reported in the participant diary (name, dose, duration).

Time to Return to Work, Driving, and Sports: Time from index surgery to return to ADLs will be calculated based on the date that participants report return to work (sedentary; laborer), return to driving, and return to sport as reported in the participant diary.

Incidence of Progression to Full Thickness Tear: An independent reviewer will assess MRIs for evidence of progression to a full-thickness tear within 12 months and 24 months of the index surgery. All MRI assessments are detailed in the Image Review Charter.

Percent Filling of Rotator Cuff: An independent reviewer will assess MRIs for the percent filling of the rotator cuff at 12 months and 24 months post-surgery. All MRI assessments are detailed in the Image Review Charter.

Rotator Cuff Tendon Thickness: An independent reviewer will assess MRIs for the rotator cuff tendon thickness at 12 and 24 months. All MRI assessments are detailed in the Image Review Charter.

Goutallier Classification: The Goutallier classification will be used to classify the fatty infiltration of the rotator cuff. The Goutallier classification ranges from a grade of 0 indicating a completely normal muscles without any fatty streaks to a grade of 4 which indicates that more fat than muscle is present.[23] An independent reviewer will assess MRIs for the fatty infiltration of the rotator cuff at 12 and 24 months post-surgery. All MRI assessments are detailed in the Image Review Charter.

Sugaya Score: The Sugaya score will be used to measure the rotator cuff integrity. The Sugaya score ranges from Type I to Type V. Type I indicates a repaired cuff that had sufficient thickness with homogeneously low intensity on the MRI image while Type V indicates the presence of a major discontinuity on the MRI images suggesting a medium or large tear.[24] An independent reviewer will use the MRI to assess rotator cuff integrity at 12 and 24 months post-surgery. All MRI assessments are detailed in the Image Review Charter.

Incidence of Revision Surgery: All revision surgeries involving the index shoulder for any cause within 24 months of the index surgery will be documented.

9.2.2 Economic Endpoints

Aggregate health care utilization costs: Related health care utilization costs over 12 months post-surgery will be calculated based on health care utilization as reported in the participant diary and/or in the participant's medical records.

Operating Time (Index surgery): Operating time for the index surgery, defined as the time from first incision to wound closure (measured in minutes) as recorded in the operative procedure notes, will be recorded.

Medication Use: Cumulative opioid and non-opioid prescription medication used to treat the index shoulder over 12 months following index surgery as reported in the participant diary and/or in the participant's medical record, will be recorded.

Number of Steroid Injections: The number of steroid injections administered to the index shoulder within 12 months of the index surgery as reported in the participant diary and/or in the participant's medical record, will be recorded.

Number of Unscheduled Clinic Visits: The number of unscheduled clinic visits (defined as a return visit to a health care provider for examination/evaluation of the index shoulder) within 12 months of the index surgery, as reported in the participant diary and/or in the participant's medical record, will be recorded.

Number of For-Cause Imaging Procedures: The number of for cause imaging procedures (e.g. MRI or ultrasound) performed on the index shoulder within 12 months of the index surgery, as reported in the participant diary and/or in the participant's medical record, will be recorded.

Number of Physiotherapy Sessions: The number of physiotherapy sessions within 12 months of the index surgery, as reported in the participant diary and/or in the participant's medical record, will be recorded.

10. STATISTICAL DESIGN

A Statistical Analysis Plan (SAP) will be written and finalized prior to database lock. The following is a brief description of the analyses to be described in this plan. If there are any changes from the analysis described below it will be detailed in the SAP and the Clinical Study Report (CSR). Any changes/additions to the analysis described in the SAP will also be detailed in the CSR.

10.1 GENERAL

The CRO's Biostatistician will conduct the statistical analyses for this study, with the exception of the economic analysis, which will be conducted by Smith & Nephew's Global Biostatistics group. For the primary outcome, the significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. Unless otherwise stated, point estimates (mean differences or odds ratios) and 95% confidence intervals will be reported descriptively for secondary outcome as an exploratory assessment. Select secondary outcomes will undergo statistical testing as outlined in section 10.4.2.

Where data summaries are specified, categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary statistics: number of observations, means and standard deviations, or median and interquartile ranges. All analyses will be performed using a statistical package such as SAS or SPSS.

10.2 ANALYSIS POPULATIONS

Due to the non-randomized nature of the study design, study participants will be analyzed as per the treatment they received. Any safety analyses will include participants who received the investigational product (IP).

10.3 BASELINE DATA

Patient demographics and baseline outcome variables will be summarized by treatment group using descriptive summary measures expressed as means with standard deviations or medians with interquartile ranges for continuous variables depending on the distribution and number (percent) for categorical and ordinal variables.

10.4 EFFICACY ANALYSIS

10.4.1 Analysis of Primary Endpoint

Multiple linear regression will be used to compare differences in the mean ASES scores between the REGENETEN cohort and the comparison cohort at 3 months post-treatment. The significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. The analysis will be adjusted for baseline ASES score and for differences in baseline characteristics between the two cohorts.

The minimal clinically important difference (MCID) will be used to determine the clinical importance of the mean difference between treatment groups for the ASES score and all other patient-reported outcomes (i.e. SANE, Constant-Murley score). The MCID defines the change in the outcome score that results in the smallest, appreciable clinical improvement[25]. The MCID for the ASES is 11.1 points for patients undergoing rotator cuff repair[1].The criteria for determining the clinical importance of the mean difference will be as follows:

- If the confidence interval of the mean difference is completely above the MCID, the difference is considered “significant”
- If the confidence interval of the mean difference contains the MCID, the difference is considered “possibly clinically significant”
- If the confidence interval of the mean difference is completely below the MCID, the difference is considered “not clinically significant”[25]

The assessment of clinical importance will be reported along with the confidence intervals for each outcome.

10.4.2 Analysis of Secondary Endpoints

Table 2 summarizes the secondary efficacy endpoint(s) and summary of planned analyses for select secondary outcomes. Unless otherwise stated, point estimates in the form of mean differences or odds ratios along with 95% confidence intervals will be reported descriptively for secondary outcomes.

An exploratory assessment using the MCID will be done for select secondary outcomes. The MCID will be used to explore the clinical importance of the mean difference between treatment groups for all patient-reported outcomes (i.e. ASES, SANE, and Constant-Murley score). The MCID used for outcomes related to the ASES score, SANE score and Constant-Murley score will be 11.1 points[1], 29.4 points[1], and 5.5 points[1], respectively. For outcomes involving the ASES-VAS pain score, the MCID used will be 1.37 cm[26].

Table 2: Analysis of Secondary Endpoints

Item	Objective	Outcome Measure	Statistical Test
Secondary Objective #1	To determine if there are early benefits (within 3 months of surgery) of arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN on participant-reported daily shoulder function/disability and pain compared to standard surgical repair techniques.	American Shoulder and Elbow Surgeons (ASES) Score weekly through 3 months post-index surgery.	Generalized linear regression adjusting for baseline ASES score and differences in baseline characteristics. The mean ASES scores will be compared using an MCID of 11.1 points.
Secondary Objective #2	To determine if there are early benefits (within 3 months of surgery) of arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN on participant-reported average shoulder function as a percentage of normal compared to standard surgical repair techniques.	Simple Assessment Numeric Evaluation (SANE) Score weekly through 3 months post-index surgery.	Generalized linear regression adjusting for baseline SANE score and differences in baseline characteristics. The mean SANE scores will be compared using an MCID of 29.4 points.
Secondary Objective #3	To determine if there are early benefits (within 3 months of surgery) of arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN on participant-reported shoulder pain compared to standard surgical repair techniques.	VAS pain score from the American Shoulder and Elbow Surgeons (ASES) Score weekly through 3 months post-index surgery.	Generalized linear regression adjusting for baseline VAS pain score and differences in baseline characteristics. The mean ASES-VAS pain score will be compared using an MCID of 1.37 cm.
Secondary Objective #4	To determine if arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN yields statistically improved participant-reported composite of daily shoulder function/disability and pain compared to standard surgical repair techniques over the	American Shoulder and Elbow Surgeons (ASES) Score at 6, 12, 18 and 24 months.	Generalized linear regression adjusting for baseline ASES score and differences in baseline characteristics. The mean ASES scores will be compared using an MCID of 11.1 points.

Item	Objective	Outcome Measure	Statistical Test
	24 months from the index shoulder surgery.		
Secondary Objective #5	To determine if arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN yields statistically improved participant-reported average shoulder function as a percentage of normal compared to standard surgical repair techniques over the 24 months from index shoulder surgery.	Simple Assessment Numeric Evaluation (SANE) Score at 6, 12, 18 and 24 months.	Generalized linear regression adjusting for baseline SANE score and differences in baseline characteristics. The mean SANE scores will be compared using an MCID of 29.4 points.
Secondary Objective #6	To determine if arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN statistically decreases participant-reported shoulder pain compared to standard surgical repair techniques over the 24 months from the index shoulder surgery.	VAS Pain score from the American Shoulder and Elbow Surgeons (ASES) Score at 6, 12, 18 and 24 months.	Generalized linear regression adjusting for baseline VAS pain score and differences in baseline characteristics. The mean ASES-VAS pain score will be compared using an MCID of 1.37 cm.
Secondary Objective #7	To determine if arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN statistically improved participant-reported and examiner-assessed shoulder pain and function compared to standard surgical repair techniques over 24 months from the index shoulder surgery.	Constant-Murley Score at 3, 6, 12 and 24 months.	Generalized linear regression adjusting for baseline Constant-Murley score and differences in baseline characteristics. The mean Constant-Murley score will be compared using an MCID of 5.5 points.
Secondary Objective #8	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN use significantly less opioids to treat the index shoulder compared to standard surgical repair over the	Dose/duration of opioid use from post-surgery to 3-months post-surgery. Defined daily dose (DDD) will be used as the outcome measure.	Generalized linear regression adjusting for baseline opioid use and differences in baseline characteristics.

Item	Objective	Outcome Measure	Statistical Test
	initial 3 months following index surgery.		
Secondary Objective #9	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN use significantly less non-opioid prescription medication to treat the index shoulder compared to standard surgical repair over the initial 3 months following index surgery.	Dose/duration of non-opioid prescription pain medication use from post-surgery to 3-months post-surgery. DDD will be used as the outcome measure.	Generalized linear regression adjusting for baseline non-opioid prescription pain medication use and differences in baseline characteristics.
Secondary Objective #10	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN use significantly less opioids to treat the index shoulder compared to standard surgical repair over the 12 months from the index shoulder surgery.	Dose/duration of opioid use from post-surgery to 12-months post-surgery. DDD will be used as the outcome measure.	Generalized linear regression adjusting for baseline opioid use and differences in baseline characteristics.
Secondary Objective #11	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN use significantly less non-opioid prescription medication to treat the index shoulder compared to standard surgical repair over the 12 months from the index shoulder surgery.	Dose/duration of non-opioid prescription pain medication use from post-surgery to 12-months post-surgery. DDD will be used as the outcome measure.	Generalized linear regression adjusting for baseline non-opioid prescription pain medication use and differences in baseline characteristics.
Secondary Objective #12	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have a shorter shoulder immobilization	Number of days in a sling	N/A

Item	Objective	Outcome Measure	Statistical Test
	time compared to participants who had standard surgical repair.		
Secondary Objective #13	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN return to work earlier than participants who had standard surgical repair.	Number of days to return to work estimated from date of surgery. Type of occupation is independent factor.	Generalized linear regression, adjusting for type of occupation and for differences in baseline characteristics.
Secondary Objective #14	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN return to driving earlier than participants who had standard surgical repair.	Number days to return to driving.	N/A
Secondary Objective #15	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN return to sports earlier than participants who had standard surgical repair.	Number days to return to sports.	Generalized linear regression, adjusting for baseline level of sporting activity and differences in baseline characteristics.
Secondary Objective #16	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have a lower incidence of progression to full-thickness tears (diagnosed by MRI) compared to participants who had standard surgical repair at 12 months from the index shoulder surgery.	Incidence of full-thickness tears (diagnosed by MRI) within 12m from the index surgery.	N/A
Secondary Objective #17	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have a lower incidence of progression of full-	Incidence of full-thickness tears (diagnosed by MRI) within 24m from the index surgery.	N/A

Item	Objective	Outcome Measure	Statistical Test
	thickness tears (diagnosed by MRI) compared to participants who had standard surgical repair at 24 months from the index shoulder surgery.		
Secondary Objective #18	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have increased percent filling of the rotator cuff (based on MRI assessment) compared to participants who had standard surgical repair at 12 months from the index shoulder surgery.	Percent filling (based on MRI assessment) at 12-months post-surgery	N/A
Secondary Objective #19	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have increased percent filling of the rotator cuff (based on MRI assessment) compared to participants who had standard surgical repair at 24 months from the index shoulder surgery.	Percent filling (based on MRI assessment) at 24-months post-surgery.	N/A
Secondary Objective #20	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have improvements in rotator cuff tendon thickness (based on MRI assessment) compared to participants who had standard surgical repair at 12 months from the index shoulder surgery.	Rotator cuff tendon thickness (based on MRI assessment) at 12-months post-surgery.	Generalized linear regression adjusting for baseline tendon thickness and differences in baseline characteristics
Secondary Objective #21	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%)	Rotator cuff tendon thickness (based on MRI	Generalized linear regression

Item	Objective	Outcome Measure	Statistical Test
	partial-thickness rotator cuff tears using REGENETEN have improvements in rotator cuff tendon thickness (based on MRI assessment) compared to participants who had standard surgical repair at 24 months from the index shoulder surgery.	assessment) at 24-months post-surgery.	adjusting for baseline tendon thickness and differences in baseline characteristics.
Secondary Objective #22	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have a statistically lower fatty infiltration of the rotator cuff (based on MRI assessment) compared to participants who had standard surgical repair at 12 months from the index surgery.	Goutallier classification of rotator cuff (based on MRI assessment) at 12-months post-surgery.	N/A
Secondary Objective #23	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have a statistically lower fatty infiltration of the rotator cuff (based on MRI assessment) compared to participants who had standard surgical repair at 24 months from the index surgery.	Goutallier classification of rotator cuff (based on MRI assessment) at 24-months post-surgery.	N/A
Secondary Objective #24	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have statistically improved rotator cuff integrity (based on MRI assessment) compared to participants who had standard surgical repair techniques at 12 months from the index surgery.	Sugaya score (based on MRI assessment) at 12-months post-surgery.	N/A

Item	Objective	Outcome Measure	Statistical Test
Secondary Objective #25	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have statistically improved rotator cuff integrity (based on MRI assessment) compared to participants who had standard surgical repair techniques at 24 months from the index surgery.	Sugaya score (based on MRI assessment) at 24-months post-surgery.	N/A
Secondary Objective #26	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have a lower incidence of revision surgeries (index shoulder; all causes) compared to participants who had standard surgical repair over the 24 months from the index shoulder surgery.	Incidence of revision surgery (index shoulder; all cause) within 24m of the index surgery.	Logistic regression analysis adjusting for differences in baseline characteristics.
Secondary Economic Objectives/Outcomes			
Item	**Objective**	**Outcome Measure**	**Statistical Test**
Secondary Objective #27	To determine if arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN results in lower aggregate heath care costs over 12 months post-index surgery than standard surgical repair.	Costs based on healthcare resource utilization as listed below.	N/A
Secondary Objective #28	To determine if arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN requires less operating room time than standard surgical repair.	Operating room time as measured from time of first incision to wound closure measured in minutes.	Generalized linear regression, adjusting for differences in baseline characteristics.

Item	Objective	Outcome Measure	Statistical Test
Secondary Objective #29	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN receive fewer shoulder steroid injections compared to standard surgical repair over the 12 months from the index shoulder surgery.	Number of steroid injections in the shoulder from post-surgery to 12-months post-surgery.	N/A
Secondary Objective #30	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have fewer index shoulder-related unscheduled clinic visits compared to standard surgical repair over the 12 months from the index shoulder surgery.	Number of index shoulder-related unscheduled clinic visits within 12 months of index surgery.	N/A
Secondary Objective #31	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have fewer for-cause imaging procedures compared to standard surgical repair over the 12 months from the index shoulder surgery.	Number of for cause imaging procedures (e.g. MRI, ultrasound) within 12 months of index surgery.	N/A
Secondary Objective #32	To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN undergo less physiotherapy compared to standard surgical repair over the 12 months from the index shoulder surgery.	Number of physiotherapy sessions within the 12 months of the index surgery	N/A

10.4.3 Analysis of Other Endpoint(s)

Not applicable.

10.5 SAFETY ANALYSES

Frequency of the treatment-emergent AEs will be calculated for: each body system, by preferred terminology, and overall; by treatment cohort, for the number of participants and percentage of participants reporting the event. The seriousness, severity of the adverse events and the relationship to the investigational product will be summarized for: each body system, preferred terminology, and overall; by treatment group. Serious adverse events (SAE) (including deaths) will be listed for individual events.

The Sponsor will prepare narratives for all deaths, non-fatal serious adverse events, and participants withdrawn due to adverse events

The number and percentage of participants reporting treatment-emergent adverse events split by treatment separately by system organ class, and preferred term will be summarized by:

1. Their relationship with the investigational device (not related or related). If the relationship is missing, the adverse event will be assumed to be treatment-related and a footnote will be added to the table. If a participant experiences more than one preferred term within a system organ class, then the relationship at the system organ class level for that subject will be reported according to their most related relationship for each preferred term.
2. The severity of the adverse event (mild, moderate or severe).
3. Whether or not the adverse event is serious
4. The adverse event outcome.
5. Whether or not the adverse event is expected or unexpected.

10.6 INTERIM ANALYSES

A data extract will be completed when the last enrolled participant has completed their three-month follow-up visit. A report will not accompany this data extract but the findings may be presented as possible podium or conference activity.

An interim analysis will be conducted when the last enrolled participant has completed their one-year follow-up from index surgery. This analysis will include a simplified statistical report and a possible peer-reviewed publication. Further details will be provided in the SAP.

11. SAMPLE SIZE JUSTIFICATION

The sample size calculation was conducted for 80% power and an alpha of 0.05. The minimal clinically important difference (MCID) used as the difference to detect for was 11.1 points on the American Shoulder and Elbow Surgeons (ASES) score at 3 months following index surgery.[1] An effect size of 0.56 was used to ensure that the difference in results represented a moderate difference in effect, as defined by Cohen's d.[27] The sample size calculations were completed in R statistical software (v3.5.0). Based on the calculation conducted, a sample size of 102 (51 per arm) was determined. To account for a dropout rate of 15%, the sample size was increased to 118 (59 per arm).

12. ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 DEFINITIONS

The categories of adverse events are shown in Table 3. The definitions for each of these categories are given in the subsequent sections.

Table 3: Categories of Adverse Event

	NOT DEVICE-RELATED	DEVICE- OR PROCEDURE-RELATED
NON-SERIOUS	ADVERSE EVENT (AE)	ADVERSE DEVICE EFFECT (ADE)
SERIOUS	SERIOUS ADVERSE EVENT	SERIOUS ADVERSE DEVICE EFFECT (SADE) (SEE 12.1.3)

	(SAE)	ANTICIPATED	UNANTICIPATED
		ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (ASADE)	UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

12.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease of untoward clinical sign (including abnormal laboratory findings) in participants, users or other persons, whether or not causally related to the IP/Ancillary Product.

Note 1: This definition includes events related to the IP, comparator or ancillary products.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the IP.

AE is used both to refer to AE which do not meet the definitions of Adverse Device Effects or Serious Adverse Events and as an umbrella term referring to adverse events of all classifications. An AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease. For reporting purposes, emphasis is placed first and foremost on whether or not the event constitutes an untoward medical occurrence.

12.1.2 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event that, in the opinion of the investigator, is related to the use of the IP.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Not Related - An AE is considered to be not related to the use of an IP or the procedure when the effect is DEFINITELY UNRELATED or UNLIKELY to have any relationship to the use of the IP or the procedure;

Related – An AE is considered to be related to the use of an IP or the procedure when there is a POSSIBLE, PROBABLE, or DEFINITE relationship between the AE and the use of the IP or the procedure.

An ADE is further categorized depending on whether the criteria in section 12.1.3 and 12.1.4 are met.

12.1.3 Serious Adverse Events and Serious Adverse Device Effects

An AE or ADE is considered a **Serious** Adverse Event (SAE) or **Serious** Adverse Device Effects (SADE) if, in the view of either the Investigator or the Sponsor, it:

- a) led to death,
- b) led to serious deterioration in the health of the participant, that either resulted in
  - 1) a life-threatening illness or injury, or
  - 2) a permanent impairment of a body structure or a body function, or
  - 3) in-patient or prolonged hospitalization, or
  - 4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
- c) led to fetal distress, fetal death or a congenital abnormality or birth defect

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious such as important medical events that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

12.1.4 Anticipated/Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is a serious ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report. There are no ASADE in this study.

12.1.5 Severity

The severity of every AE will be assessed by the PI or medically qualified site staff to whom the responsibility has been delegated and documented on the delegation of authority log. AE should be classified as mild, moderate, or severe, regardless of whether or not the AE are considered to be serious or non-serious. The classification should be based on the following definitions:

Mild - An event is mild if the participant is aware of, but can easily tolerate the sign or symptom;

Moderate - An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the participant's usual activities;

Severe - An event is severe if the sign or symptom is incapacitating and results in the participant's inability to work or engage in their usual activities.

12.1.6 Device Deficiency

A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. DD includes malfunctions, use errors and inadequate labeling.

12.2 AE Coding Dictionary

Adverse events will be coded by the Sponsor for preferred terminologies, and grouped by system organ class, using Medical Dictionary for Regulatory Activities (MedDRA).

12.3 Reporting Procedures

AE of any kind and DD will be recorded in the applicable CRF and source notes. The Investigator will evaluate all AE for relationship to the device and procedure, if applicable, seriousness, and severity. The following timescales should be followed for the AE/DD information to be submitted/entered into the CRF and reported to the Sponsor via the REDCap Cloud EDC system (see Figures 3 and 4):

- ADE and DD – without unreasonable delay
- SAE, SADE and DD with potential to cause SADE – immediately (i.e. within 24 hours of the Investigator being informed about the event)

For ADE and DD, details of the product/procedure related to the event will be included and where applicable, pictures taken of the device. The deficient product should be retained for return to unless it is contaminated (e.g., used dressings must not be retained). Updates to submitted information will be recorded in the CRF according to the timescales above.

All adverse events will be reviewed by a medically qualified person appointed by the Sponsor to determine which, if any, meet criteria for expedited reporting to the regulatory authorities.

The investigator will inform the IRB of adverse events according to the IRB requirements.

Depending on the nature of the adverse event, S&N may request copies of the participant's medical records, imaging, operative notes, as well as results of any relevant laboratory tests performed or other documentation related to the AE. If the participant was hospitalized, a copy of the discharge summary may be requested by S&N and should be forwarded as soon as it becomes available. In certain cases, S&N also may request a letter from the Investigator that summarizes the events related to the case.

Figure 3: Evaluation and Reporting of AE

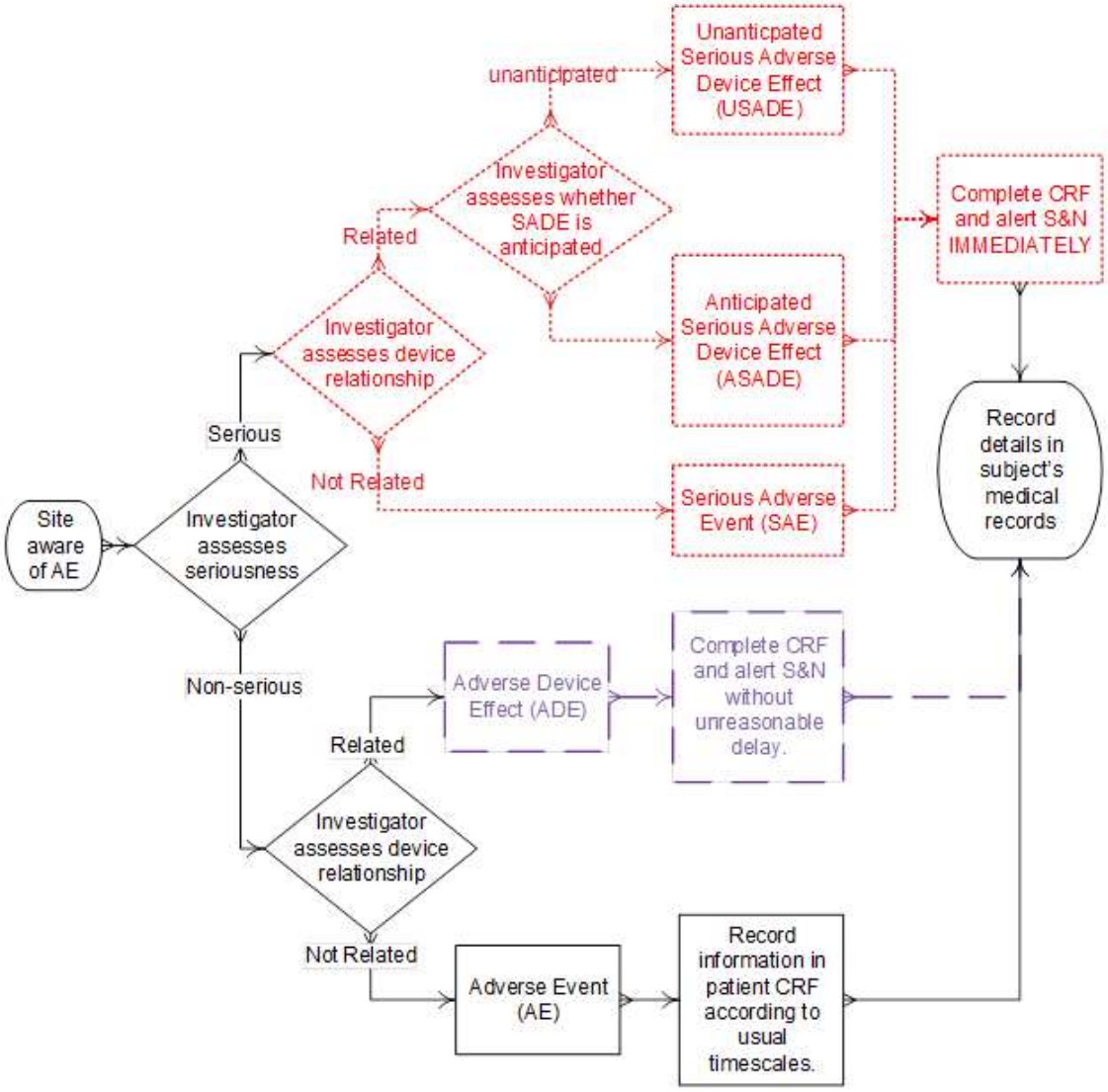
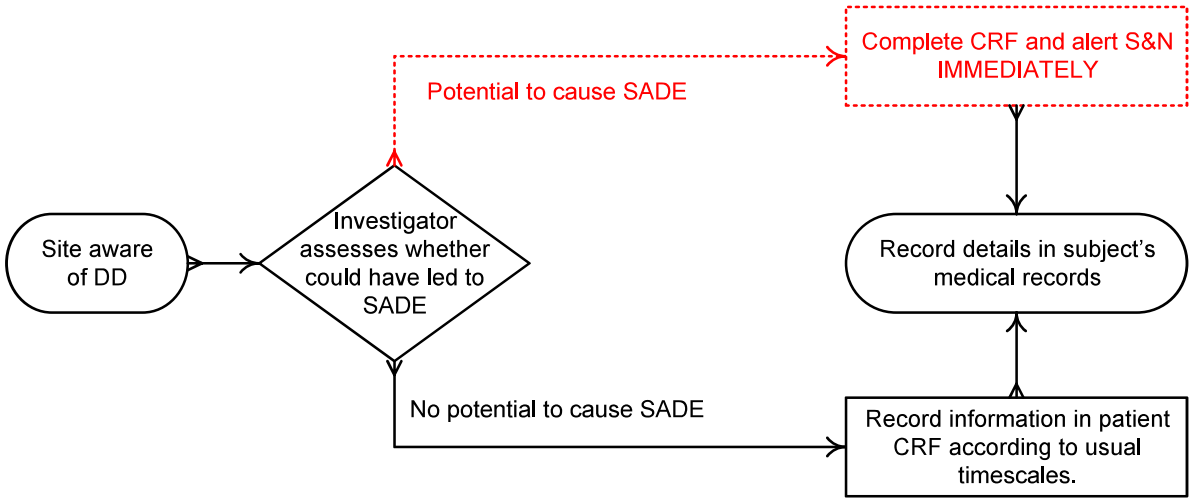


Figure 4: Evaluation and Reporting of DD



12.4 FOLLOW-UP OF PARTICIPANTS WITH ADVERSE EVENTS

For participants who are experiencing ongoing unresolved AE at the time of their study completion or early discontinuation from the study, it is recommended that the Investigator schedule an appropriate follow-up visit to determine the outcome of the event.

Any additional data must be documented and available to the Sponsor who will determine whether the data need to be documented within the CRF/Clinical Study Report.

12.4.1 Ongoing Adverse Events at Study Discontinuation

Adverse events which are **related** to a study procedure or REGENETEN Implant system and are ongoing at end of participant's participation: The event should be followed until it is either resolved or until the event has become chronic and is not expected to further improve based on Investigator's review of the event.

Adverse events which are **not related** to a study procedure or REGENETEN Implant system and are ongoing at end of participant's participation should be followed for 30 days after discontinuation or if the AE is resolved, whichever is sooner.

At the time of data analysis (e.g. interim or final), an evaluation of ongoing events should take place and be listed as ongoing in the safety table.

13. INVESTIGATOR OBLIGATIONS

The Principal Investigator (PI) will comply with the commitments outlined in the Clinical Trial Agreement (CTA) and with Good Clinical Practice (GCP), as outlined in Appendix 21.2 of this protocol.

14. SPONSOR AND MONITOR RESPONSIBILITIES

The CRO will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that: the rights and wellbeing of the participants are protected; the reported data are accurate, complete, and verifiable from the source documents; and the study is conducted in compliance with the currently approved protocol and amendment(s), if applicable, and with GCP.

14.1 CONTRACT RESEARCH ORGANIZATION

The Sponsor has engaged a Contract Research Organization (CRO) to assist in conducting this study. When appropriate, the CRO is referred in study documents as “Sponsor’s agent”.

15. PROTOCOL AMENDMENTS

Amendments should be made only in exceptional cases once the study has started. Protocol amendments must be approved by the protocol signatories prior to submission to the IRB. Protocol amendments need to be approved by the IRB prior to implementation at the site.

16. CONFIDENTIALITY OF THE STUDY

The confidentiality of this study and associated documents is governed by the terms of the Clinical Trial Agreement (CTA).

17. STATEMENTS OF COMPLIANCE

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki; ISO 14155: Clinical investigation of medical devices – Good Clinical Practice; ICH-E6.

This clinical study will not commence until the required approval/favorable opinion from the IRB has been obtained. Any additional requirements imposed by the IRB will be followed.

Public/Products Liability Insurance has been purchased by Smith & Nephew plc. Worldwide and incorporates coverage for personal injury in respect of clinical studies.

18. END OF STUDY

The end of the study is defined as the date of the last patient, last visit. No additional care for participants will be provided under the protocol once their participation in the study has ended.

Should circumstances arise which require the termination of the entire study prior to its planned completion (e.g. safety concerns) or circumstances arise which mean the end of the participation of an individual site (e.g. departure of Investigator, non-compliance), then this will be undertaken according to the Standard Operating Procedures (SOPs) of the Sponsor and/or the CRO.

19. PUBLICATION POLICY

19.1 PUBLICATION OF STUDY DATA

The preparation and submission for publication of manuscripts containing the study results shall be in accordance with a process determined by the CTAs between the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to the Health Insurance Portability and Accountability Act of 1996.

19.2 DATA SHARING

Smith & Nephew is committed to upholding the highest ethical and legal standards involved in conducting clinical trials. Smith & Nephew therefore supports the data sharing requirements of The International Committee of Medical Journal Editors (ICMJE) published on the 6th June 2017.[28] In accordance, Smith & Nephew will consider requests to share individual (deidentified) participant data that underlie the results of any interventional clinical trial, as presented from the 1st July 2018 within an ICMJE associated journal. Requests made by researchers who provide a methodologically sound proposal will be considered. Requests may include data that underlie

results presented in text, tables, figures and appendices, together with data dictionaries. Availability of these data will begin 9 months and end 36 months after article publication. Data supplied may only be used by the researcher(s) named in the approved research proposal for the purposes of achieving the aims of the analyses specified therein. All proposals should be directed to datasharing.gcs@smith-nephew.com. To gain access, data requestors will need to sign a data access agreement.

20. REFERENCES

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21. APPENDICES

21.1 PROTOCOL AMENDMENT

21.1.1 Amendment Overview

21.1.1.1 *General Purpose*

21.1.1.1.1 *Protocol Version 2.0*

An additional participant-facing questionnaire has been added to assess shoulder stiffness among study participants during the first 12 months of the study. The protocol amendment incorporates the assessment of shoulder stiffness objectives and endpoints as appropriate.

21.1.1.1.2 *Protocol Version 3.0*

The Constant-Murley score has been added to assess participant-reported and examiner assessed shoulder pain and function among study participants over 24 months following index surgery in the amended protocol (V3.0). The protocol amendment incorporates the use of the Constant-Murley score and the associated objectives and endpoints as appropriate.

The questionnaire used to assess shoulder stiffness among study participants during the first 12 months of the study has been removed in the amended protocol (V3.0). The associated shoulder stiffness objectives and endpoints have also been removed.

Study objectives related to opioid medication use and non-opioid pain medication use over the initial 3 months of the study have been added. Protocol V3.0 also includes the addition of a variety of MRI-assessed objectives examining the percent filling, tendon thickness, Goutallier classification (to classify fatty infiltration) and Sugaya score (to classify rotator cuff integrity). The new objectives and their associated endpoints have been incorporated into the protocol as appropriate.

In addition, V3.0 of the protocol, includes clarity and additional information regarding the steroid exclusion, window for weekly and monthly participant diary completion, clarification on the standard surgical repair procedure, the inclusion of the interim analysis and revisions to the type of analysis that will be conducted for some objectives. The abbreviated physiotherapy guidelines have been removed from the protocol and a reference was added to the separate cohort-specific guidelines.

21.1.1.2 *Rationale*

21.1.1.2.1 *Protocol Version 2.0*

The addition of new secondary study outcome aimed at assessing shoulder stiffness among study participants was added to determine whether the study product provides early benefits related to shoulder stiffness.

21.1.1.2.2 *Protocol Version 3.0*

The addition of a new secondary objective (Constant-Murley score) in V3.0 of the study protocol aimed at assessing participant-reported and examiner-assessed shoulder pain and function was added to determine whether the study products leads to improvements in shoulder pain and function both subjectively and objectively.

The assessment of shoulder stiffness and its associated study objectives and endpoints were removed in V3.0 after the determination that it was no longer required following the addition of the Constant-Murley score.

Additional study objectives related to opioid medication use and non-opioid pain medication use were added to determine whether there are early benefits to the use of the study product in the mentioned areas. The MRI-assessed objectives were added to determine if there were physiological benefits to the use of the study product in participants.

Some additional clarification was added in V3.0 of the protocol regarding the type of steroid use that is excluded from the study, the definition of standard surgical repair and participant diary completion windows. This will provide study sites with more clarity related to study-related processes.

Protocol V3.0 includes a description of the interim analysis that will be completed when the final participant has completed their 1-year follow-up. In addition, statistical analysis for various study objectives have been revised in order to better analyze the study data. The abbreviated physiotherapy guidelines were deleted from the study protocol due to the creation of detailed cohort-specific guidelines.

21.1.1.3 *Effect on Study Status*

21.1.1.3.1 *Protocol Version 2.0*

At the time of amendment, there is one participant enrolled in the study. This participant will not complete a baseline assessment of shoulder stiffness. The participant will begin completing the assessment of shoulder stiffness question once approval is received for this amendment. The impact on data collection is minimal.

21.1.1.3.2 *Protocol Version 3.0*

At the time of amendment to protocol V3.0, there are 27 participants treated in the study. These participants will not complete the Constant-Murley Assessment at completed study visits. These participants will begin completing the Constant-Murley Assessment once IRB approval is received for this amendment and the site has received training. The impact on data collection is not substantial.

Removal of the shoulder stiffness questionnaire will have minimal impact on the study. Once IRB approval is received for this amendment and the site has received training, participants will no longer be required to complete the assessment of shoulder stiffness questionnaire.

Additional study objectives related to opioid medication use and non-opioid pain medication use will not impact participants in the study. The data required for the additional objectives was already being collected from study participants in previously approved case report forms.

The new objectives based on the assessments of participant MRIs will not impact study participants. Study participants are already required to obtain a 12- and 24-month MRI as per the previous protocol. These MRIs will be assessed by an independent assessor to obtain data for these objectives.

21.1.2 Amendment Summary

21.1.2.1 *Revision History*

21.1.2.1.1 *Protocol Version 2.0*

Version Date: 12-Dec-2018

Version Number: 2.0

21.1.2.1.2 *Protocol Version 3.0*

Version Date: 10-Sep-2019

Version Number: 3.0

21.1.2.2 *Summary of Revisions*

21.1.2.2.1 *Protocol Version 2.0*

The protocol changes encompass the inclusion of the assessment of shoulder stiffness which will be completed by participants weekly until 12 weeks post-surgery and then at the 6- and 12-month follow-up. The objectives associated with the assessment of shoulder stiffness have been added to the protocol in additional to the statistical analysis of this objective.

Section	Current Text DD-MMM-YYYY Version # 28-Sep-2018, V 1.0	Revised Text DD-MMM-YYYY Version # 12-Dec-2018, V 2.0
2.0	N/A	Added “Assessment of shoulder stiffness over 12 months following index surgery” to Secondary Endpoints “Assessment of Shoulder Stiffness” added to study schematic
3.0	N/A	Table of Contents updated to reflect new sections/page numbers
5.2	N/A	Added “Early benefits related to participant-reported shoulder stiffness (over 12 months following index surgery)” as a secondary objective
8.3.2	N/A	Added “Assessment of shoulder stiffness over 12 months following index surgery” as a secondary endpoint
9.1.1	N/A	Added “Assessment of Shoulder Stiffness” to Table 1 (Study procedures)
9.1.2	5. Complete the ASES questionnaires and SANE questionnaires.	5. Complete the ASES questionnaire, SANE questionnaire, and assessment of shoulder stiffness.
9.1.3	6. Instruct the participant on follow-up procedures, including completing the weekly ASES and SANE questionnaires, completing the weekly diary and returning for clinical follow-up at 3 months.	6. Instruct the participant on follow-up procedures, including completing the weekly ASES and SANE questionnaires, weekly assessment of shoulder stiffness, completing the weekly diary, and returning for clinical follow-up at 3 months.
9.1.4	1. Participant will complete the ASES questionnaires and SANE questionnaires.	1. Participant will complete the ASES questionnaire, SANE questionnaire, and assessment of shoulder stiffness.

Section	Current Text DD-MMM-YYYY Version # 28-Sep-2018, V 1.0	Revised Text DD-MMM-YYYY Version # 12-Dec-2018, V 2.0
9.1.5	1. Complete the ASES questionnaires and SANE questionnaires.	1. Complete the ASES questionnaire (all visits), SANE questionnaire (all visits), and assessment of shoulder stiffness (3, 6 and 12 month visits only).
9.2.1	N/A	Added “Participant-reported Shoulder Stiffness: Stiffness in the participant’s index shoulder will be assessed using the shoulder stiffness VAS. The VAS stiffness rating will be recorded pre-operatively, weekly from 1 week to 3 months post-surgery, and at 6 and 12 months post-surgery.” to list of Performance Endpoints
10.4.2	N/A	Added Secondary Objective #7: “To determine if there are benefits (within 12 months of surgery) of arthroscopic treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN on participant-reported shoulder stiffness compared to standard surgical repaired techniques.” to Table 2 (Analysis of Secondary Endpoints) Added Outcome Measure associated with secondary objective #7: “Assessment of shoulder stiffness over 12 months post-index surgery.” to Table 2 Added Statistical Test associated with secondary objective #7: “Generalized linear regression adjusting for baseline VAS stiffness rating and differences in

Section	Current Text DD-MMM-YYYY Version # 28-Sep-2018, V 1.0	Revised Text DD-MMM-YYYY Version # 12-Dec-2018, V 2.0
		baseline characteristics." to Table 2 Revised numbering of objectives in table 2 as required

21.1.2.2.2 *Protocol Version 3.0*

Section	Current Text DD-MMM-YYYY Version # 12-Dec-2018, V 2.0	Revised Text DD-MMM-YYYY Version # 10-Sep-2019, V 3.0
All	N/A	Term "Bioinductive" removed throughout protocol.
2.0 – Statistical Rationale	"Superiority hypothesis for American Shoulder and Elbow Surgeons (ASES) score at 3 months following index surgery using a minimal clinically important difference (MCID) of 12[1] and a drop-out rate of 15%."	"Superiority hypothesis for American Shoulder and Elbow Surgeons (ASES) score at 3 months following index surgery using a minimal clinically important difference (MCID) of 11.1[1] and a drop-out rate of 15%."
2.0 – Exclusion Criteria	"On steroids within 1 month of enrollment"	"Systemic steroid use (oral, IV) or locally injected at the surgical site within 1 month of enrollment"
2.0 – Secondary Endpoints	N/A	Added: • "Constant-Murley score at 3, 6, 12 and 24 months following index surgery" • "Cumulative opioid use to treat the index shoulder over 3 months following index surgery" • "Cumulative non-opioid prescription medication use to

Section	Current Text DD-MMM-YYYY Version # 12-Dec-2018, V 2.0	Revised Text DD-MMM-YYYY Version # 10-Sep-2019, V 3.0
		treat the index shoulder over 3 months following index surgery" • "MRI assessment of percent filling at 12 months following index surgery" • "MRI assessment of percent filling at 24 months following index surgery" • "Rotator cuff tendon thickness at 12 months following index surgery" • "Rotator cuff tendon thickness at 24 months following index surgery" • "Goutallier classification of rotator cuff at 12 months following index surgery" • "Goutallier classification of rotator cuff at 24 months following index surgery" • "Sugaya score of rotator cuff at 12 months following index surgery" • "Sugaya score of rotator cuff at 24 months following index surgery" Removed: • "Assessment of shoulder stiffness over 12 months following index surgery"
2.0 – Secondary Endpoints	"- Time to return to activities of daily living (ADLs) ○ Return to work by work type (sedentary; laborer) ○ Return to driving ○ Return to sports"	"- Time to return to work by work type (sedentary; laborer) - Time to return to driving - Time to return to sports"

Section	Current Text DD-MMM-YYYY Version # 12-Dec-2018, V 2.0	Revised Text DD-MMM-YYYY Version # 10-Sep-2019, V 3.0
2.0 – Study Schematic	N/A	"Constant-Murley Score" added to study schematic. "Assessment of Shoulder Stiffness" removed from study schematic. Clarification added to windows for participant diary completion: "Participant diary will be updated weekly (7±3 days) through 3 month follow-up and monthly (30±7 days) thereafter until 12 months post-surgery." Collection of pre-op MRI added to study schematic. Additional information regarding study MRIs added: "The pre-op MRI is the participant's standard of care MRI and will not follow the study MRI Image Acquisition Protocol which is used for the 12 and 24 month MRIs. The pre-op MRI must occur within 6 months of enrollment into this study. All MRIs will be submitted to the imaging vendor per the Image Transfer Protocol."
3.0	N/A	Table of Contents updated to reflect new sections/page numbers
List of Abbreviations	N/A	Added "DDD – Defined Daily Dose"
4.1	"Patients with rotator cuff disease usually report pain and weakness in the arm, leading to impaired function and mobility, and are typically recommended conservative	"Patients with atraumatic rotator cuff disease usually report pain and weakness in the arm, leading to impaired function and mobility, and are typically recommended conservative treatments to manage

Section	Current Text DD-MMM-YYYY Version # 12-Dec-2018, V 2.0	Revised Text DD-MMM-YYYY Version # 10-Sep-2019, V 3.0
	treatments to manage symptoms in the first instance. However, such conservative treatments are often ineffective; surgical treatment may therefore be subsequently advised to remove damaged tissue or repair the damage to the rotator cuff. However, further damage and progression may be seen even after conventional surgical treatments; re-tear rates within ~4 years are reported to be as high as 79% for larger injuries." "The REGENETEN™ Bioinductive Implant is a bioabsorbable device that provides a layer of collagen over injured tendons. The induction of this layer of new tendinous tissue may reduce micro-strains within the tendon, resulting in an optimized mechanical environment for tendon healing. Use of REGENETEN in the treatment of high-grade partial-thickness tears in lieu of converting the partial tear to a full-thickness tear and surgically reattaching the tendon to bone may accelerate patient recovery and shoulder mobility while reducing post-operative pain."	symptoms in the first instance. However, such conservative treatments may be ineffective; surgical treatment may therefore be subsequently advised to remove damaged tissue or repair the rotator cuff. Tear progression may continue after conventional surgical intervention with re-tear rates as 79% for massive tears." "The REGENETEN™ Implant is a collagen implant that provides a layer of collagen over injured tendons. The induction of this layer of new tendinous tissue may reduce micro-strains within the tendon, resulting in an optimized mechanical environment for tendon healing. Use of REGENETEN in the treatment of high-grade partial-thickness tears in lieu of completion of tear and repair, which may accelerate patient recovery and shoulder mobility while reducing post-operative pain."
5.2	N/A	Added Secondary Objectives: • "Improved participant-reported and examiner-assessed

Section	Current Text DD-MMM-YYYY Version # 12-Dec-2018, V 2.0	Revised Text DD-MMM-YYYY Version # 10-Sep-2019, V 3.0
		shoulder pain and function (over 24 months following index surgery)" • "Decreased opioid use to treat the index shoulder (over initial 3 months following index surgery)" • "Decreased non-opioid prescription medication use to treat the index shoulder (over initial 3 months following index surgery)" • "Increased percent filling of rotator cuff (at 12 months following index surgery)" • "Increased percent filling of rotator cuff (at 24 months following index surgery)" • "Improvements in rotator cuff tendon thickness (at 12 months following surgery)" • "Improvements in rotator cuff tendon thickness (at 24 months following surgery)" • "Lower fatty infiltration of the rotator cuff (at 12 months following surgery)" • "Lower fatty infiltration of the rotator cuff (at 24 months following surgery)" • "Improved rotator cuff integrity (at 12 months following surgery)" • "Improved rotator cuff integrity (at 24 months following surgery)" Removed secondary objective:

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		• "Benefits related to participant reported shoulder stiffness (over 12 months following index surgery)"
5.2	13. Earlier return to activities of daily living (ADLs) ○ Return to work by work type (sedentary; laborer) ○ Return to driving ○ Return to sports	Separated sub-objectives related to return to activities of daily living (return to work, driving, and sports) into separate objectives to align with numbering of objectives and endpoints through-out protocol. 13. Earlier return to work by work type (sedentary; laborer) 14. Earlier return to driving 15. Earlier return to sports
6.1	"The REGENETEN Bioinductive implant is a bioabsorbable implant device that provides a layer of collagen over injured tendons." "The REGENETEN Bioinductive Implant system (Figure 1) is comprised of disposable instruments, a bioabsorbable scaffold, and anchors to secure the scaffold to the underlying tendon and bone. "The Bioinductive Implant consists of a resorbable type I collagen matrix derived from bovine Achilles tendon. It is contraindicated for use in patients with a history of hypersensitivity to bovine-	"The REGENETEN Implant is a collagen implant that provides a layer of collagen over injured tendons." "The REGENETEN Implant system (Figure 1) is comprised of disposable instruments, a resorbable collagen implant, and anchors to secure the scaffold to the underlying tendon and bone." "The collagen implant consists of a resorbable type I collagen matrix derived from bovine Achilles tendon. It is contraindicated for use in patients with a history of hypersensitivity to bovine-derived materials. The device is designed

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	derived materials. The device is designed to completely resorb within six to 12 months." "The bone anchors are made from polyetheretherketone (PEEK), which is a common polymer used for bone anchors in orthopedic surgery. The bone anchors are intended for fixation of soft tissue grafts. The bone anchors are not bioabsorbable."	to completely resorb within six to 12 months." "The bone anchors are made from polyetheretherketone (PEEK), which is a common polymer used for bone anchors in orthopedic surgery. The bone anchors are intended for fixation of soft tissue grafts. The bone anchors are not resorbable."
7.3	"3. On steroids within 1 month of enrollment"	"3. Systemic steroid use (oral, IV) or locally injected at the surgical site within 1 month of enrollment"
8.2	N/A	Added clarification regarding standard surgical techniques: "Standard surgical repair techniques of the rotator cuff will be defined as either: 1. Debridement and a transtendinous repair, or 2. Complete takedown and repair."
8.3.2	N/A	Added secondary endpoints: • "Constant-Murley score at 3, 6, 12 and 24 months following index surgery" • "Cumulative opioid use to treat the index shoulder over 3 months following index surgery" • "Cumulative non-opioid prescription medication use to treat the index shoulder over 3 months following index surgery"

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		• "MRI assessment of percent filling at 12 months following index surgery" • "MRI assessment of percent filling at 24 months following index surgery" • "Rotator cuff tendon thickness at 12 months following index surgery" • "Rotator cuff tendon thickness at 24 months following index surgery" • "Goutallier classification of rotator cuff at 12 months following index surgery" • "Goutallier classification of rotator cuff at 24 months following index surgery" • "Sugaya score of rotator cuff at 12 months following index surgery" • "Sugaya score of rotator cuff at 24 months following index surgery" Removed secondary endpoint: • "Assessment of shoulder stiffness over 12 months following index surgery"
8.3.2	"13. Time to return to activities of daily living (ADLs) ○ Return to work by work type (sedentary; laborer) ○ Return to driving ○ Return to sports"	"13. Time to return to work by work type (sedentary; laborer) 14. Time to return to driving 15. Time to return to sports"

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9.1.1 – Table 1	N/A	Added “Constant-Murley Score” to Table 1 (Study procedures) Removed “Assessment of Shoulder Stiffness” from Table 1 (Study procedures) Collection of Pre-Op MRI added to Table 1. Clarification added to windows for Participant Diary completion: “Participant diary will be updated weekly (7±3 days) through 3 month follow-up and monthly (30±7 days) thereafter until 12 months post-surgery.” Additional information regarding study MRIs added: “The pre-op MRI is the participant’s standard of care MRI and will not follow the study MRI Image Acquisition Protocol which is used for the 12 and 24 month MRIs. The pre-op MRI must occur within 6 months of enrollment into this study. All MRIs will be submitted to the imaging vendor per the Image Transfer Protocol.”
9.1.2	5. Complete the ASES questionnaire, SANE questionnaire, and assessment of shoulder stiffness.	5. Complete the ASES questionnaire, SANE questionnaire, and Constant-Murley assessment.
9.1.2	N/A	6. Obtain copy of standard of care MRI of index shoulder, if available. Pre-Op MRI must have occurred

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		within 6 months of enrollment into this study. Revised numbering as required
9.1.3	6. Instruct the participant on follow-up procedures, including completing the weekly ASES and SANE questionnaires, weekly assessment of shoulder stiffness, completing the weekly diary, and returning for clinical follow-up at 3 months.	6. Instruct the participant on follow-up procedures, including completing the weekly ASES and SANE questionnaires, completing the weekly diary, and returning for clinical follow-up at 3 months.
9.1.4	1. Participant will complete the ASES questionnaire, SANE questionnaire, and assessment of shoulder stiffness.	1. Participant will complete the ASES questionnaire and SANE questionnaire.
9.1.5	1. Complete the ASES questionnaire (all visits), SANE questionnaire (all visits), and assessment of shoulder stiffness (3, 6 and 12 month visits only).	Complete the ASES questionnaire (all visits), SANE questionnaire (all visits), and Constant-Murley assessment (3, 6, 12 and 24 month visits only).
9.1.6	"Participants in each cohort (i.e. REGENETEN and standard surgical repair) will be provided with cohort-specific Physiotherapy Guidelines. Participants will be required to adhere strictly to the Physiotherapy Guidelines. Study personnel will remind participants of the importance of compliance, and the completion of physiotherapy sessions will be documented in the participant diary. Participants in the standard surgical repair cohort will follow	"Participants in each cohort (i.e. REGENETEN and standard surgical repair) will be provided with cohort-specific Physiotherapy Guidelines. Participants will be required to adhere strictly to the Physiotherapy Guidelines. Study personnel will remind participants of the importance of compliance, and the completion of physiotherapy sessions will be documented in the participant diary. Refer to the cohort-specific Physiotherapy Guidelines for details."

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	standard of care physiotherapy guidelines as recommended by the surgeon to include the following: • shoulder immobilization up to 6 weeks; may be removed for therapy • passive range of motion (PROM) within the first 1-6 weeks • active assisted range of motion (AAROM) beginning at 4 weeks or later • transition to active range of motion (AROM) beginning at 8 weeks or later • resistance/strengthening beginning at 12 weeks or later • return to sport at 12 weeks post-surgery and beyond Participants in the REGENETEN treatment cohort will follow physiotherapy guidelines that consist of the following: • shoulder immobilization for first 24-48 hours; may be removed for exercise • 4-5 exercise sessions (pendulum, passive forward elevation, supine external rotation and shoulder shrugs) per day for first 5-7 days prior to physical therapy • frequent application of ice; 20 minutes at a time, 4-5 times per day for 6 weeks post-surgery	

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	• start using index arm for activities of daily living between 1-6 weeks post-surgery • PROM, AAROM, and AROM activities within 1-6 weeks post-surgery • isometric and Isotonic exercises within 1-6 weeks post-surgery • active strengthening after 6 weeks post-surgery • return to sport at 12 weeks post-surgery and beyond"	
9.1.8	N/A	Added new section for further clarification regarding MRIs: "MRI Submissions Upper extremity MRIs for study participants will be collected pre-operatively, at 12 months post-surgery and at 24 months post-surgery. The pre-operative MRI is the participant's standard of care MRI and will not follow the study MRI Image Acquisition Protocol. The pre-op MRI must occur within 6 months of enrollment into this study. Participants will receive an MRI of the index shoulder at 12 months and 24 months post-surgery per the Image Acquisition Protocol. The standard of care pre-operative MRI and the 12 and 24 month MRIs will be submitted to the imaging vendor per the Image Transfer Protocol. 3T MRIs are

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		strongly preferred for submission, wherever available, but are not required."
9.2.1	*"Incidence of Progression to Full Thickness Tear:* Participants will receive a standard MRI per the Image Acquisition Protocol of the index shoulder at 12 months and 24 months post-surgery. The standard of care pre-operative MRI and the 12 and 24 month MRIs will be submitted to the imaging vendor per the Image Transfer Protocol. An independent reviewer will assess MRIs for evidence of progression to a full-thickness tear within 12 months and 24 months of the index surgery."	Revised *"Incidence of Progression to Full Thickness Tear:* An independent reviewer will assess MRIs for evidence of progression to a full-thickness tear within 12 months and 24 months of the index surgery. All MRI assessments are detailed in the Image Review Charter."
9.2.1	N/A	Removed "*Participant reported Shoulder Stiffness*" Added "*Constant-Murley Score:* The Constant-Murley Score is a validated assessment of the level of pain and shoulder functionality among participants. The test is divided into four subscales: pain, activities of daily living, strength and range of motion (forward elevation, external rotation, abduction and internal rotation of the shoulder. At the end of the assessment, a score is obtained out of 100 points where higher scores indicate a higher quality of shoulder function. The score is

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		obtained through a combination of participant-reported and objective (examiner-assessed) shoulder outcome measures." Added "*Percent Filling of Rotator Cuff:* An independent reviewer will assess MRIs for the percent filling of the rotator cuff at 12 months and 24 months post-surgery. All MRI assessments are detailed in the Image Review Charter." Added "*Rotator Cuff Tendon Thickness*: An independent reviewer will assess MRIs for the rotator cuff tendon thickness at 12 and 24 months. All MRI assessments are detailed in the Image Review Charter." Added "*Goutallier Classification:* The Goutallier classification will be used to classify the fatty infiltration of the rotator cuff. The Goutallier classification ranges from a grade of 0 indicating a completely normal muscles without any fatty streaks to a grade of 4 which indicates that more fat than muscle is present.[23] An independent reviewer will assess MRIs for the fatty infiltration of the rotator cuff at 12 and 24 months post-surgery. All MRI assessments are detailed in the Image Review Charter." Added "*Sugaya Score:* The Sugaya score will be used to

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		measure the rotator cuff integrity. The Sugaya score ranges from Type I to Type V. Type I indicates a repaired cuff that had sufficient thickness with homogeneously low intensity on the MRI image while Type V indicates the presence of a major discontinuity on the MRI images suggesting a medium or large tear. An independent reviewer will use the MRI to assess rotator cuff integrity at 12 and 24 months post-surgery. All MRI assessments are detailed in the Image Review Charter."
10.1	"The CRO's Biostatistician will conduct the statistical analyses for this study, with the exception of the economic analysis, which will be conducted by Smith & Nephew's Global Biostatistics group. Unless otherwise stated, all significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. Where data summaries are specified, categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary	"The CRO's Biostatistician will conduct the statistical analyses for this study, with the exception of the economic analysis, which will be conducted by Smith & Nephew's Global Biostatistics group. For the primary outcome, the significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. Unless otherwise stated, point estimates (mean differences or odds ratios) and 95% confidence intervals will be reported descriptively for secondary outcomes as an exploratory assessment. Select secondary outcomes will undergo statistical testing as outlined in section 10.4.2.

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	statistics: number of observations, means and standard deviations, or median and interquartile ranges. All analyses will be performed using a statistical package such as SAS or SPSS."	Where data summaries are specified, categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary statistics: number of observations, means and standard deviations, or median and interquartile ranges. All analyses will be performed using a statistical package such as SAS or SPSS."
10.3	"Patient demographics and baseline outcome variables will be summarized by treatment group using descriptive summary measures expressed as means with standard deviations or medians with interquartile ranges for continuous variables depending on the distribution and number (percent) for categorical and ordinal variables. Chi-squared tests and t-tests will be used to determine if there are significant differences in baseline characteristics between the two cohorts."	"Patient demographics and baseline outcome variables will be summarized by treatment group using descriptive summary measures expressed as means with standard deviations or medians with interquartile ranges for continuous variables depending on the distribution and number (percent) for categorical and ordinal variables."
10.4.1	"A two-way ANOVA will be used to compare differences in the mean ASES score between the REGENETEN cohort and the comparison cohort at 3 months post-treatment. The analysis will be adjusted for baseline ASES score and for differences in baseline	"Multiple linear regression will be used to compare differences in the mean ASES scores between the REGENETEN cohort and the comparison cohort at 3 months post-treatment. The significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-

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	characteristics between the two cohorts.”	values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. The analysis will be adjusted for baseline ASES score and for differences in baseline characteristics between the two cohorts. The minimal clinically important difference (MCID) will be used to determine the clinical importance of the mean difference between treatment groups for the ASES score and all other patient-reported outcomes (i.e. SANE, Constant-Murley score). The MCID defines the change in the outcome score that results in the smallest, appreciable clinical improvement. The MCID for the ASES is 11.1 points for patients with rotator cuff disease.The criteria for determining the clinical importance of the mean difference will be as follows: • If the confidence interval of the mean difference is completely above the MCID, the difference is considered “significant” • If the confidence interval of the mean difference contains the MCID, the difference is considered “possibly clinically significant” • If the confidence interval of the mean difference is completely below the MCID,

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		the difference is considered "not clinically significant" The assessment of clinical importance will be reported along with the confidence intervals for each outcome."
10.4.2	"Table 2 summarizes the secondary efficacy endpoint(s) and summary of planned analyses. The statistical tests in Table 2 assume that the data will be normally distributed. The SAP will provide alternative approaches should the assumption of normality not be met."	"Table 2 summarizes the secondary efficacy endpoint(s) and planned analysis for select secondary outcomes. Unless otherwise stated, point estimates in the form of mean differences or odds ratios along with 95% confidence intervals will be reported descriptively for secondary outcomes. An exploratory assessment using the MCID will be done for select secondary outcomes. The MCID will be used to explore the clinical importance of the mean difference between treatment groups for all patient-reported outcomes (i.e. ASES, SANE, and Constant-Murley score). The MCID used for outcomes related to the ASES score, SANE score and Constant-Murley score will be 11.1 points, 29.4 points, and 5.5 points, respectively. For outcomes involving the ASES-VAS pain score, the MCID used will be 1.37 cm."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	Statistical Test for Secondary Objective #1: "Generalized linear regression adjusting for baseline ASES score and	Statistical Test for Secondary Objective #1: "Generalized linear regression adjusting for baseline ASES score and differences in

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	differences in baseline characteristics."	baseline characteristics. The mean ASES scores will be compared using an MCID of 11.1 points."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	Statistical Test for Secondary Objective #2: "Generalized linear regression adjusting for baseline SANE score and differences in baseline characteristics."	Statistical Test for Secondary Objective #2: "Generalized linear regression adjusting for baseline SANE score and differences in baseline characteristics. The mean SANE scores will be compared using an MCID of 29.4 points."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	Statistical Test for Secondary Objective #3: "Generalized linear regression adjusting for baseline VAS pain score and differences in baseline characteristics."	Statistical Test for Secondary Objective #3: "Generalized linear regression adjusting for baseline VAS pain score and differences in baseline characteristics. The mean ASES-VAS pain score will be compared using an MCID of 1.37 cm."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	Statistical Test for Secondary Objective #4: "Generalized linear regression adjusting for baseline ASES score and differences in baseline characteristics."	Statistical Test for Secondary Objective #4: "Generalized linear regression adjusting for baseline ASES score and differences in baseline characteristics. The mean ASES scores will be compared using an MCID of 11.1 points."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	Statistical Test for Secondary Objective #5: "Generalized linear regression adjusting for baseline SANE score and differences in baseline characteristics."	Statistical Test for Secondary Objective #5: "Generalized linear regression adjusting for baseline SANE score and differences in baseline characteristics. The mean SANE scores will be compared using an MCID of 29.4 points."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	Statistical Test for Secondary Objective #6: "Generalized linear regression adjusting for baseline ASES score and differences in baseline characteristics."	Statistical Test for Secondary Objective #6: "Generalized linear regression adjusting for baseline VAS pain score and differences in baseline characteristics. The mean ASES-VAS pain score will be

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		compared using an MCID of 1.37 cm."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	• Removed "Secondary Objective #7": "To determine if there are benefits (within 12 months of surgery) of arthroscopic surgical treatment of high-grade (>50%) partial thickness rotator cuff tears using REGENETEN on participant reported shoulder stiffness compared to standard surgical repair techniques" ➢ Removed associated outcome measure ➢ Removed associated statistical test
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	• Added "Secondary Objective #7": To determine if arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN statistically improved participant-reported and examiner-assessed shoulder pain and function compared to standard surgical repair techniques over 24 months from the index shoulder surgery." ➢ Added Outcome Measure associated with secondary objective #7: "Constant-Murley Score at 3, 6, 12 and 24 months." ➢ Added Statistical Test associated with secondary objective #7: "Generalized linear regression adjusting for baseline Constant-Murley score and

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		differences in baseline characteristics. The mean Constant-Murley score will be compared using an MCID of 5.5."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	• Added "Secondary Objective #8: To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN use significantly less opioids to treat the index shoulder compared to standard surgical repair over the initial 3 months following index surgery." ➢ Added Outcome Measure associated with secondary objective #8: "Dose/duration of opioid use from post-surgery to 3-months post-surgery. Defined daily dose (DDD) will be used as the outcome measure." ➢ Added Statistical Test associated with secondary objective #8: "Generalized linear regression adjusting for baseline opioid use and differences in baseline characteristics."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	• Added "Secondary Objective #9: To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN use significantly less non-opioid

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		prescription medication to treat the index shoulder compared to standard surgical repair over the initial 3 months following index surgery." ➢ Added Outcome Measure associated with secondary objective #9: "Dose/duration of non-opioid prescription pain medication use from post-surgery to 3-months post-surgery. DDD will be used as the outcome measure." ➢ Added Statistical Test associated with secondary objective #9: "Generalized linear regression adjusting for baseline non-opioid prescription pain medication use and differences in baseline characteristics."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #8: ➢ Outcome Measure: "Dose/duration of opioid use from post-surgery to 12-months post-surgery." ➢ Statistical Test: "Two way ANOVA adjusting for baseline opioid use and differences in baseline characteristics."	• Secondary Objective #10: ➢ Revised Outcome Measure: "Dose/duration of opioid use from post-surgery to 12-months post-surgery. DDD will be used as the outcome measure." ➢ Revised Statistical Test: "Generalized linear regression adjusting for baseline opioid use and differences in baseline characteristics."
10.4.2 – Table 2 (Analysis of	• Secondary Objective #9: ➢ Outcome Measure: "Dose/duration of non-	• Secondary Objective #11: ➢ Revised Outcome Measure: "Dose/duration of

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Secondary Endpoints)	opioid prescription pain medication use from post-surgery to 12-months post-surgery." ➢ Statistical Test: "Two way ANOVA adjusting for baseline non-opioid prescription pain medication use and differences in baseline characteristics."	non-opioid prescription pain medication use from post-surgery to 12-months post-surgery. DDD will be used as the outcome measure." ➢ Revised Statistical Test: "Generalized linear regression adjusting for baseline non-opioid prescription pain medication use and differences in baseline characteristics."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #10: ➢ Statistical Test: "Linear regression analysis, adjusting for differences in baseline characteristics."	• Secondary Objective #12: ➢ Removed Statistical Test
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #11: ➢ Statistical Test: "Two way ANOVA, adjusting for type of occupation and for differences in baseline characteristics."	• Secondary Objective #13: ➢ Revised Statistical Test: "Generalized linear regression, adjusting for type of occupation and for differences in baseline characteristics."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #12: ➢ Statistical Test: "Two way ANOVA, adjusting for differences in baseline characteristics."	• Secondary Objective #14: ➢ Removed Statistical Test
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #13: ➢ Statistical Test: "Two way ANOVA, adjusting for baseline level of	• Secondary Objective #15: • Revised Statistical Test: "Generalized linear regression, adjusting for baseline level of

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	sporting activity and differences in baseline characteristics."	sporting activity and differences in baseline characteristics."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #14: ➢ Statistical Test: "Logistic regression analysis adjusting for baseline opioid use and for differences in baseline characteristics."	• Secondary Objective #16: ➢ Removed Statistical Test
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #15: ➢ Statistical Test: "Logistic regression analysis adjusting for differences in baseline characteristics."	• Secondary Objective #17: ➢ Removed Statistical Test
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	• Added "Secondary Objective #18: To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have increased percent filling of the rotator cuff (based on MRI assessment) compared to participants who had standard surgical repair at 12 months from the index shoulder surgery." ➢ Added Outcome Measure associated with secondary objective #18: "Percent filling (based on MRI assessment) at 12-months post-surgery."
10.4.2 – Table 2 (Analysis of	N/A	• Added "Secondary Objective #19: To determine if participants

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Secondary Endpoints)		who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have increased percent filling of the rotator cuff (based on MRI assessment) compared to participants who had standard surgical repair at 24 months from the index shoulder surgery." ➢ Added Outcome Measure associated with secondary objective #19: "Percent filling (based on MRI assessment) at 24-months post-surgery."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	• Added "Secondary Objective #20: To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have improvements in rotator cuff tendon thickness (based on MRI assessment) compared to participants who had standard surgical repair at 12 months from the index shoulder surgery." ➢ Added Outcome Measure: "Rotator cuff tendon thickness (based on MRI assessment) at 12-months post-surgery." ➢ Added Statistical Test: "Generalized linear regression adjusting for baseline tendon thickness and differences in baseline characteristics."

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10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	• Added "Secondary Objective #21: To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have improvements in rotator cuff tendon thickness (based on MRI assessment) compared to participants who had standard surgical repair at 24 months from the index shoulder surgery." ➢ Added Outcome Measure: "Rotator cuff tendon thickness (based on MRI assessment) at 24-months post-surgery." ➢ Added Statistical Test: "Generalized linear regression adjusting for baseline tendon thickness and differences in baseline characteristics."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	• Added "Secondary Objective #22: To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have a statistically lower fatty infiltration of the rotator cuff (based on MRI assessment) compared to participants who had standard surgical repair at 12 months from the index surgery." ➢ Added Outcome Measure associated with secondary objective #22: "Goutallier

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		classification of rotator cuff (based on MRI assessment) at 12-months post-surgery."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	• Added "Secondary Objective #23: To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have a statistically lower fatty infiltration of the rotator cuff (based on MRI assessment) compared to participants who had standard surgical repair at 24 months from the index surgery." ➢ Added Outcome Measure associated with secondary objective #23: "Goutallier classification of rotator cuff (based on MRI assessment) at 24-months post-surgery."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	• Added "Secondary Objective #24: To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have statistically improved rotator cuff integrity (based on MRI assessment) compared to participants who had standard surgical repair techniques at 12 months from the index surgery." ➢ Added Outcome Measure associated with secondary objective #24: "Sugaya

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		score (based on MRI assessment) at 12-months post-surgery."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	• Added "Secondary Objective #25: To determine if participants who undergo arthroscopic surgical treatment of high-grade (>50%) partial-thickness rotator cuff tears using REGENETEN have statistically improved rotator cuff integrity (based on MRI assessment) compared to participants who had standard surgical repair techniques at 24 months from the index surgery." ➢ Added Outcome Measure associated with secondary objective #25: "Sugaya score (based on MRI assessment) at 24-months post-surgery."
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #17: ➢ Statistical Test: "Compare the mean total healthcare utilization costs between the two cohorts using multiple linear regression adjusting for baseline differences."	• Secondary Objective #27: ➢ Removed Statistical Test
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #18: ➢ Statistical Test: "Two way ANOVA, adjusting for differences in baseline characteristics."	• Secondary Objective #28: ➢ Revised Statistical Test: "Generalized linear regression, adjusting for differences in baseline characteristics."

Section	Current Text DD-MMM-YYYY Version # 12-Dec-2018, V 2.0	Revised Text DD-MMM-YYYY Version # 10-Sep-2019, V 3.0
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #19: ➢ Statistical Test: "Mann-Whitney U test" •	• Secondary Objective #29: ➢ Removed Statistical Test
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #20: ➢ Statistical Test: "Poisson regression analysis adjusting for differences in baseline characteristics." •	• Secondary Objective #30: ➢ Removed Statistical Test
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #21: ➢ Statistical Test: "Poisson regression analysis adjusting for differences in baseline characteristics." •	• Secondary Objective #31: ➢ Removed Statistical Test
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	• Secondary Objective #22: ➢ Statistical Test: "Mann-Whitney U test adjusting for differences in baseline characteristics." •	• Secondary Objective #32: ➢ Removed Statistical Test
10.4.2 – Table 2 (Analysis of Secondary Endpoints)	N/A	Revised numbering in Table 2 as required
10.6	Not Applicable	Added Interim Analysis: "A data extract will be completed when the last enrolled participant has completed their three-month follow-up visit. A report will not accompany this data extract but the findings may be presented as possible podium or conference activity.

Section	Current Text DD-MMM-YYYY Version # 12-Dec-2018, V 2.0	Revised Text DD-MMM-YYYY Version # 10-Sep-2019, V 3.0
		An interim analysis will be conducted when the last enrolled participant has completed their one-year follow-up from index surgery. This analysis will include a simplified statistical report and a possible peer-reviewed publication."
11 – Sample Size Justification	"The sample size calculation was conducted for 80% power and an alpha of 0.05. The minimal clinically important difference (MCID) used as the difference to detect for was 12 points on the American Shoulder and Elbow Surgeons (ASES) score at 3 months following index surgery."	"The sample size calculation was conducted for 80% power and an alpha of 0.05. The minimal clinically important difference (MCID) used as the difference to detect for was 11.1 points on the American Shoulder and Elbow Surgeons (ASES) score at 3 months following index surgery."
20	N/A	References and reference numbers updated as required

21.2 PRINCIPAL INVESTIGATOR OBLIGATIONS (ISO14155)

1. General:
   a. The role of the PI is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, U, and well-being of the participants involved in the clinical investigation.
2. Qualification of the PI. The PI shall:
   a. be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this International Standard; evidence of such qualifications of the PI and key members of the investigation site team shall be provided to the Sponsor through up-to-date Curriculum Vitae (CV) or other relevant documentation,

b. be experienced in the field of application and trained in the use of the investigational device under consideration,
c. disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results, and
d. be knowledgeable with the method of obtaining informed consent.

3. Qualification of investigation site. The PI shall be able to demonstrate that the proposed investigation site:
   a. has the required number of eligible participants needed within the agreed recruitment period, and
   b. has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation.
4. Communication with the IEC. The PI shall:
   a. provide the Sponsor with copies of any clinical-investigation-related communications between the PI and the IEC,
   b. comply with the requirements described in 4.5 of ISO 14155:
      i. Submit to the IEC the following information, any amendments and any additional documentation required by the IEC: the Protocol; IB or equivalent; informed consent form and any other written information provided to participants; procedures for recruiting participants and advertising materials, if any; a copy of the CV of the PI(s) for with the IEC has oversight.
      ii. Provide documentation of the IECs approval/favorable opinion, identifying the documents and amendments on which the opinion was based, to the Sponsor, prior to commencing the clinical investigation.
      iii. Submit the following to the IEC if required by national regulations, the protocol or IEC, whichever is more stringent:
         1. SAEs
         2. Requests for deviations, and reports of deviations, if the deviation affects participant's rights, safety, and well-being, or the scientific integrity of the clinical investigation. Document and report to the Sponsor and IEC a report of

deviations made to protect the rights, safety, and well-being of human participants under emergency circumstances.

3. Progress reports, including safety summary and deviations
4. Amendments to any documents already approved by the IEC.
5. If applicable, notifications of suspension or premature termination
6. If applicable, justification and request for resuming the clinical investigation after suspension.
7. Clinical investigation report or summary.

iv. As a minimum, during the clinical investigation, the following information shall be obtained in writing from the IEC prior to implementation:

1. Approval/favorable opinion of amendments
2. Approval of the request for deviations that can affect the participant's rights, safety, and well-being or scientific integrity of the clinical investigation
3. Approval for resumption of a suspended clinical investigation if applicable.

c. obtain the written and dated approval/favorable opinion of the IEC for the clinical investigation before recruiting participants and implementing all subsequent amendments, if required,

d. promptly report any deviations from the protocol that affect the rights, safety or well-being of the participant or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the IEC, protocol or national regulations. In particular circumstances, the communication with the IEC can be performed by the Sponsor, partly or in full, in which case the Sponsor shall keep the Principal Investigator informed.

5. Informed consent process. The PI shall:

a. General:

i. Informed consent shall be obtained in writing from the participant and the process shall be documented before any procedure specific to the clinical investigation is applied to the participant; except when special circumstances for emergency treatments apply (see below)

ii. The informed consent form consists of an information form and informed consent signature form. These two forms can either be combined in one document or separated into two documents

b. Process of obtaining informed consent. The general process for obtaining informed consent shall be documented in the protocol and shall comply with the following. These requirements also apply with respect to informed consent obtained from a participant's legally authorized representative:

i. Ensure that the PI or his/her authorized designee conducts the informed consent process

ii. Include all aspects of the clinical investigation that are relevant to the participant's decision to participate throughout the clinical investigation

iii. Avoid any coercion or undue improper influence on, or inducement of, the participant to participate

iv. Not waive or appear to waive the participant's legal rights

v. Use native non-technical language that is understandable to the participant

vi. Provide ample time for the participant to read and understand the informed consent form and to consider participation in the clinical investigation

vii. Include personally dated signatures and the PI or an authorized designee responsible for conducting the informed consent process

viii. Show how informed consent will be obtained in special circumstances (see below) where the participant is unable to provide him or herself, and

ix. Ensure important new information is provided to new and existing participants throughout the clinical investigation.

c. Special circumstances for informed consent (the following provisions are subject to national regulations):

i. Participant needing legally authorized representatives: informed consent may be given by the legally authorized representative only if a participant is unable to make the decision to participate in a clinical investigation (e.g. infant, child, or juvenile, seriously ill or unconscious participant, mentally ill person, mentally handicapped

person). In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.

ii. Participant unable to read or write: informed consent shall be obtained through a supervised oral process if a participant or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective participant or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent for attesting that the information was accurately explained and that the informed consent was freely given.

iii. Emergency treatments:

1. For clinical investigations involving emergency treatments, when prior informed consent of the participant is not possible because of the participant's medical condition, the informed consent of the participant's legally authorized representative, if present, shall be requested.
2. When it is not possible to obtain prior informed consent from the participant, and the participant's legally authorized representative, is not available, the participant may still be enrolled if a specific process has been described in the protocol.
3. Arrangements shall be made to inform the participant or legally authorized representative, as soon as possible, about the participant's inclusion in the clinical investigation and about all aspects of the clinical investigation.
4. The participant shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows.

d. The Principal Investigator may not enroll a participant without obtaining informed consent of the participant or his/her legally authorized representative only when the following conditions are fulfilled: the prospective participant fulfils the emergency conditions and is obviously in a life-threatening situation; no sufficient clinical benefits are anticipated from

the currently available treatment; there is a fair possibility that the life-threatening risk to the prospective participant can be avoided if the investigational device is used; anticipated risks are outweighed by the potential benefits of applying the investigational device ; the legally authorized representative cannot be promptly reached and informed.

e. Information provided to the participant. All information pertinent to the clinical investigation, including at least the following, shall be provided in writing and in native, non-technical language that is understandable to the participant (or the participant's legally authorized representative):
   i. Description and purpose
   ii. Potential benefits
   iii. Risks and inconveniences or the participant and, when applicable, for any embryo, foetus or nursing infant
   iv. Alternative procedures
   v. Confidentiality
   vi. Compensation
   vii. Anticipated expenses, if any, to be borne by the subject for participating in the clinical investigation
   viii. Information on the role of Sponsor's representative in the clinical investigation
   ix. Contact persons
   x. Statement declaring that new findings or the reasons for any amendment to the protocol that affect the participant's continued participation shall be made available to the participant.
   xi. Statement indicating that, upon the participant's approval, the participant's personal physician will be informed of the participant's participation in the clinical investigation
   xii. Termination procedures
f. Informed consent signature shall contain the following:
   i. The voluntary agreement to participate in the clinical investigation and follow the investigator's instructions

ii. A statement declaring that refusal of participation incurs no penalty for the participant

iii. A statement declaring that discontinuation at any time incurs no penalty for the participant

iv. A statement with regard to the possible consequences of withdrawal

v. An acknowledgement of the information provided and confirmation that all the participant's questions were answered

vi. A statement confirming that the participant or his/her legally authorized representative agrees to the use of the participant's relevant personal data for the purpose of the clinical investigation

vii. A statement confirming that the participant or his/her legally authorized representative agrees that Sponsor's representatives, regulatory authorities and IEC representatives will be granted direct access to the participant's medical records.

g. New information: if new information becomes available that can significantly affect a participant's future health and medical care, that information shall be provided to the participant(s) affected in written form. If relevant, all affected participants shall be asked to confirm their continuing consent in writing.

h. ensure compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent, and

i. ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.

6. Compliance with the protocol. The Principal Investigator shall:

a. indicate his/her acceptance of the protocol in writing,

b. conduct the clinical investigation in compliance with the protocol,

c. create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits,

d. ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the protocol and instructions for use,

e. propose to the Sponsor any appropriate modification(s) of the protocol or investigational device or of the use of the investigational device,
f. refrain from implementing any modifications to the protocol without agreement from the Sponsor, IEC and regulatory authorities, if required,
g. document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation,
h. ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
i. ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,
j. ensure the accuracy, completeness, legibility and timeliness of the data reported to the Sponsor in the CRF and in all required reports,
k. maintain the device accountability records,
l. allow and support the Sponsor to perform monitoring and auditing activities,
m. be accessible to the monitor and respond to questions during monitoring visits,
n. allow and support regulatory authorities and the IEC when performing auditing activities,
o. ensure that all clinical-investigation-related records are retained as required taking measures to prevent accidental or premature destruction, and
p. review and sign the clinical investigation report, as applicable.

7. Medical care of participants. The Principal Investigator shall
   a. provide adequate medical care to a participant during and after a participant's participation in a clinical investigation in the case of adverse events,
   b. inform the participant of the nature and possible cause of any adverse events experienced,
   c. provide the participant with the necessary instructions on proper use, handling, storage, and return of the investigational device, when it is used or operated by the participant,
   d. inform the participant of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required,

e. provide the participant with well-defined procedures for possible emergency situations related to the clinical investigation, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed,

f. ensure that clinical records are clearly marked to indicate that the participant is enrolled in a particular clinical investigation,

g. if appropriate, participants enrolled in the clinical investigation shall be provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided),

h. inform, with the participant's approval or when required by national regulations, the participant's personal physician about the participant's participation in the clinical investigation, and

i. make all reasonable efforts to ascertain the reason(s) for a participant's premature withdrawal from the clinical investigation while fully respecting the participant's rights.

8. Safety reporting. The Principal Investigator shall:

a. record every adverse event and observed device deficiency, together with an assessment,

b. report to the Sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the protocol,

c. c) report to the IEC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or protocol or by the IEC,

d. report to regulatory authorities serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and

e. supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.