Sponsor Name and Address:	Smith+Nephew Inc. 150 Minuteman Road Andover, MA 01810 USA
Investigational Product(s):	REGENETEN™ Bioinductive Implant System (hereinafter referred to as REGENETEN)
Protocol Author(s):	Abigail Murphy, Clinical Study Manager Michelle Foster, Senior Biostatistician Carol Carrigan, MHA, Medical Writer, Global Scientific Affairs

1. SIGNATURES

1.1 PRINCIPAL INVESTIGATOR SIGNATURE PAGE

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

I have read the attached protocol entitled "A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Efficacy of ARCR augmented with REGENETEN™ Bioinductive Implant System in Full-thickness Tears (large or massive) Repair versus ARCR alone", version 2.0, dated 08Dec2021, and agree to abide by all provisions set forth herein.
I agree to comply with the Investigator's Obligations stipulated in Section 21.5 Principal Investigator Obligations (ISO14155:2020) and Section 21.6 Responsibilities of Clinical Trial Institution and Investigator (cFDA).
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.

Name, Address, Professional Position	Signature	Date Signed (DD/MMM/YYYY)

1.2 COORDINATING INVESTIGATOR APPROVAL

I have read the attached protocol entitled "A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Efficacy of ARCR augmented with REGENETEN™ Bioinductive Implant System in Full-thickness Tears (large or massive) Repair versus ARCR alone", version 2.0, dated 08Dec2021, and agree to abide by all provisions set forth therein.

Name, Address, Professional Position	Docusign Stamp
Prof. Chris Peach Consultant Orthopaedic Surgeon Manchester University NHS Foundation Trust Southmoor Road, Manchester M23 9L	DocuSigned by: Chris Peach Signer Name: Chris Peach Signing Reason: I approve this document Signing Time: 09-Dec-2021 | 15:21:41 GMT 2CC4DBD564934412813AED387BA5F527

1.3 SPONSOR APPROVAL

	Job title	DocuSign Stamp
Head of Global Clinical Operations	Rachael Winter, Senior Director, Global Clinical Operations	DocuSigned by: Rachael Winter Signer Name: Rachael Winter Signing Reason: I approve this document Signing Time: 09-Dec-2021 | 17:38:22 GMT A32F12A80F1B4490986E80ACCB7471CB
Head of Global Clinical Strategy	Lori Fontaine, VP, Global Clinical Strategy	DocuSigned by: Laura England Signer Name: Laura England Signing Reason: I approve this document Signing Time: 09-Dec-2021 | 13:59:29 GMT E7E03F2AD4D64D37BA26BED5CDB2513A
Head of Global Biostatistics	Alan Rossington, Director Biostatistics & Data Management	DocuSigned by: Alan Rossington Signer Name: Alan Rossington Signing Reason: I approve this document Signing Time: 09-Dec-2021 | 13:36:03 GMT 556E7DBFCA8A4287A7EE3EE9B5B3ABFD
Medical Affairs Representative	Martin Ma, Director Clinical Evidence Evaluation	DocuSigned by: Martin Ma Signer Name: Martin Ma Signing Reason: I approve this document Signing Time: 09-Dec-2021 | 14:37:14 GMT 01600B76EFFA4F53899A9447514407BF
Regulatory Affairs Representative	Jenna Horsley, Sr Regulatory Manager, SPM and ENT	DocuSigned by: Jenna Horsley Signer Name: Jenna Horsley Signing Reason: I approve this document Signing Time: 09-Dec-2021 | 17:35:24 GMT D937708856824455AD125770F99CE9B0

2. SYNOPSIS

Title of Study:	A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Efficacy of ARCR augmented with REGENETEN™ Bioinductive Implant System in Full-thickness Tears (large or massive) Repair versus ARCR alone.
Study Design:	A prospective, randomized, multi-center, controlled clinical study, 3 study arms, 24 months follow up, adaptive design with up to 300 subjects (130 ARCR augmented with REGENETEN; 130 ARCR alone and up to 40 revision repair subjects).
Study Type:	Pre-market (China), Post-market, randomized controlled trial (RCT).
Study Product:	REGENETEN Bioinductive Implant System™ is comprised of disposable instruments, a resorbable bovine collagen scaffold, poly-l/d-lactide (PDLLA) tendon anchors to secure the scaffold to the underlying tendon, and PEEK bone anchors to secure the implant to bone. REGENETEN is indicated for the management and protection of tendon injuries/rotator cuff tendon injuries (see Indications Section 4.4.1) in which there has been no substantial loss of tendon tissue.
Comparison Group(s):	Arthroscopic rotator cuff repair (ARCR) treatment alone.
Study Purpose:	To assess the safety and efficacy of ARCR augmented with REGENETEN in subjects requiring full-thickness rotator cuff tear repair or revision repair versus ARCR alone. The study results will be used to support product registration in China and post market clinical follow-up (PMCF) primary in Europe, Australia (AUS), New Zealand (NZL) and reimbursement to relevant countries.
Primary Objective:	To assess the cumulative 6 months retear rate after full thickness ARCR augmented with REGENETEN and ARCR alone.

Secondary Objective(s):	To assess safety and efficacy of full-thickness ARCR augmented with REGENETEN versus ARCR alone.
Other Objective(s):	To assess safety and efficacy of full-thickness ARCR augmented with REGENETEN versus ARCR alone in at-risk-groups (diabetics, smokers, hypertensive, heavy laborer, age > 65 years); To assess safety and efficacy of full-thickness ARCR augmented with REGENETEN in revision repair subject group (observational); To generate health economic evidence.
Sample Size:	Up to 300 subjects will be enrolled into the study: • 130 ARCR augmented with REGENETEN • 130 ARCR alone • Up to 40 revision repair subjects will be recruited into one additional single group (ARCR supplemented with REGENETEN in recurrent tears (full-thickness tears [large or massive]). This group will follow the same follow-up as the RCT group. The initial RCT power analysis is based on a Lan-DeMets (O'Brien Fleming) spending function with hypothesized retear incidence of 15% for REGENETEN and 30% for ARCR with 80% power and 5% significance level. The sample size of 260 RCT is based on a primary hypothesis of 50% reduction in retear rates. Using a group sequential design, a formal interim analysis will be conducted once 50% of the planned subjects reach the 6-month follow-up at which point a sample size re-estimation will be performed along with options considered to terminate early for efficacy or futility or increase sample size. Up to 40 revision repair subjects will be

	enrolled into one additional group for sub-group analysis. Further details will be specified within the Statistical Analysis Plan (SAP).
Number of Study Sites:	Up to 30 study sites
Targeted Global Regions:	Singapore, Hong Kong, China, United Kingdom, Germany, Switzerland, France, Canada, Australia, Netherlands, Japan, New Zealand and United States sites.
Inclusion Criteria:	1. Subject requires Arthroscopic rotator cuff repair (ARCR); 2. Subjects with a diagnosis of a symptomatic primary or recurrent (revision repair subject group), large or massive tear (≥ 3 cm AP/ML) of the supraspinatus and/or infraspinatus tendons amenable to repair. For screening purposes, a ≥ 2 cm AP/ML tear as measured on MRI will be eligible to proceed to the operative visit but will have to be confirmed as ≥ 3 cm on arthroscopy using a calibrated probe to proceed; 3. Subject is > 40 years of age (no upper limit); 4. Subject provides written informed consent for study participation using an Independent Ethical Committee (IEC) / Institutional Review Board (IRB) approved consent form; 5. Subject is willing and able to participate in required follow-up visits and is able to complete study activities.
Exclusion Criteria:	1. Subjects who are unable to tolerate magnetic resonance imaging (MRI), due to psychiatric or medical contraindications; 2. Subjects with Samilson-Prieto osteoarthritis > 2; 3. Subjects with current or prior infection of the ipsilateral shoulder; 4. Subjects with known hypersensitivity to bovine-derived materials; 5. Subjects with known inflammatory arthropathy, history of inflammatory arthropathy, or chronic joint disease;

	6. Subjects with prior shoulder surgery (not including rotator cuff repair [revision repair subject group only], biceps tenodesis/tenotomy, distal clavicle excision [DCE], subacromial decompression); 7. Subjects with an irreparable or partially reparable rotator cuff tear; 8. Subjects with a subscapularis tear requiring repair; 9. Subjects requiring a concomitant labral fixation procedure; 10. Subjects requiring a concomitant os acromiale fixation procedure; 11. Subjects with glenohumeral joint instability (multiple dislocations/subluxations); 12. Subjects with a subacromial or intra-articular injection within 3 months prior to surgery; 13. Subjects with condition(s) that contraindicate or complicate outcomes of ARCR e.g., > Hamada 3 rotator cuff arthropathy on X-ray, Goutallier atrophy > Grade 3, proximal humeral fracture or scapular fracture, avascular necrosis of the humeral head or glenoid, history of immunodeficiency disorders, history of chronic inflammatory disorders, oral or injected steroid use in last 4 weeks; 14. Subjects who are pregnant or breast feeding; 15. Subjects who are currently involved in any injury litigation or workers compensation claims; 16. Subjects who are enrolled, or plan to enroll, in another clinical trial during this study that would affect the outcomes of this study;

	17. Subjects with a history of noncompliance with medical treatment, physical therapy (PT)/rehabilitation, or clinical study participation; 18. Subject who, in the opinion of the Investigator, has an emotional or neurological condition that would pre-empt their ability or willingness to participate in the study including mental illness, mental retardation, and drug or alcohol abuse; 19. Subjects who do not meet the indication or are contraindicated according to specific Smith+Nephew REGENETEN System's Instructions for Use (IFUs); 20. Subject that meets the definition of a Vulnerable Subject per ISO14155:2020 Section 3.44.
Study Duration:	48 months (24 month enrollment period and 24 months follow-up period).
Primary Endpoint:	The cumulative 6 months retear rate after full-thickness ARCR augmented with REGENETEN versus ARCR alone. Failure is defined as Sugaya Type IV or V retear/recurrence (full-thickness discontinuity seen on both coronal and oblique sagittal MRI images).

Secondary Endpoint(s):	• The cumulative 3, 12, and 24 months retear rate after full-thickness ARCR augmented with REGENETEN (confirmed on MRI) versus ARCR alone;
	• Overall performance of full-thickness ARCR augmented with REGENETEN versus ARCR alone at Baseline and at 3, 6, 12 and 24 months assessed by:
	  ○ Oxford Shoulder Score (OSS),
	  ○ Western Ontario Rotator Cuff (WORC)/Chinese version WORC (C-WORC) Index,
	  ○ Constant-Murley Score (CM),

	○ Subjective shoulder value (SSV), ○ EuroQol 5 Dimension 5 Level (EQ-5D-5L) Score, ○ Patient satisfaction Questionnaire, ○ Pain, Visual analog scale (VAS) Score (additionally at baseline, 2 weeks, 6 weeks, 3 months and 6 months); • MRI Tendon Findings in ARCR augmented with REGENETEN versus ARCR alone postoperatively at Baseline, 3, 6, 12 and 24 months including ○ Sugaya score, ○ Goutallier grading, ○ Total tendon thickness, tendon length, ○ Size of retear (anteroposterior [AP]/mediolateral [ML]), ○ Shape of retear; • Outcome of Return to Work Questionnaire in ARCR augmented with REGENETEN versus ARCR alone (additionally at 2 and 6 weeks); • Cumulative duration of opioid use in ARCR augmented with REGENETEN versus ARCR alone at 2 weeks postoperatively; • Total operative time ARCR augmented with REGENETEN versus ARCR alone; • Sling type and mobilization time in ARCR augmented with REGENETEN versus ARCR alone.
Other Exploratory Endpoint(s):	• To assess safety and efficacy as summarized in secondary endpoints in at-risk groups (diabetics, smokers, hypertensive,

	heavy laborer, age > 65 years) after full-thickness ARCR augmented with REGENETEN versus ARCR alone; • To assess safety and efficacy as summarized in secondary endpoints in revision repair subject group after full-thickness ARCR augmented with REGENETEN; • To collect health economic evidence in ARCR augmented with REGENETEN versus ARCR alone: o Aggregate health care utilization costs, o Number of unscheduled visits, o Reoperation rate, o Surgeon recommendation for reoperation, type of surgery, o Time of operation to time of retear, o Level of service (LOS): In the case of reoperation: How many nights did the subject spend in the hospital as a result of surgery? 0, 1, 2, 3, 4, 5, >5.
Safety Data	• All adverse events (AEs) and complications occurring from the time of subject enrollment until study termination or study completion including intra-operative adverse events and complications; • Device Deficiencies (DD)

STUDY SCHEDULE

Schedule of Event	Screening (Baseline) Day -60 to Day -1	Operation Day 0	2 Weeks Follow-up 14 ± 5 Days	6 Weeks Follow-up 42 ± 7 Days	3 Months Follow-up 91 ± 15 Days	6 Months Follow-up 182 ± 30 Days	M F up 6
Informed Consent	X[1]						
Inclusion/Exclusion	X[2]	X[2]					
Demographics/Medical History/BMI	X						
Operative/Discharge Data		X					
Oxford Shoulder Score	X				X	X	
WORC/C-WORC	X				X	X	
Constant-Murley Score	X				X	X	
Subjective Shoulder Value	X				X	X	
EQ-5D-5L	X				X	X	
Patient Satisfaction	X				X	X	
VAS Pain Score	X		X	X	X	X	
Return to Work Questionnaire	X		X[3]	X[3]	X[3]	X[3]	
Opioid Use			X[4]				
Reoperation			X	X	X	X	
MRI Assessment	X[2]				X	X	
Concomitant Medication/Therapy	X	X	X	X	X	X	
Safety Assessment (AEs, DDs)		X	X	X	X	X	
End of Study/Exit		X[3]	X[3]	X[3]	X[3]	X[3]	

[1] Date of Informed consent may be the same day or another day before screening giving the subject enough time to consider particip
[2] Inclusion/exclusion confirmation will be performed at the time of screening and study procedure to confirm subject meets eligibility c be confirmed on arthroscopy using a calibrated probe. X-Ray and MRI to confirm eligibility criteria must be within 12 months of surge
[3] As appropriate.
[4] Opioid use will be documented daily from day 0 to day 14.

3. CONTENTS

3.1 TABLE OF CONTENTS

3.2 LIST OF TABLES

3.3 LIST OF FIGURES

3.4 LIST OF ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
ADE	Adverse device effect
AE	Adverse event
AP	Anteroposterior
ARCR	Arthroscopic rotator cuff repair
ASADE	Anticipated serious adverse device effect
BMI	Body Mass Index
CAN	Canada
CH	Switzerland
Constant/CM	Constant-Murley
CRA	Clinical research associate
CRC	Clinical research coordinator
CTA	Clinical trial agreement
CV	Curriculum Vitae
C-WORC	Chinese version Western Ontario Rotator Cuff
DCE	Distal clavicle excision
DD	Device deficiency
DE	Germany
DICOM	Digital Imaging and Communications in Medicine
EC	Ethics committee
eCRF	Electronic case report form
EMA	European Medicines Agency
EQ-5D-5L	EuroQol 5 Dimension 5 Level
EU	European Union
FAS	Full analysis set

Abbreviation	Definition
FDA	US Food and Drug Administration
FR	France
FTT	Full-thickness tear
GCP	Good Clinical Practice
GDPR	Global Data Protection Regulation
HIPAA	Health Information Portability Accountability Act
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation of Technical Requirements For Pharmaceuticals For Human Use
ICMJE	International Committee of Medical Journal Editors
IEC	Independent Ethics Committee
IFU	Instructions for Use
IP	Investigational product
IRB	Independent Review Board
ISF	Investigator site file
ISO	International Organization for Standardization
ITT	Intention-to-treat
LOCF	Last observation carried forward
LOS	Level of service
LTFU	Lost to follow-up
MHRA	Medicines and Healthcare Products Regulatory Agency
ML	Mediolateral
MRCT	Massive rotator cuff tear
MRI	Magnetic resonance imaging
NDA	Non-disclosure agreement

Abbreviation	Definition
NMPA	National Medical Products Administration
N, n, or No.	Number
NSAID	Nonsteroidal anti-inflammatory drug
NZL	New Zealand
OSS	Oxford Shoulder Score
PDF	Portable document format
PG	Performance goal
PI	Principal Investigator
PLDLA	Poly-l/d-lactide
PMCF	Post market clinical follow-up
PP	Per protocol set
PRO	Patient-reported outcome
PT	Physical therapy
PTT	Partial-thickness tear
Q1	Lower quartile
Q3	Upper quartile
QA	Quality assurance
QC	Quality control
R&D	Research and development
RCT	Randomized controlled trial
SADE	Serious adverse device effect
SAE	Serious adverse event
SAP	Statistical analysis plan
SD	Standard deviation
SOP	Standard operating procedure
SAF	Safety analysis set

Abbreviation	Definition
TENS	Transcutaneous electrical nerve stimulation
UK	United Kingdom
US	United States
USADE	Unanticipated serious adverse device effect
VAS	Visual analog scale
WORC	Western Ontario Rotator Cuff

4. INTRODUCTION

4.1 BACKGROUND

Musculoskeletal disorders are some of the most common causes of disability in the United States (US) with approximately 50% of the adult population having experienced a chronic musculoskeletal condition lasting longer than 3 months. That doesn't affect only people in their ability to work and live full lives but also puts unnecessary burden on the healthcare system [1]. The direct cost of treating shoulder pain is approximately $7 billion annually and this figure excludes the indirect cost burden (i.e., missed work, lost productivity) [2]. After knee-related disorders, shoulders are the second most common joint causing chronic pain with an estimated 18.7 million adults affected [3]. The most common cause of shoulder pain is rotator cuff disease [4, 5]. In UK, rotator cuff abnormalities represent 70% of the shoulder-related general practitioner consultations [6]. In separate studies conducted in Sweden and Netherlands found that the productivity losses due to sick leave accounted for 84% and 47% respectively within 6 months of shoulder pain incidence [7, 8].

Rotator cuff disease are affecting millions of people globally and is prevalent in the elderly patient population [9, 10]. In a global systematic review and pooled analysis of 30 studies, Teunis et al. (2014) concluded that prevalence of rotator cuff abnormalities rose steeply with increasing age, from 9.7% in patients aged $\leqslant$20 years to 62% in patients aged $\geqslant$80 years [11].

Rotator cuff tears can be split into different types of tears: Partial Tear and Full-thickness tear [12]. Full-thickness tears which are also the focus of this study are characterized as interruption of tendon continuity [13] which can lead to considerable morbidity and impairment of activities of daily living.

There is considerable controversy among surgeons as to the best management of rotator cuff tears, resulting in variation in treatment pathways and guidelines [9]. However, the majority of full-thickness tear repairs (<74%) are performed arthroscopically [14, 15]. In terms of the type of

suture repair technique used, there was a trend for double-row repair to be used more frequently than single-row repair in full-thickness tears [16].

Arthroscopic rotator cuff repair has been reported to have a good clinical result but high retear rates [17, 18, 19]. The retear rate of surgically repaired full-thickness rotator cuff tears have shown to increase in association with preoperative tear size [15] and patient age [20]. In a large multi-center RCT in the UK, the overall healing rate of full-thickness tears was 122/217 (56%) at 12 months. When broken down by tear size, the retear rates were 34% (20/58), 36% (27/75), 47% (24/51), and 73% (24/33) for small, medium, large, and massive tears, respectively [21]. Revision rates are relatively high for full-thickness tears [17, 18, 19, 21]. These results suggest that the existing standard of care improves patient outcomes but may be associated with significant postoperative retears.

4.2 LITERATURE SUMMARY

Advances in treatment have occurred over the past several years in an effort to reduce retears and improve patients' overall postoperative outcomes [22]. Biologic scaffolds are a recent development in which surgeons are using to augment repairs of rotator cuff tears in patients with rotator cuff pathology. The REGENETEN Bioinductive Implant system is designed to support the body's natural healing response to support new tendon growth and disrupt disease progression [23, 24]. Derived from highly purified bovine Achilles tendon, it creates an environment that is conducive to healing [23, 24]. It is clinically proven to increase tendon thickness [23, 24] and delivers excellent outcomes in patient satisfaction, recovery, and pain scores [23]. The ability to induce new tissue formation and limit tear progression may represent a significant advancement in the treatment of rotator cuff tears [23].

4.3 STUDY PURPOSE

The purpose of this study is to assess the safety and efficacy of ARCR augmented with the REGENETEN in subjects requiring Full-thickness tear repair. The study results will be used to support post market clinical follow-up (PMCF) and reimbursement in relevant countries.

4.4 SAFETY CONSIDERATIONS

4.4.1 Indications

The REGENETEN Bioinductive implant System has different indications depending on the country and shown below:

Singapore, Hong Kong, United States: The REGENETEN Bioinductive Implant System (compromised of disposable instruments, a resorbable collagen implant, anchors to secure the scaffold to the underlying tendon and PEEK anchors to secure implant to the bone) is indicated for the management and protection of tendon injuries which there has been no substantial loss of tendon tissue.

China, United Kingdom, Germany, Switzerland, France, Canada, Australia, Netherlands, Japan New Zealand: The REGENETEN Bioinductive Implant System (compromised of disposable instruments, a resorbable collagen implant, anchors to secure the scaffold to the underlying tendon and PEEK anchors to secure implant to the bone) is indicated for the management and protection of rotator cuff tendon injuries which there has been no substantial loss of tendon tissue.

4.4.2 Contraindications

The Bioinductive Implant is not designed, sold, or intended for use except as described in the indications for use and is contraindicated in the following situation:

- The Bioinductive Implant is not indicated to replace damaged tendon or to reinforce the strength of any tendon repair.
- The Bioinductive Implant is not indicated for patients with a known history of hypersensitivity to bovine-derived materials.

Tendon Anchors are not designed, sold, or intended for use except as described in the indications for use and are contraindicated in the following situations:

- Tendon Anchors are not indicated to affix soft tissue to adjoining soft tissue or to reinforce the strength of any tendon repair.
- Tendon Anchors are not indicated where there is inadequate soft tissue support or an irreparable tendon system.

The Bone Anchors are not designed, sold, or intended for use except as described in the indications for use and are contraindicated in the following situations:

- Bone Anchors are not indicated to affix soft tissue to bone or to reinforce the strength of any tendon repair.
- Bone Anchors are not indicated where there is inadequate quality of bone.

The Bioinductive Implant Placement Cannula is not designed, sold, or intended for use except as described in the indications for use and is contraindicated in the following situation:

- The Bioinductive Implant Placement Cannula is not indicated for use with implants manufactured by any company other than Rotation Medical/Smith+Nephew.

The Tendon Stabilizing Guide is not designed, sold, or intended for use except as described in the indications for use and is contraindicated in the following situation:

- The Tendon Stabilizing Guide is not indicated for use with delivery instruments manufactured by any company other than Rotation Medical/Smith+Nephew.

The Tendon Marker is not designed, sold, or intended for use except as described in the indications for use.

The Manual Placement Instruments are not designed, sold, or intended for use except as described in the indications for use.

The Tendon Anchor Inserter is not indicated for use with tendon anchors manufactured by any company other than Rotation Medical/ Smith+Nephew.

The Bone Anchor Inserter is not indicated for use with bone anchors manufactured by any company other than Rotation Medical/Smith+Nephew.

4.4.3 Device Application Environment

REGENETEN System is intended for use by trained medical professionals in a hospital or clinical environment (equivalent to an orthopaedic operating room). The components in REGENETEN instrument kit will be used in a sterile environment.

All REGENETEN components (bioinductive implant, bioinductive implant delivery system, tendon marker, tendon stabilizing guide, manual placement instruments, bone anchors and tendon anchors) are provided sterile, non-pyrogenic, for single-use only, and are packaged in a dual sterile seal, tray-in-tray configuration as described in Instructions for Use (IFUs) and surgical technique documents provided by Smith+Nephew [25, 26, 27, 28, 29, 30, 31].

4.4.4 Potential Adverse Effects

As with any surgery, this surgery will cause risks. Potential complications of this type of surgery include but are not limited to anesthesia complications; incision healing problems; trauma and bleeding; infection; failure of the repair or retear; nerve damage; vascular damage; pain or stiffness that persists; tissue inflammation.

Warnings and Precautions stated in the IFU:

<u>Bioinductive Implant:</u>

- Do no reuse or re-sterilize.
- Do not use if the product package is damaged or opened.
- The Bioinductive Implant should not be applied until bleeding and infection are controlled.
- Application of the Bioinductive Implant does not modify the postoperative treatment. The surgeon must determine motion and strength requirements according to standard practice.

Tendon Anchors:

- Do not use if the temperature indicator on the product packaging is black.
- Do not use if the product package is damaged or opened.
- Do not reuse or re-sterilize.
- Excessive force applied during anchor deployment may result in damage to the tissue, to the material being fixated, to the anchor.
- Overlapping anchors may result in damage to the anchor.

Bone Anchors:

- Do not use if the product package is damaged or opened.
- Do not reuse or re-sterilize.
- Excessive force applied during anchor deployment may result in damage to the tissue, to the material being fixated, to the anchor.
- Inserting the Bone Anchor through excessive soft tissue and failing to engage the anchor into bone may not provide adequate fixation.

Bioinductive Implant Placement Cannula:

- Do not use if the product package is damaged or opened.
- Do not reuse or re-sterilize.
- The cannula should be tapped lightly when inserting into bone. Do not drive the frame that holds the Bioinductive Implant into the bone.
- Do not advance cannula against resistance or damage to device may occur.

Manual Placement Instruments:

- Do not use if the product package is damaged or opened.
- Do not reuse or re-sterilize.

- Excessive force applied during Bone Anchor deployment may result in damage to the material being fixated or to the anchor.
- Positioning the Bioinductive Implant with the Bone Anchor Inserter nubs may result in damage to the Bioinductive Implant.
- Driving the Bone Punch with a mallet before the bone punch is engaged with the Bone Anchor Inserter may result in an inability to advance the Bone Anchor into the holes.

Tendon Stabilizing Guide:

- Do not use if the product package is damaged or opened.
- Do not reuse or re-sterilize.
- The guide wire should be tapped lightly when inserting it into bone. Do not drive the shaft of the Tendon Stabilizing Guide into the bone.
- The tip of the guide wire is sharp. Take proper care for handling and disposal of a sharp instrument.

Tendon Marker:

- Do not use if the product package is damaged or opened.
- Do not reuse or re-sterilize.
- The Tendon Marker is sharp. Take proper care for handling and disposal of a sharp instrument.

Tendon Marker and Tendon Stabilizing Guides are not mandatory to be used.

5. OBJECTIVE(S)

5.1 PRIMARY OBJECTIVE

The primary objective of this study is to assess the cumulative 6 months retear rate after full-thickness ARCR augmented with REGENETEN versus ARCR alone.

5.2 SECONDARY OBJECTIVE(S)

To assess safety and efficacy of full-thickness ARCR augmented with REGENETEN versus ARCR alone.

5.3 OTHER OBJECTIVE(S)

To assess safety and efficacy of full-thickness ARCR augmented with REGENETEN versus ARCR alone in at-risk-groups (diabetics, smokers, hypertensive, heavy laborer, age > 65 years);

To assess safety and efficacy of full-thickness ARCR augmented with REGENETEN in revision repair group (observational);

To generate health economic evidence.

5.4 CLAIMS

The REGENETEN Bioinductive Implant creates an environment that facilitates rotator cuff tendon repair [23, 24, 32, 33], supports the body's natural healing response to induce new tendon-like tissue growth and disrupt disease progression [23, 24, 33, 34, 35] and indicates a reduction in retear rates compared to standard of care [17, 24,].

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6. INVESTIGATIONAL PRODUCT(S)

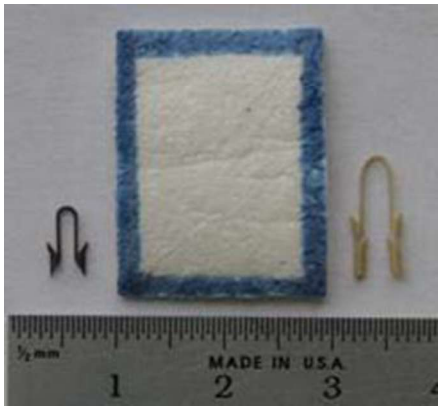
6.1 IDENTIFICATION

6.1.1 Investigational Product

6.1.1.1 *Description*

The REGENETEN Implant System is a manual arthroscopic instrument that is used to assist in the arthroscopic delivery and placement of the Bioinductive Implant and is comprised of disposable instruments, a resorbable collagen implant, and anchors to secure the scaffold to the underlying tendon and bone (Figure 1).

Figure 1 REGENETEN Bioinductive Implant and Anchors



Shown from the left to right, Tendon Anchor,
Bioinductive Implant and Bone Anchor

The REGENETEN Bioinductive Implant is a bioabsorbable implant that provides a layer of collagen over injured tendons. After hydration, the implant is an easy-to-handle, pliable, nonfriable, porous collagen sheet. The REGENETEN Bioinductive Implant is available in size large for the study. 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 6 to 12 months.

The REGENETEN Bioinductive Implant Delivery System is provided sterile, for single-use only in a dual sterile seal, tray-in-tray configuration.

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 disposable instrument system (Figure 2) includes the arthroscopic implant delivery instrument, tendon anchor delivery instruments, and bone anchor delivery instruments. There is also tendon markers and a tendon stabilizing guide that can be used if necessary but is not mandatory. The tendon guide wire is a useful tool for new and infrequent users.

Figure 2 REGENETEN Disposable Instruments

Implant delivery instrument which comes with patch pre-loaded

Bone Anchor inserter

Tendon Anchor Inserter, Cannula, Tendon Anchors with Cartridge

The placement instruments include the Cannula Sleeve, Cannulas, Tendon Anchor Inserter, Bone Anchor Inserter, and Bone Punch. The Cannula Sleeve, Cannulas, and Tendon Anchor Inserters are used to place and deploy the Tendon Anchors. The Bone Anchor Inserter and Bone Punch are used to place the Bone Anchors.

The Tendon Marker consists of a hypodermic needle that contains an internal anchor which advances to maintain the position of the marker. After insertion of the Tendon Marker, a slide on the handle is advanced to extend an anchor out of the shaft of the needle. Tendon Marker should only be used if available but are not mandatory.

The Tendon Stabilizing Guide consists of a flexible guide wire that is housed within the shaft of the instrument. After insertion of the guide wire into bone, the shaft of the instrument is removed and the guide wire is used to assist in guiding the Arthroscopic Delivery System to the proper location. The Tendon Stabilizing Guide is optional and can be used by new and infrequent users but is not mandatory.

Generation	Part#	Implant & Instrument SKU
US Gen 3.5	4566 4403 2504-1 4402 (1) 4173-1	Bioinductive Implant with Arthroscopic Delivery System, Large Bone Anchors with Delivery System Advanced Tendon Anchors (8) Tendon Stabilizing Guide Tendon Marker (2)
International Gen 3.0*	72205198 72205200 72205201 72205206 72205202	Large Arthroscopic Bioinductive Implant Bone Anchors (3) with Arthroscopic Delivery System Tendon Anchors (8) Tendon Stabilizing Guide (1) Tendon Marker (2)
International Gen 3.5	72205307 72205205 72205201 72205206 72205202	Bioinductive Implant with Arthroscopic Delivery System, Large Bone Anchors with Delivery System Advanced Tendon Anchors (8) Tendon Stabilizing Guide (1) Tendon Marker (2)

A complete description of the REGENETEN™ System is available in the IFUs and surgical technique documents provided by Smith+Nephew:

	Gen 3.5 US	Gen 3.5 Intl	Gen 3.0
Part	IFU Version	IFU Version	IFU Version
Bioinductive Implant	02/2020 10601445 Rev. D	02/2020 10601447 Rev. B	02/2020 10601401 Rev. C
Tendon Anchors	01/2019 10601404 Rev. B	02/2020 10601391 Rev. C	02/2020 10601391 Rev. C
Bone Anchors	01/2019 10601405 Rev. B	02/2020 10601392 Rev. C	02/2020 10601392 Rev. C

Tendon Stabilising Guide	10/2018 10601407 Rev. A	02/2020 10601394 Rev. C	02/2020 10601393 Rev. C
Tendon marker	10/2018 10601408 Rev. A	02/2020 10601395 Rev. C	02/2020 10601395 Rev. C
Manual Placement Instruments	05/2019 10601411 Rev. B	02/2020 10601399 Rev. D	02/2020 10601399 Rev. D
Bioinductive Implant Delivery System	02/2020 10601444 Rev. D	02/2020 10601448 Rev. B	02/2020 10601393 Rev. C

The IFUs may be updated periodically, in which case, the latest version will be used as a guide.

6.1.1.2 *Manufacturer*

The REGENETEN Bioinductive Implant manufacturer is:

Smith+Nephew Inc.
150 Minuteman Road
Andover, MA 01810
USA

6.1.1.3 *Intended Purpose*

The REGENETEN Bioinductive Implant is indicated for the management and protection of rotator cuff tendon injuries in which there has been no substantial loss of tendon tissue.

Tendon Anchors are indicated for fixation of prosthetic material to soft tissues in various minimally invasive and open rotator cuff tendon surgical procedures, such as the management and protection of tendon injuries in which there has been no substantial loss of tendon tissue.

The Bone Anchor is indicated for fixation of soft tissue grafts during rotator cuff repair.

The Bioinductive Implant Delivery Instrument is indicated for arthroscopic delivery of the REGENETEN Bioinductive Implant into the subacromial space.

The Manual placement instruments are orthopedic, manual, surgical instruments used during the placement of Bioinductive Implant, Bone Anchors, and Tendon Anchors.

The Tendon Stabilizing Guide is indicated for assisting in the arthroscopic placement and location of the Bioinductive Implant in the subacromial space. The Stabilizing Guide is not mandatory to be used.

The Tendon Marker is indicated for assisting in the arthroscopic placement and location of the Bioinductive Implant in the subacromial space. The Tendon Market is not mandatory to be used.

6.1.2 Comparator Treatment

Arthroscopic rotator cuff repair (ARCR) alone.

6.1.3 Ancillary Products

Arthroscopic measuring probe to confirm the tear size for eligibility (reusable).

6.2 PRODUCT USE

Each device is packaged with Instructions for Use and provided with surgical technique to ensure that the device is used properly and for the intended purpose as described in the specifications or IFUs or Investigator's Brochure (IB) (for China only). It is the Investigator's responsibility to ensure adherence to the IFU. Investigators must go through all steps of procedure at least once using all provided instruments on a test case, either in Arthroscopy Wet Lab or similar environment or real patient before enrollment. Investigators will be trained on the Investigational Product beforehand.

Recommended post-operative physical therapy guidelines for ARCR augmented with REGENETEN:

- Shoulder immobilization for 4-8 weeks,
- passive Range of Motion (PROM) begin at surgeon's discretion,

- active Range of Motion (AROM) begin after sling is discontinued,
- no lifting >1-2 kg for 12-16 weeks,
- strengthening beginning after 12-16 weeks.

6.3 PACKAGING AND LABELING

Packaging and labeling will be prepared to meet regulatory requirements. Package integrity and labelling should be verified prior to use of the product.

6.3.1 Labeling of Investigational Product

The REGENETEN Bioinductive Implant System is an investigational product in China. Addition labels will be included on the commercial packaging to specify that the product is for clinical trial use only in order to meet regulatory requirements for use of investigational devices.

In the United States, Singapore, Hong Kong, Europe, Canada, Australia and New Zealand, the REGENETEN Bioinductive Implant System is a commercial product and will be used as cleared/licensed. Product labeling will be the same as per standard commercial packaging.

In Japan, the REGENETEN Bioinductive Implant System is a product that will be cleared/registered before study enrollment. The product will only be used either through market approval and/or special access approval.

For China only, labels on the REGENETEN Bioinductive Implant System contain the following information in addition to standard commercial packaging:

- Study number,
- Clinical Investigation Use Only.

Any regulatory status updates that may impact labeling requirements moving forward will be managed via TMP-CD-18-01 Investigational Products/Ancillary Products/Supplies Protocol.

6.4 PRODUCT ACCOUNTABILITY PROCEDURES

This study is a post-market study in Unites States, Singapore and Hong Kong and the products will only be used when cleared/registered in Australia, New Zealand, Europe and Canada. However, the sponsor provides the study sites with the REGENETEN System. Therefore, a site level accountability log will be completed for all supplied products at each study site for compliance. The investigational site will maintain an inventory of the Investigational Device. The Sponsor or its designee will provide a log(s) to facilitate Investigational Device inventory control. The log will contain details of receipt, use, returns etc. of Investigational Devices. All Investigational Device accountability logs must be retained in the Investigator Site File (ISF). These records must be available for inspection by the Sponsor, its designees, or by regulatory agencies at any time. Investigational Device Management Instructions will be provided by the Sponsor to the site detailing all additional forms that might need completion (e.g., confirmation of receipt) for Investigational Device control.

The study monitor will ensure that the procedures and records are in place for the appropriate reconciliation of all Investigational Devices. As part of monitoring, the study monitor will check that site personnel are following the proper procedures for accountability and completing all necessary documentation.

6.5 SURGICAL TECHNIQUE

The REGENETEN System should be used according to the surgical technique and IFUs provided with the investigational device per Section 6.1.1.1

Investigators participating in this study must be proficient in arthroscopic rotator cuff repairs.

In addition, prior to implantation of the REGENETEN System, all principal surgical investigators involved in the REGENETEN procedure must be trained with respect to surgical technique, use of the device and surgical approach, so as to ensure consistency in the implementation of the clinical trial protocol and the use of the investigational device. Investigators must go through all

steps of procedure at least once, using all provided instruments on a test case, either in Arthroscopy Wet Lab or similar environment or real patient before enrollment.

7. SUBJECT ENROLLMENT AND WITHDRAWAL

7.1 SUBJECT POPULATION

Up to 300 subjects will be enrolled into the study in up to 30 sites in the United States, Canada, United Kingdom, France, Switzerland, Germany, China, Singapore, Hong Kong, Australia and New Zealand, Japan and Netherlands:

- 130 ARCR augmented with REGENETEN;
- 130 ARCR alone;
- Up to 40 revision repair subjects will be recruited into one additional single group (ARCR supplemented with REGENETEN in recurrent tears (full-thickness tears [large or massive]).

Subjects selected for this clinical trial are in need of full-thickness rotator cuff tear repair or revision repair (for revision repair subject group only).

7.2 INCLUSION CRITERIA

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

1. Subject requires Arthroscopic rotator cuff repair (ARCR).
2. Subjects with a diagnosis of a symptomatic primary or recurrent (revision repair subject group), large or massive tear (⩾ 3 cm AP/ML) of the supraspinatus and/or infraspinatus tendons amenable to repair. For screening purposes, a ≥ 2 cm AP/ML tear as measured on MRI will be eligible to proceed to the operative visit but will have to be confirmed as ≥ 3 cm on arthroscopy using a calibrated probe to proceed.
3. Subject is > 40 years of age (no upper limit).
4. Subject provides written informed consent for study participation using an Independent Ethical Committee (IEC) / Institutional Review Board (IRB) approved consent form.

5.	Subject is willing and able to participate in required follow-up visits and is able to complete study activities.

7.3 EXCLUSION CRITERIA

Any of the following criteria will disqualify a potential subject from participation in the study:

1.	Subjects who are unable to tolerate magnetic resonance imaging (MRI), due to psychiatric or medical contraindications.
2.	Subjects with Samilson-Prieto osteoarthritis > 2.
3.	Subjects with current or prior infection of the ipsilateral shoulder.
4.	Subjects with known hypersensitivity to bovine-derived materials.
5.	Subjects with known inflammatory arthropathy, history of inflammatory arthropathy, or chronic joint disease.
6.	Subjects with prior shoulder surgery (not including rotator cuff repair [revision repair subject group only], biceps tenodesis/tenotomy, distal clavicle excision [DCE], subacromial decompression).
7.	Subjects with an irreparable or partially reparable rotator cuff tear.
8.	Subjects with a subscapularis tear requiring repair.
9.	Subjects requiring a concomitant labral fixation procedure.
10.	Subjects requiring a concomitant os acromiale fixation procedure.
11.	Subjects with glenohumeral joint instability (multiple dislocations/subluxations).
12.	Subjects with a subacromial or intra-articular injection within 3 months prior to surgery.

13. Subjects with condition(s) that contraindicate or complicate outcome of ARCR e.g., > Hamada 3 rotator cuff arthropathy on X-ray, Goutallier atrophy > Grade 3, proximal humeral fracture or scapular fracture, avascular necrosis of the humeral head or glenoid, history of immunodeficiency disorders, history of chronic inflammatory disorders, oral or injected steroid use in last 4 weeks.
14. Subjects who are pregnant or breast feeding.
15. Subjects who are currently involved in any litigation or workers compensation claims.
16. Subjects who are enrolled, or plan to enroll, in another clinical trial during this study that would affect the outcomes of this study.
17. Subjects with a history of noncompliance with medical treatment, PT/rehabilitation, or clinical study participation.
18. Subject who, in the opinion of the Investigator, has an emotional or neurological condition that would pre-empt their ability or willingness to participate in the study including mental illness, mental retardation, and drug or alcohol abuse.
19. Subjects who do not meet the indication or are contraindicated according to specific Smith+Nephew REGENETEN System's IFUs.
20. Subject that meets the definition of a Vulnerable Subject per ISO14155:2020 Section 3.44.

7.4 SCREENING

The Investigators will continuously screen subjects during recruitment, which will continue until a total of up to 300 subjects (130 ACRC augmented with REGENETEN, 130 ARCR alone and up to 40 revision repair subjects) are recruited. It remains the decision of the Sponsor to increase or decrease enrollment, as necessary.

Once a subject has completed the informed consent procedure and signed the Informed Consent Form (IFU), the Principal Investigator (PI), or delegated study research staff, can complete the

screening process to determine whether they meet all inclusion and none of the exclusion criteria. This might be the same day or another day, giving the subject enough time to consider participation.

Participating study sites are required to document all screened subjects considered for inclusion in this study on a Screening and Enrollment Log. If a subject is excluded from the study, the reasons for exclusion will be noted on the Screening and Enrollment Log.

In the event that a subject has the need for sequential bilateral ARCR augmented with REGENETEN or standard arthroscopic rotator cuff repair (ARCR), both shoulders may be enrolled in the study after informed consent process. Post-operative physical standard of care therapy guidelines and restrictions as stated in section 6.2 Product Use should be maintained for best outcome.

In the event that operation is delayed and outside Screening Visit Day time window, screening process has to be repeated to confirm eligibility.

7.5 INFORMED CONSENT

Before conducting any study related procedures, informed consent shall be obtained from all participating subjects according to ISO14155:2020 guidelines or applicable NMPA requirements in China. This can be done on the same day as the screening eligibility confirmation or another day giving the subject enough time to consider participation. Investigators are responsible for obtaining and documenting the voluntary informed consent as well as obtaining the IRB/EC approval for the Informed Consent Form (ICF) and any other written information provided to the subject.

The ICF and any other written information provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's continued consent. All revised ICFs must have written and dated IRB/EC approval prior to use.

The purpose and nature of the study and the potential risks and benefits known as described in the written ICF should be explained to the subject in their native language.

The subject will have sufficient opportunity to consider participation in the study. The subject, will **read**, **sign**, and **personally date** the IRB/EC-approved informed consent document(s), indicating their consent for enrollment. Additionally, the individual who obtains consent from the subject will sign and date the informed consent document. The communications with the subject regarding informed consent process (initial and subsequent) will be documented in the medical record. Subjects should receive a copy of the initial signed and dated ICF (in their native language) and any revised ICFs during the study.

ICFs will comply with Health Information Portability Accountability Act (HIPAA) regulations the EU Global Data Protection Regulation (GDPR), The Privacy Act 1988 in Australia and the New Zealand Privacy Act 1993 and or applicable national regulations and laws.

7.6 ENROLLMENT

Every subject that has signed consent, met inclusion/exclusion criteria, and received either ARCR augmented with REGENETEN or ARCR alone will be considered enrolled in the study.

In the event that a subject has a sequential bilateral ARCR augmented with REGENETEN or ARCR alone, both shoulders treated after informed consent can be enrolled in the study.

A subject that has been randomized into the ARCR augmented with REGENETEN arm and with a diagnosis of a recurrent large or massive tear will not be enrolled into the revision repair subject group. However subjects that were randomized into the ARCR alone arm can be enrolled into the revision repair subject group in case of recurrent large or massive tears.

Subjects that provided informed consent but do not receive the study treatment for any reason will be considered as screen failure.

7.7 LOST TO FOLLOW-UP

Some actively enrolled subjects may not return for follow-up exams due to a variety of reasons. Study personnel must make reasonable efforts to contact the subject and document the following contact attempts prior to declaring a subject to be lost to follow-up (LTFU): the subject has been contacted according to the site's policies, but no less than 2 documented phone contacts and 1 certified letter without response. Copies of all attempts to reach the subjects per regular mail or email and/or the attempts to contact the subject via other means should be documented and that documentation should be kept with the subject's source documents at site. A subject will be considered LTFU if he/she does not appear for the scheduled study visit for 2 consecutive visits and does not return for a final visit, and study personnel are unable to contact the subject.

7.8 WITHDRAWAL

7.8.1 Withdrawal from Treatment

Subjects may be withdrawn from having the study device implanted at a date close to surgery or during surgery for the following reasons:

- At the discretion of the Investigator due to:
  - A change in treatment being clinically warranted
  - An adverse event
  - Any other significant reason identified by the Investigator.

If at any point during the study, the study device needs to be revised for any reason intraoperative data from the reoperation will be collected according to the Reoperation Case Report Form (CRF).
Reoperation cases will not be enrolled into the revision repair subject group if the subjects has been randomized previously into the ARCR augmented with REGENETEN arm. However subjects that have been randomized into the ARCR alone arm can be enrolled into the Revision Repair subject group.

Following reoperation subjects shall continue to have follow-up visits in order to monitor the subject's health status only. Potential data following the reoperation will not be included as study data but presented separately as safety data.

7.8.2 Withdrawal from Study

The Investigator may withdraw subjects from the study for many reasons, including but not limited to the following:

- subject noncompliance (e.g., did not follow instructions)
- subject lost to follow-up
- safety reasons (e.g., AEs, ADEs, SAEs)
- if the Investigator or the Sponsor stops the study for any reason and decides to withdraw subject(s) from the study
- concurrent illness
- any other significant reason identified by the Investigator.

For each case, information will be obtained in the source document and the eCRF, detailing circumstances leading to the withdrawal. Data collected upon point of withdrawal will be included as study data.

Subjects who drop out or are withdrawn will not be re-entered into the study at a later date.

7.8.3 Subject's Withdrawal of Consent to Participate in Study

Study participation is voluntary, and subjects may withdraw at any point during the study without giving their reason for doing so. Where subjects withdraw consent, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's privacy. The reason for withdrawal will be recorded in the eCRF and source documents.

7.8.4 Use of Data Following Withdrawal

In cases where the subject withdraws consent, the data collected up to the point of withdrawal may be used, but no additional data for that subject may be collected.

8. STUDY DESIGN

8.1 STUDY DESIGN

This study is a prospective, multi-center, randomized, controlled clinical study intended to evaluate the safety and efficacy of ARCR augmented with REGENETEN versus ARCR alone in the treatment of full-thickness tears of the rotator cuff (large or massive ≥3 cm in AP or ML according to Cofield classification) including a single group of revision repair subjects. This clinical trial is supporting the registration of a medical device in China and will support the post market clinical follow up in Europe, Australia and New Zealand after market approval and reimbursement to relevant countries and therefore is required to follow the requirements of relevant regulations issued by NMPA, PMDA MHRA, EMA, TGA, Medsafe, HealthCanada or FDA.

Study duration is planned to take approximately 42 months (18-month enrollment and 24-month follow-up).

The subjects meeting the inclusion/exclusion criteria specified in the protocol will receive either ARCR augmented with REGENETEN or ARCR alone. Subjects enrolled into the revision repair subject group will receive ARCR augmented with REGENETEN.

For primary hypothesis a total of up to 260 subjects (130 ARCR augmented with REGENETEN; 130 ARCR alone) and additionally up to 40 revision repair subjects if applicable, for sub-group analysis are planned to be included in up to 30 study sites. Using a group sequential design, a formal interim analysis will be conducted once 50% of the planned 260 subjects reach the 6-month follow-up at which point a sample size re-estimation will be performed along with options considered to terminate early for efficacy or futility or to increase the sample size.

The clinical follow-up evaluation will be performed preoperatively (Baseline), 2 weeks, 6 weeks, 3, 6, 12, and 24 months after surgery, respectively.

Figure 8.1-1 Study Flowchart - Main Arms

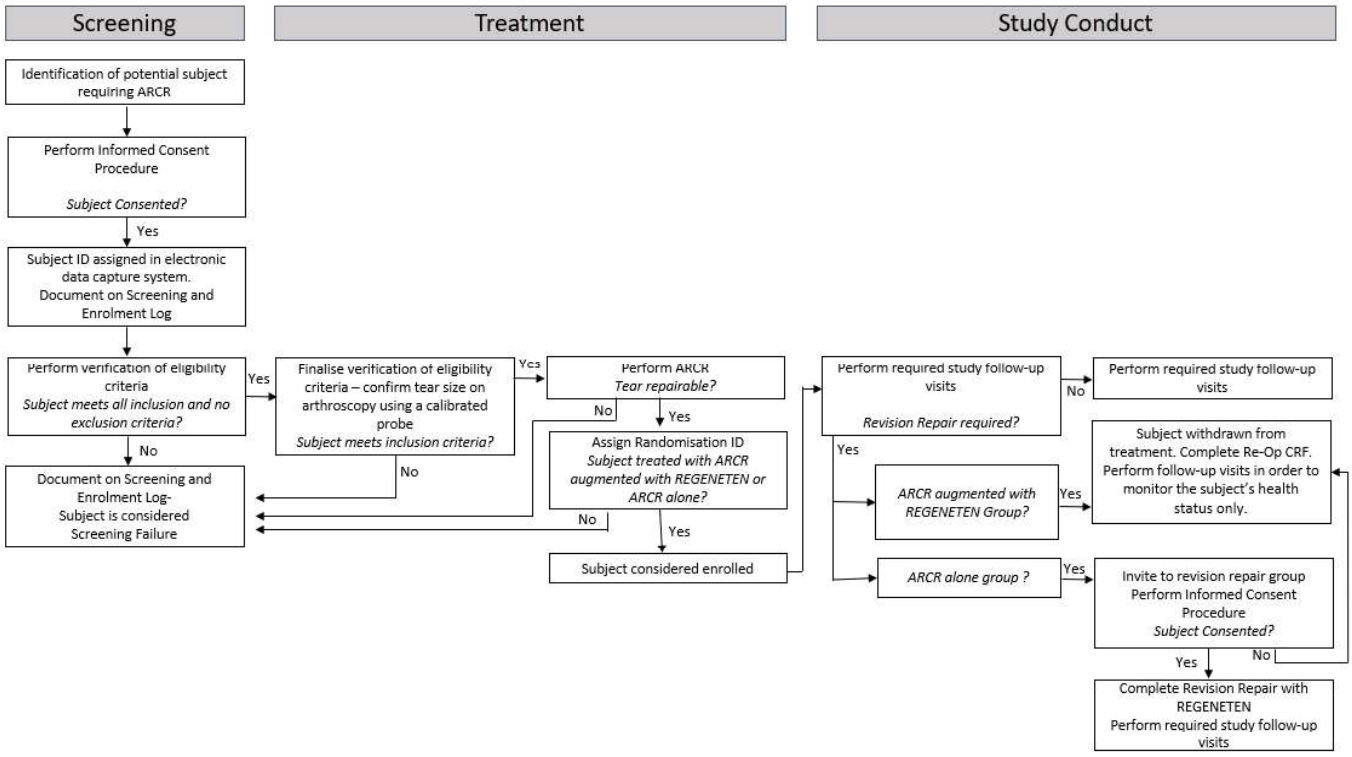
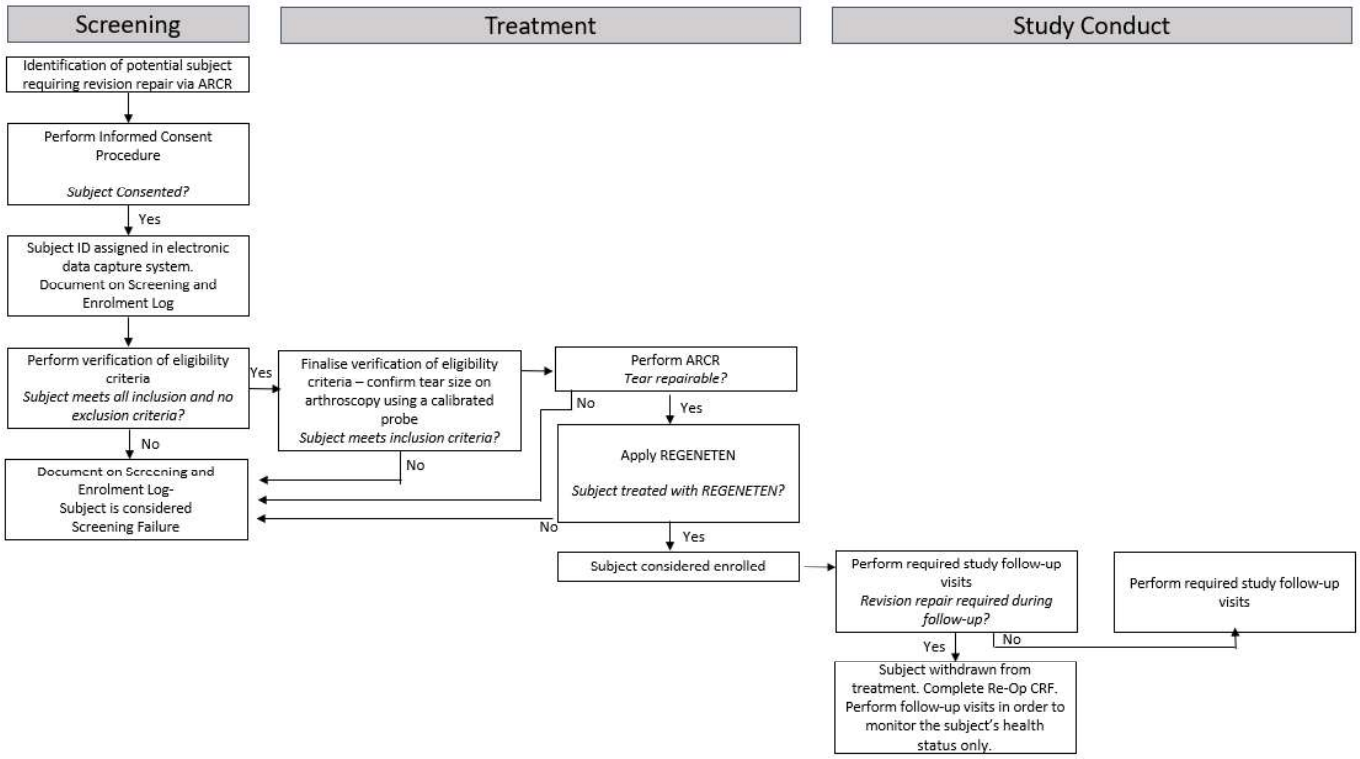


Figure 8.1.2 – Revision Repair Arm



8.2 ALLOCATION AND BLINDING

8.2.1 Treatment Allocation

Enrolled primary subjects entering the randomized controlled part of the study will be randomized to either ARCR augmented with REGENETEN or ARCR alone. The randomization will be a 1:1 blocked scheme using an external online system to conceal allocation. The online system will assign a Randomization ID only after the subject meets all eligibility criteria. Details of the blocked scheme will be presented within the SAP.

Enrolled revision repair subjects will not be randomized. All subjects will be treated with ARCR augmented with REGENETEN.

8.2.2 Blinding

This is not a blinded study.

8.3 STUDY ENDPOINTS

8.3.1 Primary Endpoint

The primary study endpoint is the cumulative 6 months retear rate after full-thickness ARCR augmented with REGENETEN versus ARCR alone. Failure is defined as Sugaya Type IV or V retear/recurrence (full-thickness discontinuity seen on both coronal and oblique sagittal MRI images).

8.3.2 Secondary Endpoints

The secondary study endpoints are:

- The cumulative 3, 12, and 24 months retear rate after full-thickness ARCR augmented with REGENETEN (confirmed on MRI) versus ARCR alone;
- Overall performance of full-thickness ARCR augmented with REGENETEN versus ARCR alone at Baseline and at 3, 6, 12 and 24 months assessed by:
    - Oxford Shoulder Score (OSS),
    - Western Ontario Rotator Cuff (WORC)/Chinese version WORC (C-WORC) Index,
    - Constant-Murley Score,
    - Subjective shoulder value (SSV),
    - EuroQol 5 Dimension 5 Level (EQ-5D-5L) Score,
    - Patient satisfaction Questionnaire,
    - Pain, Visual analog scale (VAS) Score (additionally at baseline, 2 weeks, 6 weeks, 3 months and 6 months);
- MRI Tendon Findings in ARCR augmented with REGENETEN versus ARCR alone postoperatively at Baseline, 3, 6, 12 and 24 months including:
    - Sugaya score,

- Goutallier grading,
- Total tendon thickness, tendon length,
- Size of retear (anteroposterior [AP]/mediolateral [ML]),
- Shape of retear;

- Outcome of Return to Work Questionnaire in ARCR augmented with REGENETEN versus ARCR alone (additionally at 2 and 6 weeks);
- Cumulative duration of opioid use in ARCR augmented with REGENETEN versus ARCR alone at 2 weeks postoperatively;
- Total operative time in ARCR augmented with REGENETEN versus ARCR alone;
- Sling type and mobilization time in ARCR augmented with REGENETEN versus ARCR alone.

8.3.3 Other Endpoints

Other Study Endpoints are:

- To assess safety and efficacy as summarized in secondary endpoints in at-risk groups (diabetics, smokers, hypertensive, heavy laborer, age > 65 years) after full-thickness ARCR augmented with REGENETEN versus ARCR alone;
- To assess safety and efficacy as summarized in secondary endpoints in revision repair subjects group after full-thickness ARCR augmented with REGENETEN;
- To collect health economic evidence in ARCR augmented with REGENETEN versus ARCR alone:
  - Aggregate health care utilization costs,
  - Number of unscheduled visits,
  - Reoperation rate,
  - Reoperation type, type of surgery,
  - Time of baseline operation to time of reoperation,
  - Level of service (LOS): In the case of reoperation: How many nights did the subject spend in the hospital as a result of the surgery? 0, 1, 2, 3, 4, 5, >5.

8.3.4 Safety Endpoints

Safety endpoints include the collection of the following events:

- All adverse events (AEs) occurring from the time of subject enrollment until study termination or study completion including intra-operative adverse events,
- Device Deficiencies.

8.4 METHODS USED TO MINIMIZE BIAS AND MAXIMIZE VALIDITY

8.4.1 Multi-center

The samples from multi-center are more representative than those from single center, and the latter may lead to deviation of study results due to its systematic errors. The required number of cases can be enrolled in a shorter period, and the samples are more representative and the results are more generalizable.

In this study, subjects will be enrolled at multiple sites, utilizing up to 30 sites globally. This will reduce the effect of observer bias that might arise at any one investigational site as well as maximize the diversity of subjects treated.

8.4.2 Randomization

Subjects meeting all inclusion/exclusion criteria will be randomly allocated into any of two study groups in a 1:1 allocation ratio. Blocked randomization will be used to balance this allocation ratio by investigational site and overall. Randomization will be conducted through an online system. Randomization will occur and a treatment will be assigned only when subject has signed the ICF and satisfied all study eligibility criteria.

8.4.3 Measurement Consistency

For the primary endpoint (cumulative 6 months retear rate on MRI) of each site, consistency measurement should be performed. Failure is defined as Sugaya Type IV or V retear/recurrence

(full-thickness discontinuity seen on both coronal and oblique sagittal MRI images).There is a preference for 3.0Tesla MRI imaging, wherever available. 1.5Tesla systems will only be approved if 3.0Tesla MRI is not available. Images will be obtained as described in the image acquisition protocol (IAP).

8.4.4 Imaging Evaluation

For further details of imaging evaluation, refer to Image Review Guidelines. Imaging observation indicator is a reasonable and necessary indicator to evaluate the success rate of retear rates, MRI grading, and tendon thickness. To reflect the importance of imaging change over time, measurements should be made before surgery as well as 3, 6, 12, and 24 months after surgery.

8.4.5 Screening of Subjects

In order to eliminate selection bias, the Investigators will continuously screen all subjects. Subject recruitment continues until the completion of recruitment of 260 RCT subjects and up to 40 revision repair subjects.

8.4.6 Investigator Training

Prior to the clinical trial, the clinical research associate (CRA), coordinating with the persons in charge of the study sites, will train the Investigators on the study protocol, making sure they are familiar with the use of investigational medical device, and implement subject enrollment strictly in accordance with the inclusion criteria and exclusion criteria, conduct relevant examinations according to the protocol requirements, also master all new device-related information found during the clinical trial, thus to minimize the interferential factors.

8.4.7 Clinical Trial Monitoring

Detailed monitoring requirements will be documented in the Clinical Monitoring Plan for this study. The monitor is selected and appointed by the Sponsor to conduct a regular on-site monitoring visit, making sure that all contents in the study protocol are strictly followed. The

source documents are inspected to ensure consistent contents with the eCRF. Monitoring visits will be conducted at the start, during and at the closure of the clinical study in accordance with Smith+Nephew standard operating procedures (SOPs) and the Clinical Monitoring Plan.

9. STUDY PROCEDURES

9.1 VISITS AND EXAMINATIONS

9.1.1 Summary

For a summary of the required procedures by visit, refer to the Study Schematic Table 9.1.1-1: Study Procedures by Visit.

Table 9.1.1-1: Study Procedures by Visit

Schedule of Event	Screening (Baseline) Day -60 to Day -1	Operation Day 0	2 Weeks Follow-up 14 ± 5 Days	6 Weeks Follow-up 42 ± 7 Days	3 Months Follow-up 91 ± 15 Days	6 Months Follow-up 182 ± 30 Days	M F up 6
Informed Consent	X[1]						
Inclusion/Exclusion	X[2]	X[2]					
Demographics/Medical History/BMI	X						
Operative/Discharge Data		X					
Oxford Shoulder Score	X				X	X	
WORC/C-WORC	X				X	X	
Constant-Murley Score	X				X	X	
Subjective Shoulder Value	X				X	X	
EQ-5D-5L	X				X	X	
Patient Satisfaction	X				X	X	
VAS Pain Score	X		X	X	X	X	
Return to Work Questionnaire	X		X[3]	X[3]	X[3]	X[3]	
Opioid Use			X[4]				
Reoperation			X	X	X	X	
MRI Assessment	X[2]				X	X	
Concomitant Medication/Therapy	X	X	X	X	X	X	
Safety Assessment (AEs, DDs)		X	X	X	X	X	
End of Study/Exit		X[3]	X[3]	X[3]	X[3]	X[3]	

[1] Date of Informed consent may be the same day or another day before screening giving the subject enough time to consider particip
[2] Inclusion/exclusion confirmation will be performed at the time of screening and study procedure to confirm subject meets eligibility c be confirmed on arthroscopy using a calibrated probe. X-Ray and MRI to confirm eligibility criteria must be within 12 months of surge
[3] As appropriate.
[4] Opioid use will be documented daily from day 0 to day 14.

9.1.2 Screening (Baseline) Visit 1 (Day - 60 to Day -1)

1. Obtain written informed consent from the subject as detailed in Section 7.5. This might be the same day or another day before screening giving the subject enough time to consider participation.

   ----- Do not proceed until consent has been obtained -----

2. Assign the subject a study ID in electronic data capture system.
3. Screen the subject for protocol inclusion/exclusion criteria and surgery indication. Any subject who signs an informed consent but fails to meet the eligibility criteria is considered to be a Screen Failure.
4. Obtain Demographic information, BMI and medical/surgical history, including information on all concomitant medications/therapies that is considered relevant.
5. Obtain MRI and X-Ray (must be within 12 months of surgery) and confirm eligibility criteria. The tear size measurement may be provided by the radiography report or as determined by the Investigator.
6. Complete the Constant-Murley Questionnaire (Physician/Examiner completed portion).
7. Have the subject complete the OSS Questionnaire.
8. Have the subject complete the WORC/C-WORC Questionnaire.
9. Have the subject complete the subjective part of Constant-Murley Questionnaire.
10. Have the subject complete the SSV Questionnaire.
11. Have the subject complete the EQ-5D-5L Questionnaire.
12. Have the subject complete Patient satisfaction Questionnaire.
13. Have the subject complete Work Status for Return to Work Questionnaire.
14. Have the subject complete VAS pain questionnaire.

15. Instruct the subject to return for the Operation Visit on the scheduled date.

9.1.3 Operation – Visit 2 (Day 0)

1. Query subject regarding any changes in general health and the use of concomitant medications (e.g. oral or injected steroid use in last 4 weeks).
2. Confirm eligibility based on arthroscopic visualization of the tear and confirm size using a calibrated probe.
3. Assign the Randomization ID per randomization schedule. Screen Failure subjects should not be assigned randomization numbers, but their demographic information must be captured in the appropriate CRF with the reason for screen failure specified.
4. Commence operation as per the randomization schedule.
5. Collect operative and discharge data (including implant information) according to the CRF.
6. If any AEs, ADEs or DD are observed or reported, they must be recorded as instructed in Section 12 – Adverse Events and Device Deficiencies.
7. Instruct the subject on proper postoperative care/procedures as per standard of care and/or Sponsor's recommendation given in section 6.2 Product Use.
8. Instruct the subject to document Opioid Use over the next 2 weeks on a daily basis.
9. Instruct the subject on follow-up procedures, including returning the treatment facility for follow-up at Visit 3 in 14 (± 5) days.

9.1.4 Postoperative Follow-up Visit 3 (2 Weeks [14 days ± 5 days])

1. Query subject regarding any changes in general health and the use of concomitant medications. If any AEs, ADEs or DDs are observed or reported, they must be recorded as instructed in Section 12 – Adverse Events and Device Deficiencies.
2. Have the subject complete VAS pain score.
3. Have the subject complete the Return to Work Questionnaire (if appropriate).

4.	Collect daily Opioid Use documentation from subject and enter into eCRF.
5.	If any Reoperation occurred complete reoperation CRF.
6.	Complete End of Study/exit information (if appropriate).
7.	Instruct the subject on follow-up procedures, including returning the treatment facility for follow-up at Visit 4 at 42 (± 7) days.

9.1.5 Postoperative Follow-up Visit 4 (6 Weeks [42 days ± 7 days])

1.	Query subject regarding any changes in general health and the use of concomitant medications. If any AEs, ADEs or DDs are observed or reported, they must be recorded as instructed in Section 12 – Adverse Events and Device Deficiencies.
2.	Have the subject complete VAS pain score.
3.	Have the subject complete the Return to Work Questionnaire (if appropriate).
4.	If any Reoperation occurred complete reoperation CRF.
5.	Complete End of Study/exit information (if appropriate).
6.	Instruct the subject on follow-up procedures, including returning the treatment facility for follow-up at Visit 5 at 3 months (91 ± 15 days).

9.1.6 Postoperative Follow-up Visit 5 (3 Months [91 ± 15 days)

1.	Query subject regarding any changes in general health and the use of concomitant medications. If any AEs, ADEs or DDs are observed or reported, they must be recorded as instructed in Section 12 – Adverse Events and Device Deficiencies.
2.	Have the subject complete VAS pain score.
3.	Complete the Constant-Murley Questionnaire (Physician/Examiner completed portion).
4.	Have the subject complete the OSS Questionnaire.
5.	Have the subject complete the WOR/C-WORC Questionnaire.
6.	Have the subject complete the subjective part of Constant-Murley Questionnaire.
7.	Have the subject complete the SSV Questionnaire.
8.	Have the subject complete the EQ-5D-5L Questionnaire.

9.	Have the subject complete Patient satisfaction Questionnaire.
10.	Have the subject complete the Return to Work Questionnaire (if appropriate).
11.	Complete MRI assessment.
12.	If any Reoperation occurred complete reoperation CRF.
13.	Complete End of Study/exit information (if appropriate).
14.	Instruct the subject on follow-up procedures, including returning the treatment facility for follow-up at Visit 6 at 6 months (182 ± 30 days).

9.1.7 Postoperative Follow-Up Visit 6 (6 Months [182 ± 30 days])

1.	Query subject regarding any changes in general health and the use of concomitant medications. If any AEs, ADEs or DDs are observed or reported, they must be recorded as instructed in Section 12 – Adverse Events and Device Deficiencies.
2.	Have the subject complete VAS pain score.
3.	Complete the Constant-Murley Questionnaire (Physician/Examiner completed portion).
4.	Have the subject complete the OSS Questionnaire.
5.	Have the subject complete the WOR/C-WORC Questionnaire.
6.	Have the subject complete the subjective part of Constant-Murley Questionnaire.
7.	Have the subject complete the SSV Questionnaire.
8.	Have the subject complete the EQ-5D-5L Questionnaire.
9.	Have the subject complete Patient satisfaction Questionnaire.
10.	Have the subject complete the Return to Work Questionnaire (if appropriate).
11.	Complete MRI assessment.
12.	If any Reoperation occurred complete reoperation CRF.
13.	Complete End of Study/exit information (if appropriate)
14.	Instruct the subject on follow-up procedures, including returning the treatment facility for follow-up at Visit 7 at 12 months (365 ± 60 days).

9.1.8 Postoperative Follow-Up Visit 7 (12 Months [365 ± 60 days])

1. Query subject regarding any changes in general health and the use of concomitant medications. If any AEs, ADEs or DDs are observed or reported, they must be recorded as instructed in Section 12 – Adverse Events and Device Deficiencies.
2. Complete the Constant-Murley Questionnaire (Physician/Examiner completed portion).
3. Have the subject complete the OSS Questionnaire.
4. Have the subject complete the WOR/C-WORC Questionnaire.
5. Have the subject complete the subjective part of Constant-Murley Questionnaire.
6. Have the subject complete the SSV Questionnaire.
7. Have the subject complete the EQ-5D-5L Questionnaire.
8. Have the subject complete Patient satisfaction Questionnaire.
9. Have the subject complete the Return to Work Questionnaire (if appropriate).
10. Complete MRI assessment.
11. If any Reoperation occurred complete reoperation CRF.
12. Complete End of Study/exit information (if appropriate).
13. Instruct the subject on follow-up procedures, including returning the treatment facility for follow-up at Visit 8 at 24 months (730 ± 60 days).

9.1.9 Postoperative Follow-Up Visit 8 (24 Months [730 ± 60 days])

1. Query subject regarding any changes in general health and the use of concomitant medications. If any AEs, ADEs or DDs are observed or reported, they must be recorded as instructed in Section 12 – Adverse Events and Device Deficiencies.
2. Complete the Constant-Murley Questionnaire (Physician/Examiner completed portion).
3. Have the subject complete the OSS Questionnaire.
4. Have the subject complete the WOR/C-WORC Questionnaire.
5. Have the subject complete the subjective part of Constant-Murley Questionnaire.
6. Have the subject complete the SSV Questionnaire.

7.	Have the subject complete the EQ-5D-5L Questionnaire.
8.	Have the subject complete Patient satisfaction Questionnaire.
9.	Have the subject complete the Return to Work Questionnaire (if appropriate).
10.	Complete MRI assessment.
11.	If any Reoperation occurred complete reoperation CRF.
12.	Complete Exit Visit CRF and inform subject of End of Study.

9.1.10 Unscheduled Visits

Unscheduled examinations related to the study shoulder may be conducted at the discretion of the Investigator with all obtained information recorded in the source documents. The reason for the unscheduled visit as well as surgical status should be transcribed to the appropriate eCRF. If any adverse events or device deficiencies are observed or reported, they must be recorded as instructed in Section 12. - Adverse Events and Device Deficiencies. The subject should be scheduled to return for the next scheduled study visit within the acceptable time window.

9.1.11 Concomitant Medications and Therapies

Concomitant medications and concomitant therapies (e.g. use of opioids, non-opioid prescription medication, steroid injections to treat the index shoulder) are recorded at any time from enrollment into the study through the subject's last study visit.

9.1.11.1 *Concomitant Medications*

9.1.11.1.1 Excluded Concomitant Medications

No restrictions on concomitant medications.

9.1.11.1.2 Recording Concomitant Medication in the eCRF

Only medication related to the study treatment and therapies used to treat an adverse event related to study device and/or study procedure and device deficiency will be recorded in the eCRF according to the eCRF Completion Guidelines.

9.1.11.2 *Concomitant Therapies*

9.1.11.2.1 Therapies Prohibited During the Study

No restriction on concomitant therapies.

9.1.11.2.2 Recording Concomitant Therapies in the eCRF

Only therapies related to the study treatment and therapies used to treat an adverse event related to study device will be recorded in the eCRF according to the eCRF Completion Guidelines.

9.1.12 Discontinued Subjects

Discontinued subjects are those who voluntarily discontinue participation, who are withdrawn for reasons of safety, who are LTFU, or meet any of the criteria listed in Section 7.8 of this protocol. Where possible, a full Exit Visit should be completed for all subjects who discontinue the study early. Where consent is withdrawn, the date and any reason given for discontinuation should be captured, at a minimum.

Finally, if appropriate, the Investigator will also advise the subject of subsequent therapy and/or procedures necessary for their medical condition.

9.1.13 Subject Pregnancy

Pregnant or breast-feeding females are excluded from the study. If during the course of the study a subject becomes pregnant, study procedures that are contraindicated during pregnancy

and/or lactation (e.g. X-Rays, MRI) will not be obtained; however, the subject will continue to be followed for study visits and information will be collected regarding the outcome of the birth.

9.2 STUDY METHODS AND MEASUREMENTS

9.2.1 Cofield classification

The Cofield classification system will be used for all MRI analyses to assess the size of FTTs [38]:

- Small = < 1 cm
- Medium = 1-3 cm
- Large = 3-5 cm
- Massive = > 5 cm

9.2.2 OSS Questionnaire

The Oxford Shoulder Score (OSS) is a questionnaire for the assessment of outcomes of shoulder surgery, which can reduce the observer's errors in the evaluation. It contains 12-item patient-reported outcome (PRO) measures specifically designed and developed for assessing outcomes of shoulder surgery such as assessing the impact on patients' quality of life of degenerative conditions (e.g., arthritis and rotator cuff problems). Because of its reliability and effectiveness, this scoring tool is widely used in clinical practice and studies related to shoulder surgery outcomes [39].

The OSS consists of 12 questions each scored 0 to 4 (0=unbearable, 1=severe, 2=moderate, 3=mild, 4=none) with 4 representing the best outcome. When the 12 items are summed, this produces overall scores that run from 0 to 48, with zero (0) representing a severe shoulder problem and 48 representing no related problem. Higher scores represent better clinical outcomes [39]

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses will be recorded in the eCRF.

9.2.3 WORC/C-WORC Index

The WORC/C-WORC Index is a 21-item questionnaire assessing quality of life, evaluating the change in symptoms and functional ability, specific to rotator cuff tendinopathy; it is often used to compare pre- and postoperative changes in patients with a clinical diagnosis of an impingement syndrome, rotator cuff tendinopathy as well as ARCRs [40].

The WORC/C-WORC Index is self-administered, and includes a 5 different domains (physical symptoms, sports and recreation, work, social function, and emotions). Each question uses a visual analog scale (VAS) representing a 100-point scale ranging from 0 to 100. The maximum score is 2100 (worst possible symptoms). Zero (0) represents no symptoms at all. The final score can also be presented as a percentage by subtracting the total from 2100, dividing by 2100, and multiplying by 100. This will give you an overall percentage. The total final WORC/C-WORC Index scores can, therefore, range from 0% (lowest functional status level) to 100% (highest functional status level) [40].

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses will be recorded in the eCRF.

9.2.4 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. The subjective findings (severity of pain, activities of daily living and working in different positions) comprise 35 points and the objective (examiner assessed) measurements (arm range of motion

without pain, measurements of exo- and endorotation via reference points and measuring muscle strength) comprise the remaining 65 points, for a total of 100 points [41].

The Constant Score is divided into 4 subscales: pain (15 points; VAS score range of 0-15), activities of daily living (20 points; range 0=worst, 5=best), strength (25 points; 1 point given per 0.5 kg of weights raised), and range of motion – forward flexion, external rotation, abduction and internal rotation of the shoulder (40 points; range 0=worst, 10=best). The higher the score, the higher the quality of function [41].

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses will be recorded in the eCRF.

9.2.5 Subjective Shoulder Value (SSV) (also known as Single Assessment Numeric Evaluation [SANE])

Note: The SANE and the SSV are the same, 'How would you rate your shoulder today as a percentage of normal (0% to 100% scale with 100% being normal)?'

The SSV is defined as a patient's subjective shoulder assessment expressed as a percentage of an entirely normal shoulder, which would score 100% [42].

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses will be recorded in the eCRF.

9.2.6 Patient Satisfaction Questionnaire

The Patient Satisfaction Questionnaire is a simple subjective assessment of the success of surgery from the patient's perspective. It has not been formally validated [42].

Pre-Op:

The Patient satisfaction pre-Op will be documented on a visual analogue score of 0-100 'How satisfied are you with your medical care?' Rated by the subject with 0 is the least satisfied, 100 the most satisfied [43].

Post-Op:

This includes the VAS Patient Satisfaction Score as for pre-Op and additional five questions ask of the patient:

1. How well did the surgery relieve the pain?
2. How well did the surgery increase your ability to perform regular activities?
3. How well did the surgery allow you to perform heavy work or sport activities (if allowed by Dr)?
4. How well did the surgery meet your expectations?

Questions rated by the patient with excellent, very good, good, fair and poor.

5. Would you have the operation again if needed on another joint?

Question rated by the patient with Definitely yes, Probably yes, Possibly not, Definitely not [42].

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses will be recorded in the eCRF.

9.2.7 VAS Pain Score

Pain is assessed on a 100-point scale ranging from 0 to 100, with zero (0) representing no pain and 100 representing the worst pain imaginable [42].

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses will be recorded in the eCRF.

9.2.8 Sugaya Score

The Sugaya score will be used to determine postoperative cuff integrity through magnetic resonance imaging classified into 5 categories: Type I to Type V. Type I indicates sufficient thickness with homogenously low intensity. Type II indicates sufficient thickness with partial high intensity. Type III indicates insufficient thickness without discontinuity. Type IV indicates presence of a minor discontinuity, suggesting a small full-thickness tear. Type V indicates the presence of a major discontinuity, suggesting a medium or large full-thickness tear [43]

9.2.9 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 [44].

Grade 0: Completely normal muscle, without any fatty streaks,

Grade 1: Some fatty streaks,

Grade 2: Increased fatty infiltration, but more muscle than fat,

Grade 3: Equal amounts of fat and muscle,

Grade 4: more fat than muscle.

9.2.10 Return to Work Questionnaire

Generic questionnaire, covering work related questions, including demographics on laborer/sedentary [42].

1. Were you working before surgery? Y/N
   a. If yes, what was your job type and the nature of your work?
2. Have you returned to work? Y/N

a. If yes, how long after your operation did you return to work
b. if you couldn't get back to work was there a particular reason?

3. Have you been able to return to the job you did before your surgery (doing the same activities)? Y/N
   a. If No, is there a particular reason you couldn't return to the same activities?
4. If RTW, did you feel ready to go back to work physically? Y/N
5. Since returning to work, did you have to take further time off due to shoulder pain or weakness? Y/N
   a. If so, how long?

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses will be recorded in the eCRF.

9.2.11 Duration of Opioid Use

Self-reported opioid use diary completed by the patient on a daily basis, from day 0-14, documenting opioid use. Consumption daily (YES/NO) x14 days, 'Have you taken any opioid medication today for shoulder pain?' Y/N.

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses will be recorded in the eCRF.

9.2.12 Imaging Examinations

Upper extremity MRIs for study participants will be collected at Baseline, at 3, 6, 12 and 24 months. The Baseline (pre-operative) MRI follows standard of care imaging and will not follow the study MRI Image Acquisition Protocol. The Baseline MRI must occur within 12 months of enrollment into this study. MRI at 3, 6, 12 and 24 months post-surgery will be collected per Image Acquisition Protocol. All diagnostic images collected by the site will be modified in order to protect subject's identity and provided to an external reviewer as detailed in the Image Transfer

Protocol. The independent reviewer will be a certified radiologist selected by the Sponsor based on experience in orthopaedic imaging. The following reviewer assessments will be performed for all MRIs collected post-OP throughout the study (for endpoint analysis):

- Sugaya score
- Goutallier grading
- Total tendon thickness, tendon length
- Size of retear (anteroposterior [AP]/mediolateral [ML])
- Shape of retear

All MRI assessments are detailed in the Image Review Charter. All imaging data will be stored in electronic Digital Imaging and Communications in Medicine (DICOM) format at the site until they are no longer needed in case further evaluation by an independent centralized reviewer is requested by NMPA, PMDA, MHRA, EMA, TGA, Medsafe, HealthCanada, or FDA.

The specific imaging evaluation requirements will be provided in a separate document to radiologists.

9.3 HEALTH ECONOMICS/QUALITY OF LIFE

Health economic evidence will be collected throughout the study.

9.3.1 EQ-5D-5L Questionnaire

The EQ-5D-5L questionnaire will be collected at the pre-operative visit and at 3-, 6-, 12- and 24-months after surgery. A paper questionnaire will be provided by the Sponsor to be completed by the subject.

The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system is used to describe the subject's health state and consists of five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension has 5 levels to choose the most appropriate answer: no problems, slight problems, moderate problems, severe problems and extreme problems. The subject is asked to indicate his/her health state by marking the most appropriate statement in each of the five areas [45].

The EQ VAS records the subject's self-rated health on a vertical visual analogue scale. The endpoints on the scale are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome as judged by the individual respondents.

Responses for the EQ-5D-5L Score will be recorded in the eCRF.

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.

10.1 GENERAL

Smith+Nephew's Global Biostatistics group or designee will conduct the statistical analysis for this study. Unless otherwise stated, all significance tests will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted. Point estimates and their corresponding 95% two-sided confidence intervals will be generated where appropriate. Where data summaries are specified, categorical or ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary statistics: number of observations, mean, median, standard deviation, minimum and maximum values. All analyses will be performed in SAS 9.4 (or later).

10.2 ANALYSIS POPULATIONS

The following study populations and analysis sets will be defined.

- Full analysis set (FAS): following the Intention to Treat principle including all randomized patients who were recruited into the study and attended at least one post-surgery assessment. This analysis population includes all randomized patients in the groups to which they were randomly assigned, regardless of their adherence with the entry criteria, regardless of the treatment they actually received, and regardless of subsequent withdrawal from treatment or deviation from the protocol.
- Per protocol set (PP): including all patients in the full analysis set who have no significant protocol deviations and met the inclusion/exclusion criteria.
- Safety analysis set (SAF): including all patients who have received the study device.

10.3 BASELINE DATA

Demographic and medical variables at baseline (including but not limited to, age, gender, race, job type (laborer/sedentary), medical history, medication history, and disease diagnosis) will be used to describe subjects and summarize subject information. Summary statistics will be given based on the nature of variables (continuous or categorical variables). Job role will be analyzed by Sedentary, Light, Medium and Heavy (heavy and very heavy) according to the US Social Security Administrations classification of labor by physical exertion requirements.

10.4 EFFICACY ANALYSIS

10.4.1 Analysis of Primary Endpoint

A binary variable will be defined based on whether each patient has a Sugaya score of Type IV or V retear/recurrence. This variable will be used to present the number of retears at the 6 month post-operative visit, together with a percentage and 95% confidence interval for a single proportion (calculated using the Clopper-Pearson Exact method).

To test whether ARCR augmented with REGENETEN is superior to ARCR alone, the null hypothesis is that the retear rate of the ARCR augmented with REGENETEN group is not better than, or the same as, the retear rate of the ARCR alone group (standard of care):

H_0: $\mu - \mu_0 \geq 0$

H_1: $\mu - \mu_0 < 0$

In the stated hypothesis, μ represents the rate of retear for those patients which received REGENETEN and μ_0 represents the rate of retear for the standard of care group. A binary variable of success/failure will be created to fit a logistic model adjusting for differences in baseline characteristics.

As a further analysis of the primary endpoint, the time taken for retear to occur will be assessed as a survival endpoint for both treatment groups in order to compare the trend of incidence of retear over time.

Analysis will be carried out using the FAS and PP population.

10.4.2 Analysis of Secondary Endpoints

The following secondary endpoints will be analyzed for this study:

- Retear rate at 3, 12 and 24 months post-operative will be summarized and presented as per the Primary Endpoint analysis.
- OSS, WORC/C-WORC, Constant, SSV and EQ-5D-5L PRO scores will be calculated and summarized for each visit using descriptive statistics for continuous variables, separately for the ARCR augmented with REGENETEN group and the ARCR alone (standard of care) group. Changes from baseline to each subsequent follow up visit will be similarly summarized. Repeated measures ANCOVA models will be used to assess statistical significance in the change from baseline to each time point. The null hypothesis will be that there is no difference between baseline and the respective time point. An estimate of the LS mean difference between the time points for the scores will be reported, along with the corresponding 95% confidence interval and p-value. A separate model will be used to assess statistical significance between the treatment groups at each time point. Minimal Clinically Important Differences will be assessed and presented where appropriate.
- Patient satisfaction and return to work questionnaire will be presented as number and percentage of patients who have selected each of the responses at each time point. The duration a patient has taken away from work will be summarized descriptively.
- VAS Pain score (1-100mm) will be summarized at baseline, 2 and 6 weeks, 3, 6, 12 and 24 months using descriptive statistics for continuous variables. Change from baseline to each follow up assessment will be similarly summarized and p-values will be presented.

- MRI analysis will be conducted by an external vendor at baseline, 3, 6, 12 and 24 months and will be presented appropriately for continuous or categorical variables.
- Opioid use will be collected each day for 2 weeks following surgery. The number of days of opioid use will be calculated for each patient and this will be presented descriptively for all patients, by treatment type (ARCR augmented with REGENETEN or ARCR alone).
- Total operative time will be calculated for each treatment arm and presented descriptively.
- The type of sling will be collected and presented for each treatment arm summarizing if standard sling, shoulder immobilizer, abduction sling, ER sling, or other were advised and mobilization time will be calculated for both arms summarizing mobilization duration.

10.4.3 Analysis of Other Endpoints

A logistic regression model will be used to evaluate retear rates in at-risk groups at each time point. The following binary variables will be created and included in the final model:

- Age (>65 years vs ⩽65 years)
- Diabetic status (diabetic vs not diabetic)
- Smoking status (smoker vs non-smoker)
- Blood pressure (hypertensive vs not hypertensive)
- Job role (heavy laborer vs not heavy laborer)

The safety and efficacy in the revision repair subject group and at-risk groups will be summarized and presented as per the Secondary Endpoint analysis.

The following health economic evidence endpoints will be analyzed for this study:

- Aggregate health care utilization costs;
- Number of unscheduled visits;
- Reoperation rate;

- Surgeon recommendation for reoperation, type of surgery;
- Time of operation to time of retear;
- Level of service (LOS): In the case of reoperation: How many nights did the subject spend in the hospital as a result of surgery? 0, 1, 2, 3, 4, 5, >5

10.5 SAFETY ANALYSES

All safety endpoints will be summarized using the safety population.

- Adverse Events

The number of subjects reporting: adverse events, serious adverse events, adverse device effects, serious adverse device effects, and unanticipated serious device effects will be summarized. In addition, for each adverse event, the following will be summarized: severity, the relationship to investigational device use, outcome and duration of the resolved adverse events and the duration of the adverse events at trial discontinuation.

- Device deficiencies

The number of device deficiencies and the number of patients reporting a device deficiency will be summarized as well as a summary of device deficiencies with the potential to cause SADE.

Additional summaries of safety endpoints, if applicable, will be described in the SAP.

10.6 INTERIM ANALYSES

A formal interim analysis will be conducted once 50% of the planned subjects reach the 6-month follow-up visit to assess how the relative performance of the two treatments differ over time.

11. SAMPLE SIZE JUSTIFICATION

Using a group sequential design, a formal interim analysis will be conducted once 50% of the planned 260 subjects reach the 6-month follow-up at which point a sample size re-estimation will be performed along with options considered to terminate early for efficacy or futility or to increase sample size for power. Further details will be specified within the SAP.

The initial RCT power analysis is based on a Lan-DeMets (O'Brien-Fleming) spending function with hypothesized retear incidence of 15% for REGENETEN and 30% for conventional ARCR with 80% power and 5% significance level.

The sample size of 260 RCT (130 ARCR augmented with REGENETEN and 130 ARCR alone) is based on a primary hypothesis of 50% reduction in retear rates.

12. ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 DEFINITIONS

The categories of AEs are shown in Table 12.1-1. The definitions for each of these categories are given in the subsequent sections.

Table 12.1-1: Categories of Adverse Events

<table>
<tr><th></th><th>NOT DEVICE-RELATED</th><th colspan="2">DEVICE- OR PROCEDURE-RELATED</th></tr>
<tr><td>NON-SERIOUS</td><td>ADVERSE EVENT (AE)</td><td colspan="2">ADVERSE DEVICE EFFECT (ADE)</td></tr>
<tr><td rowspan="3">SERIOUS</td><td rowspan="3">SERIOUS ADVERSE EVENT (SAE)</td><td colspan="2">SERIOUS ADVERSE DEVICE EFFECT (SADE) (SEE 12.1.3)</td></tr>
<tr><td>ANTICIPATED</td><td>UNANTICIPATED</td></tr>
<tr><td>ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT</td><td>UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT</td></tr>
</table>

		(ASADE)	(USADE)

12.1.1 Adverse Event

An Adverse Event is any untoward medical occurrence, unintended disease or untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not causally related to the IP and whether anticipated or unanticipated.

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 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.

Note 3: This includes comparator or if the comparator is a 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 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, 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 Effect (SADE) if, in the view of either the Investigator or the Sponsor, it led to any of the following:

a) death,

b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function including chronic disease, 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) foetal distress, foetal death or a congenital abnormality or birth defect including physical or mental impairment.

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.

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.

Guidance Regarding the Determination of Unanticipated Events:

During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Protocol or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered. [MEDDEV 2.7/3 Rev 3 Sec 8].

Note: An 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 (see Section 4.4 for details).

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 subject 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 subject's usual activities;

Severe - An event is severe if the sign or symptom is incapacitating and results in the subject'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.

Note: DD includes malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence

a. if either suitable action had not been taken,
b. if intervention had not been made, or
c. if circumstances had been less fortunate,

are considered Device Deficiencies with potential to cause SADE and shall be reported as specified in section 12.3.

12.2 AE Coding Dictionary

AE coding for this study will be done per International Medical Device Regulators Forum (IMDRF) AE Terminology Annex E – Clinical Signs, Symptoms and Conditions.

12.3 REPORTING PROCEDURES

AE of any kind and DD will be recorded in the applicable eCRF and source notes. The Investigator will evaluate all AE for relationship to the device and procedure, seriousness, and severity. DD will be evaluated for potential to cause SADE. The following timescales should be followed for the AE/DD information to be entered into the eCRF and reported to the Sponsor or designee (see Figure 12.3-1 and Figure 12.3-2):

- 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 Smith+Nephew unless it is contaminated (e.g., used dressings must not be retained). Updates to submitted information will be recorded in the eCRF 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/EC of adverse events according to the IRB/EC requirements.

Depending on the nature of the adverse event, Smith+Nephew may request copies of the subject'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 subject was hospitalized, a copy of the discharge summary may be requested by Smith+Nephew and should be forwarded as soon as it becomes available. In certain cases, Smith+Nephew also may request a letter from the Investigator that summarizes the events related to the case. Refer to the ISF Sponsor Contact Information Sheet to report SAE, unanticipated SADE, anticipated SADE, and DD.

Figure 12.3-1: Evaluation and Reporting of Adverse Events

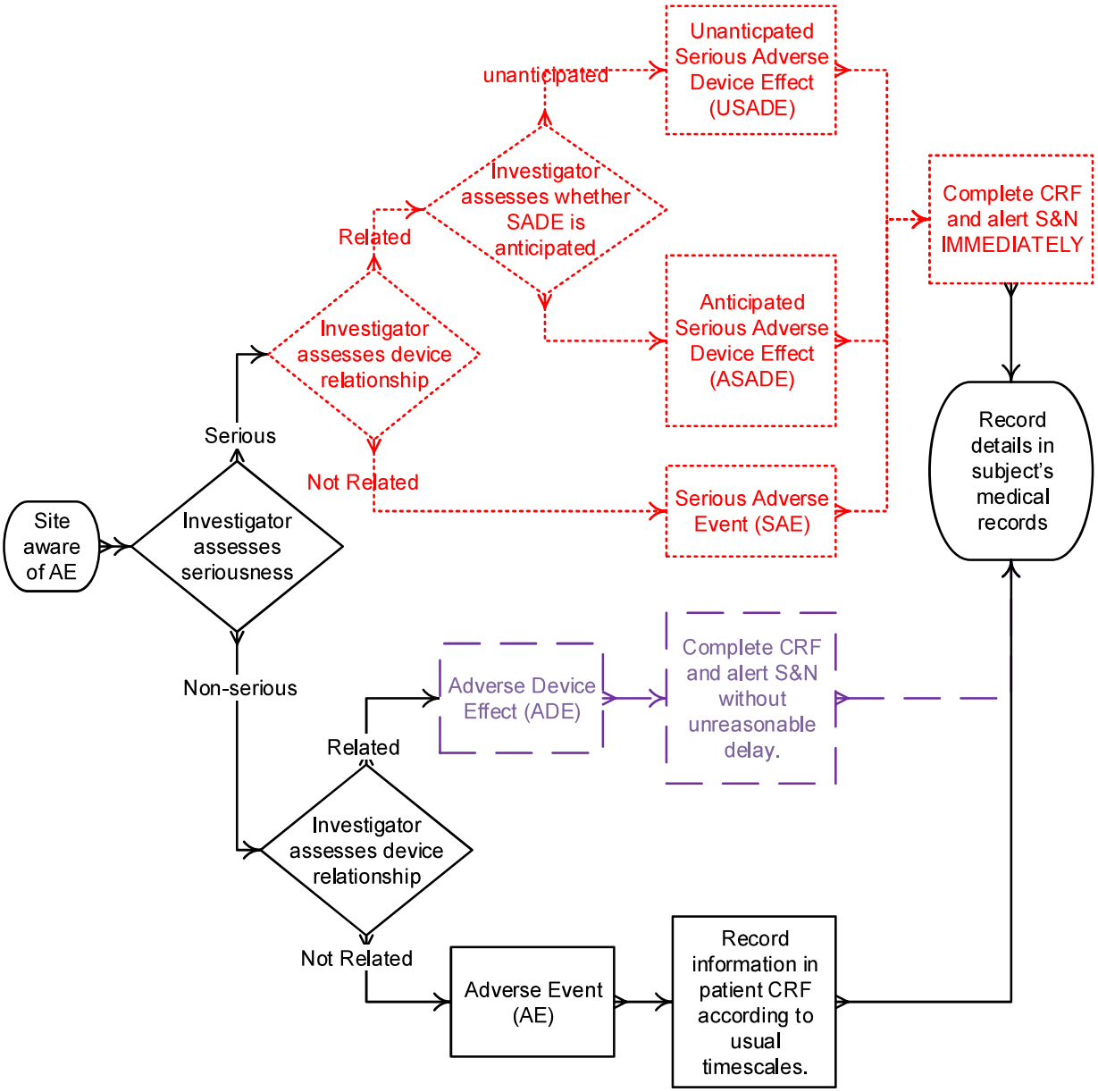
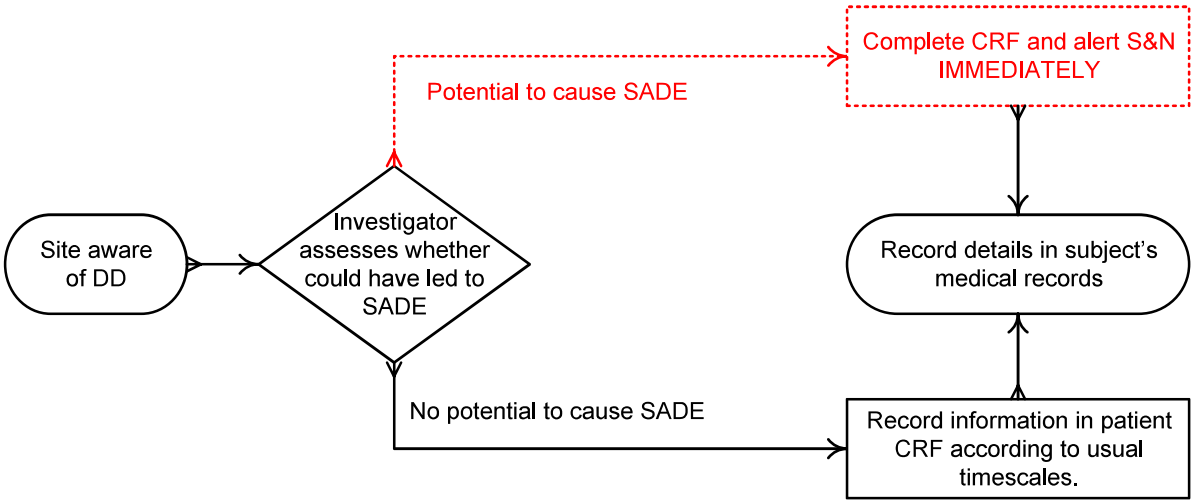


Figure 12.3-2: Evaluation and Reporting of Device Deficiencies



12.4 UNBLINDING OF INVESTIGATIONAL PRODUCT

Not applicable.

12.5 FOLLOW-UP OF SUBJECTS WITH ADVERSE EVENTS

For subjects 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 in the eCRF/Clinical Study Report.

12.5.1 Ongoing Adverse Events at Study Discontinuation

AEs which are **related** to a study procedure or REGENETEN Implant system and are ongoing at end of the subject'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 the Investigator's review of the event.

AEs which are **not related** to a study procedure or REGENETEN Implant system and are ongoing at end of the subject'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 Investigators will comply with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Appendix 21.5 and 21.6 of this protocol.
In addition, the PI will ensure that the Financial Disclosure Statements will be completed by the PI and the Sub-Investigator upon entry into the study and as any changes that affect their financial disclosure status occur during the course of the study and up to one year after study completion.

14. SPONSOR AND MONITOR RESPONSIBILITIES

The Sponsor 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 subjects 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, with GCP regulations, and with applicable regulatory requirements.

Detailed monitoring requirements will be documented in the Clinical Monitoring Plan for this study.

14.1 SITE QUALIFICATION VISIT

A site qualification visit may be performed by the Sponsor prior to the execution of a clinical agreement to ensure that all Investigators have the appropriate training, staff, facilities, and resources to adequately conduct the study.

14.2 SITE INITIATION VISIT

A site initiation visit to provide training on the specifics of the study, site obligations and expectations of study conduct will be performed by the Sponsor or qualified person designated by the Sponsor following the execution of the CTA and documented IEC approval.

14.3 SPONSOR AUDITS AND REGULATORY INSPECTION

Quality Assurance auditors, whether an employee of the Sponsor or its designee, may evaluate study conduct at the study sites. These parties must have access to any and all study reports and source documentation, regardless of location and format.

14.4 CLOSE-OUT VISIT

A study close-out visit will be performed by the Sponsor or designee to retrieve and account for all remaining clinical data and to resolve outstanding queries. During study close-out, the monitor will review investigator files to ensure required documents and records are on file, confirm the disposition of any other ancillary items used for the study, and review regulatory requirements regarding records retention and IEC reporting requirements. When no subjects have been included, a remote close-out visit may be conducted.

15. PROTOCOL AMENDMENTS

Amendments should be made only in necessary cases once the study has started. Protocol amendments must be approved by the protocol signatories prior to submission to the IRB/IEC. Protocol amendments need to be approved by the IRB/IEC and Regulatory Authority(ies), according to the applicable requirements 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 and ISO14155:2020 Clinical investigation of medical devices – Good Clinical Practice (GCP) [37, 38, 46], and all applicable local Singapore, Hong Kong, China, United Kingdom, Germany, Switzerland, France, Canada, United States, Australia, New Zealand, Japan and Netherlands regulations.

This clinical study will not commence until the required approval/favorable opinion from the IRB/IEC and/or regulatory authority has been obtained. Any additional requirements imposed by the IRB/IEC and/or regulatory authority 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. The Sponsor agrees to operate in good faith and in accordance with ABHI (Association of British Healthcare Industries) guidelines regarding compensation for injury arising in the course of clinical studies.

18. END OF STUDY

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 SOPs of the Sponsor.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to other parties (Investigator, IRB/IEC, Sponsor and regulatory authorities). If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB/IEC and the study sites, and will provide

the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance with study protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, study protocol compliance, data quality are addressed and satisfy the Sponsor and IRB/IEC.

A specific study site in this multi-center study may also warrant termination under the following conditions:

- Non-compliance to GCP or protocol
- Failure to enroll subjects
- Major protocol deviations
- Inaccurate or incomplete data
- Unsafe or unethical practices
- Safety or performance considerations
- Investigator involuntarily discontinues participation in study

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 Clinical Trial Agreements 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 HIPAA.

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 [47]. In accordance, Smith+Nephew will consider requests to share individual (de-identified) 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 nine 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.

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21. APPENDICES

21.1 PROTOCOL AMENDMENTS

21.1.1 General Purpose

This amendment has been completed to update the inclusion criteria, visit schedule, correct some errors in statistical section and perform administrative changes. The total number of sites have also been increased to reflect the challenges of recruiting for this indication.

21.1.2 Rationale

Following discussions with the sites and internal reviewers, the rationale for the changes made are as follows:

Section	Change	Rationale
Authors	Abigail Murphy replaces Aleksandra Vidakovic as CSM	Administrative.

1.2 Principal Investigator Signature Page 1.2 Coordinating Investigator Approval	Reference to version date updated from V1.0 to V2.0 ISO14155 revision updated from 2011 to 2020	Administrative.
1.3 Sponsor Approval	Update to Clinical Strategy and Regulatory Approvers	Administrative.
2.0 Synopsis Study Product	Corrected typographic error (PDLLA instead of PLDLA), clarified type of anchors (tendon and bone) as well as updated the slight difference in wording for study product indication depending on generation of product applicable to a site.	Administrative and clarificatory
2.0 Synopsis Number of study sites	Increase from 20 to 30 planned sites	Response to more challenging recruitment climate.
2.0 Synopsis Targeted global regions	Added Japan and Netherlands as potential countries	Expanded targeted regions to fulfil 30 sites requirement.
2.0 Synopsis Inclusion Criteria and 7.2 Inclusion Criteria	Relaxed screening cut-off for tear size (final eligibility remains >/=3cm)	Usual course of large or massive rotator cuff tear is to progress rather than improve. Investigators have reported seeing patients that had ineligible measurements in MRI but are actually large or massive tears once measured with the calibrated probe. Relaxing the screening cut-off reduces the chances of missing tears that are actually eligible per the tear size definition.

2.0 Synopsis Exclusion Criteria And 7.3 Exclusion Criteria	14. “Subject who is pregnant or breastfeeding updated” to “Subjects who are pregnant or breastfeeding”	Administrative.
2.0 Synopsis Exclusion Criteria And 7.3 Exclusion Criteria	Update from “Subjects who are currently involved in any injury litigation relating to the index shoulder” to “Subjects who are currently involved in any injury litigation or workers compensation claims	Language added for workers compensation which is applicable to some geographies involved in the study and broadened the coverage of injury litigation. This change was instituted to minimise potential impact of workers compensation. claims/injury litigation in patient reported outcomes.
2.0 Synopsis Exclusion Criteria And 7.3 Exclusion Criteria	20. “Subject that meets the definition of a Vulnerable Subject per ISO14155:2011 Section 3.44.” updated to “Subject that meets the definition of a Vulnerable Subject per ISO14155:2020 Section 3.44.”	Administrative.
2.0 Synopsis Study Duration	Extended from 42 to 48 months	Reflect extended recruitment period.
2.0 Synopsis Secondary Endpoint	Constant-Murley added at 3 month visit Pain VAS Score added at baseline, 3 and 6 months	Correct error in earlier protocol as pain outcome measures were not documented correctly.
2.0 Synopsis Secondary Endpoint	Removed MRI tendon findings of “retear divided into symptomatic/asymptomatic” as a secondary endpoint	It is not possible to assess whether a tear is symptomatic or not via MRI.
2.0 Synopsis Study Schedule	Schedule of Event: Demographics/Medical History- added BMI	Reflect the actual requirements of the study endpoints.

	Return to Work Questionnaire: marked for screening visit as there is baseline info being collected here Constant Murley added to 3 month visit VAS Pain Score: marked for baseline, 3 and 6 mos as this was missed in last version X-Ray and MRI to confirm eligibility criteria must be within 12 months of surgery (*extended from 6 months*)	
3.4 List of Abbreviations and Definitions	Added CM as Abbreviation for Constant-Murley	Administrative
4.2 Literature Summary	Updated “The REGENETEN Bioinductive Implant system is designed to stimulate the body’s natural healing response to stimulate new tendon growth and disrupt disease progression” to “The REGENETEN Bioinductive Implant system is designed to support the body’s natural healing response to support new tendon growth and disrupt disease progression.”	Maintain consistency with available literature.
4.2 Literature Summary	Updated “The ability to induce new tissue formation and limit tear progression may represent a significant advancement in the treatment of rotator cuff lesions.” to “The ability to induce new tissue formation and limit tear progression may represent a significant advancement in the treatment of rotator cuff tears.”	Used more precise term.

4.3 Study Purpose	Updated "The study results will be used to support registration in China and post market clinical follow-up (PMCF) in Europe, Australia and New Zealand and reimbursement in relevant countries." to "The study results will be used to support post market clinical follow-up (PMCF) and reimbursement in relevant countries."	Changes were made to reflect updates to the regulatory status of REGENETEN in the different geographies and subsequent update to its use of data.
4.4.1 Indications	Added specific indication wording for depending on which device generation is applicable to the study country.	To be consistent with the IFU indications wording in the different versions.
6.1.1.1 Investigational Product(S), Description	*Updated IFU version in table format.* The IFUs may be updated periodically, in which case, the latest version will be used as a guide.	Administrative.
6.3.1 Labelling of Investigational Product	Europe, Canada, Australia and New Zealand added to list of countries where REGENETEN is a commercial product. Added Japan as a country where the product will be cleared/licensed before study enrolment. Added statement on how further regulatory status updates will be managed via TMP-CD-18-01.	Changes were made to reflect updates to the regulatory status of REGENETEN in the different geographies and the subsequent labelling requirements. Regulatory status updates will be expected during the duration of the study. This statement avoids the need for a protocol amendment for labelling requirement changes related to regulatory status updates.
6.5 Surgical Technique	The REGENETEN System should be used according to the surgical	Administrative.

	technique and IFUs provided with the investigational device per Section 6.1.1.1 *(removed list of outdated IFUs)*	
7.1 Subject Population	Increased site number to 30 and added Netherlands and Japan	Updated with plan for new sites.
7.2 Inclusion Criteria	Relaxed screening cut-off for tear size (final eligibility remains >/=3cm)	Usual course of large or massive rotator cuff tear is to progress rather than improve. Investigators have reported seeing patients that had ineligible measurements in MRI but are actually large or massive tears once measured with the probe. Relaxing the screening cut-off reduces the chances of missing tears that are actually eligible per the tear size definition.
7.5 Informed Consent	Reference to ISO14155 version updated from 2011 to 2020 version	Administrative.
8.1 Study Design	Added competent authority for Japan and updated number of sites to 30. Increased total study duration from 42 to 48 months.	Updated with plan for new sites to achieve recruitment targets in the extended timeline.
8.1.1 Study Flowchart	The flow diagram has been updated to have the randomization process after performing repair and to include process for patients requiring re-operation. Title updated to Study Flowchart-Main Arms	Updated per feedback from sites. Tears have to be repairable to be considered eligible to doing the randomization after the repair ensures we do not randomise a patient that will end up as a “screen fail”. Addition of process for revision repair added for clarity.

8.1.2 Study Flowchart	Created new flowchart for Revision Repair Group	Added in this version as this was missed in v1.0.
8.3.2 Secondary Endpoints	Constant-Murley added at 3 month visit Pain VAS Score added at baseline and 3 and 6 months	Correct error in earlier protocol as pain outcome measures were not documented correctly.
	Removed MRI tendon findings of "retear divided into symptomatic/asymptomatic" as a secondary endpoint	It is not possible to assess whether a tear is symptomatic or not via MRI.
8.4.1	Increase planned sites from 20 to 30.	Updated with plan for new sites to expedite recruitment.
8.4.2	Removed statement about assignment of randomization number.	Randomization number is actually not assigned by the system, only treatment group name is assigned.
9.1.1.1 Study Procedures by Visit	Schedule of Event: Demographics/Medical History/*BMI added* Return to Work Questionnaire: marked for screening visit as there is baseline info being collected here Constant Murley added to 3 month visit VAS Pain Score: marked for baseline, 3 and 6 mos as this was missed in last version X-Ray and MRI to confirm eligibility criteria must be within 12 months of surgery *(extended from 6 months)*	Reflect the actual requirements of the study endpoints.

9.1.2 Screening (Baseline) Visit 1 (Day -60 to Day-1)	4. Other demographic information updated to include BMI	Added BMI as this is part of the standard eCRF Demographics/Med Hx form.
	5. Obtain MRI and X-Ray (must be within 12 months of surgery - *extended from 6 months*). The tear size measurement may be provided by the radiography report or as determined by the Investigator.	We expect tear to progress over time so there is very low risk that tear will be ineligible in size. Extending the timeframe means we can expand the recruitment pool as not all sites may repeat MRIs older than 6 months if already scheduled for an ARCR.
	13. Have the subject complete Work Status for Return to Work Questionnaire	Return to Work Questionnaire: marked for screening visit as there is baseline info being collected here.
	14. Have the subject complete VAS pain questionnaire.	VAS Pain Score: marked for baseline as this was missed in last version.
9.1.6 Postoperative Follow-up Visit 5 (3 Months [91 ± 15 days)	*Added the following:* 2. Have the subject complete VAS pain score Added as point 3. Complete the Constant-Murley Questionnaire (Physician/Examiner completed portion) 6. Have the subject complete the subjective part of Constant-Murley Questionnaire. *The rest of the activities renumbered automatically.*	VAS Pain Score and Constant-Murley Questionnaire: marked for 3 months as these were missed in last version.

9.1.7 Postoperative Follow-Up Visit (6 Months [182 ± 30 days])	*Added the following:* 2. Have the subject complete VAS pain score *The rest of the activities renumbered automatically*	VAS Pain Score marked for 3 months as this was missed in last version.
9.2.10 Return to Work Questionnaire	- 1 updated to. Were you working before surgery? Y/N If yes, what was your job type and nature of your work? - 3 updated to. Have you been able to return to the job you did before your surgery (doing the same activities)? Y/N a. If No, is there a particular reason you couldn't return to the same activities? - 4. If RTW, did you feel ready to go back to work or did you have to take further time off due to shoulder pain or weakness? Y/N b. If so, how long?	Wording updated to be consistent with Return to Work questionnaire
9.2.12 Imaging Examinations	The Baseline MRI must occur within 12 months *(extended from 6 months)* of enrollment into this study.	We expect tear to progress over time so there is very low risk that tear will be ineligible in size with MRI older than 6 months. Extending the timeframe means we can expand the recruitment pool as not all sites may repeat MRIs older than 6 months if already scheduled for an ARCR.

9.2.12 Imaging Examinations	Removed one of the MRI secondary endpoints: Retear: Divided into symptomatic and asymptomatic Added Competent Authority for Japan	MRI cannot provide assessment on whether tear is symptomatic or not. Administrative.
10.4.1 Analysis of Primary Endpoint	Reworded hypotheses, updated inequality signs on the hypothesis test, removed t-test from primary endpoint and added a logistic model instead	T-test was removed as we do not have continuous data. Language updated to reflect superiority.
10.4.2 Analysis of Secondary Endpoints	*Baseline added below.* MRI analysis will be conducted by an external vendor at <u>baseline</u>, 3, 6, 12 and 24 months and will be presented appropriately for continuous or categorical variables.	Clarification. Endpoints will be compared to baseline.
10.6 Interim Analyses	*Added underlined and removed strucktrough phrases:* A formal interim analysis will be conducted <u>once 50% of the planned subjects</u> reach the 6-month ~~and 1 year~~ follow-up visits to assess how the relative performance of the two treatments differ over time.	To be consistent with wording of interim analyses elsewhere in the protocol. There is no plan to conduct another interim analysis at 1 year as the main endpoint is at 6 months.
17 Statements of Compliance	Reference to ISO14155 version updated from 2011 to 2020 version. Added Japan and Netherlands.	Administrative.
20. References	Updated references 25-31 by removing old version dates and referencing current versions of IFUs in 6.1.1.1	Administrative

21.1.1 Protocol Amendments General Purpose	This amendment has been completed to update the inclusion criteria, visit schedule, correct some errors in statistical section and perform administrative changes. The total number of sites have also been increased to reflect the challenges of recruiting for this indication.	*Added to document this amendment*
21.1.2 Rationale	*Added table of rationale for changes made (refer to actual section)*	*Added to document this amendment*
21.1.3 Effect on Study Status	*New section added* The changes made with this protocol amendment allows the study to improve recruitment by expanding the patient pool in the screening stage so as not to miss large tears that appear smaller on MRI as well as increase in number of sites that can recruit to the study. Some changes were also added to reflect the patient reported outcomes that need to be collected at each visit. Finally, the statistical section has been updated to reflect that the study is an superiority study and has continuous variables. The database will be updated according to the new protocol once approved.	*Added to document this amendment*
21.1.4 Details	*This table*	*Added to document this amendment*
21.1.5 Approval/Notification	*Added:* These updates will be submitted for REC/IRB approval. The changes	*Added to document this amendment*

	will only be implemented after REC/IRB approval confirmation.	
21.2	Updated to be consistent with current IFU versions and to reflect there are three generations of device that are in use in the study	Administrative
21.5 Principal Investigator Obligations	References to ISO14155:2011 update to ISO14155:2020	Administrative

21.1.3 Effect on Study Status

The changes made with this protocol amendment allows the study to improve recruitment by expanding the patient pool in the screening stage so as not to miss large tears that appear smaller on MRI as well as increase in number of sites that can recruit to the study. Some changes were also added to reflect the patient reported outcomes that need to be collected at each visit. Finally, the statistical section has been updated to reflect that the study is an superiority study and has continuous variables.

The database will be updated according to the new protocol once approved.

21.1.4 Details

The following revisions were made:

Section	Current Text **Protocol Version 1.0 Dated 16/APR/2020**	Revised Text **Protocol Version 2.0 Dated 08/DEC/2021**
Authors	Aleksandra Vidakovic, Clinical Study Manager	Abigail Murphy, Clinical Study Manager

1.1 Principal Investigator Signature Page and 1.2 Coordinating Investigator Approval	I have read the attached protocol entitled "A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Efficacy of ARCR augmented with REGENETEN™ Bioinductive Implant System in Full-thickness Tears (large or massive) Repair versus ARCR alone", version 1.0, dated 16Apr2020, and agree to abide by all provisions set forth herein. I agree to comply with the Investigator's Obligations stipulated in Section 21.5 Principal Investigator Obligations (ISO14155:2011) and Section 21.6 Responsibilities of Clinical Trial Institution and Investigator (cFDA).	I have read the attached protocol entitled "A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Efficacy of ARCR augmented with REGENETEN™ Bioinductive Implant System in Full-thickness Tears (large or massive) Repair versus ARCR alone", version 2.0, dated 08Dec2021, and agree to abide by all provisions set forth herein. I agree to comply with the Investigator's Obligations stipulated in Section 21.5 Principal Investigator Obligations (ISO14155:2020) and Section 21.6 Responsibilities of Clinical Trial Institution and Investigator (cFDA).
1.3 Sponsor Approval	Cristin Taylor, Global Clinical Strategy Lead Kerry Geng, Head of Regulatory Affairs and Quality, Great China	Lori Fontaine, Global Clinical Strategy Lead Jenna Horsley Sr Manager Regulatory Affairs, SPM and ENT
2.0 Synopsis Study Product	REGENETEN Bioinductive Implant System™ is comprised of disposable instruments, a resorbable bovine collagen scaffold, poly-l/d-lactide (PLDLA) anchors to secure the scaffold to the underlying tendon, and PEEK anchors to secure the implant to bone. REGENETEN is indicated for the management and protection of tendon injuries in which there has been no substantial loss of tendon tissue.	REGENETEN Bioinductive Implant System™ is comprised of disposable instruments, a resorbable bovine collagen scaffold, poly-l/d-lactide (PDLLA) tendon anchors to secure the scaffold to the underlying tendon, and PEEK bone anchors to secure the implant to bone. REGENETEN is indicated for the management and protection of tendon injuries/rotator cuff tendon injuries (see Indications Section 4.4.1) in which there has been no substantial loss of tendon tissue.

2.0 Synopsis Number of study sites	Up to 20 study sites	Up to 30 study sites
2.0 Synopsis Targeted global regions	Singapore, Hong Kong, China, United Kingdom, Germany, Switzerland, France, Canada, Australia, New Zealand and United States sites.	Singapore, Hong Kong, China, United Kingdom, Germany, Switzerland, France, Canada, Australia, Netherlands, Japan, New Zealand and United States sites.
2.0 Synopsis Inclusion Criteria	Subjects with a diagnosis of a symptomatic primary or recurrent (revision repair subject group), large or massive tear (≥ 3 cm AP/ML as measured on MRI and confirmed on arthroscopy using a calibrated probe) of the supraspinatus and/or infraspinatus tendons amenable to repair;	Subjects with a diagnosis of a symptomatic primary or recurrent (revision repair subject group), large or massive tear (≥ 3 cm AP/ML) of the supraspinatus and/or infraspinatus tendons amenable to repair. For screening purposes, a ≥ 2 cm AP/ML tear as measured on MRI will be eligible to proceed to the operative visit but will have to be confirmed as ≥ 3 cm on arthroscopy using a calibrated probe to proceed;
2.0 Synopsis Exclusion Criteria	14. Subject who is pregnant or breastfeeding	14. Subjects who are pregnant and breastfeeding
2.0 Synopsis Exclusion Criteria	Subjects who are currently involved in any injury litigation relating to the index shoulder	Subjects who are currently involved in any injury litigation or workers compensation claims
2.0 Synopsis Exclusion Criteria	20. Subject that meets the definition of a Vulnerable Subject per ISO14155:2011 Section 3.44.	20. Subject that meets the definition of a Vulnerable Subject per ISO14155:2020 Section 3.44.
2.0 Synopsis Study Duration	42 months (18 month enrollment period and 24 months follow-up period).	48 months (24 month enrollment period and 24 months follow-up period).
2.0 Synopsis Secondary Endpoint	Overall performance of full-thickness ARCR augmented with REGENETEN versus ARCR alone at Baseline and at 3, 6, 12 and 24 months assessed by:	Overall performance of full-thickness ARCR augmented with REGENETEN versus ARCR alone at Baseline and at 3, 6, 12 and 24 months assessed by: • Constant-Murley Score (CM)

	• Constant-Murley Score (except at 3 months) • Pain, Visual analog scale (VAS) Score (additionally at 2 and 6 weeks);	• Pain, Visual analog scale (VAS) Score (additionally at baseline, 2 weeks, 6 weeks, 3 months and 6 months);
2.0 Synopsis Secondary Endpoint	MRI Tendon Findings in ARCR augmented with REGENETEN versus ARCR alone postoperatively at 3, 6, 12 and 24 months including ○ Sugaya score, ○ Goutallier grading, ○ Total tendon thickness, tendon length, ○ Retear: Divided into symptomatic and asymptomatic	MRI Tendon Findings in ARCR augmented with REGENETEN versus ARCR alone postoperatively at Baseline, 3, 6, 12 and 24 months including ○ Sugaya score, ○ Goutallier grading, ○ Total tendon thickness, tendon length, ~~○ Retear: Divided into symptomatic and asymptomatic~~
2.0 Synopsis Study Schedule	Schedule of Event: Demographics/Medical History Return to Work Questionnaire Constant-Murley VAS Pain Score X-Ray and MRI to confirm eligibility criteria must be within 6 months of surgery	Schedule of Event: Demographics/Medical History/BMI Return to Work Questionnaire: marked for screening visit as there is baseline info being collected here Constant-Murley added to 3-month visit VAS Pain Score: marked for baseline, 3 months and 6 mos as this was missed in last version X-Ray and MRI to confirm eligibility criteria must be within 12 months of surgery

3.4 List of Abbreviations and Definitions	Abbreviation: Constant Definition: Constant-Murley	Abbreviation: Constant/CM Definition: Constant-Murley
4.2 Literature Summary	The REGENETEN Bioinductive Implant system is designed to stimulate the body's natural healing response to support new tendon growth and disrupt disease progression	The REGENETEN Bioinductive Implant system is designed to support the body's natural healing response to support new tendon growth and disrupt disease progression
4.2 Literature Summary	The ability to induce new tissue formation and limit tear progression may represent a significant advancement in the treatment of rotator cuff lesions.	The ability to induce new tissue formation and limit tear progression may represent a significant advancement in the treatment of rotator cuff tears.
4.3 Study Purpose	The study results will be used to support registration in China and post market clinical follow-up (PMCF) in Europe, Australia and New Zealand and reimbursement in relevant countries.	The study results will be used to support post market clinical follow-up (PMCF) and reimbursement in relevant countries.
4.4.1 Indications	The REGENETEN Bioinductive Implant System (compromised of disposable instruments, a resorbable collagen implant, anchors to secure the scaffold to the underlying tendon and PEEK anchors to secure implant to the bone) is indicated for the management and protection of rotator cuff in which there has been no substantial loss of tendon tissue.	The REGENETEN Bioinductive implant System has different indications depending on the country and shown below: Singapore, Hong Kong, United States: The REGENETEN Bioinductive Implant System (compromised of disposable instruments, a resorbable collagen implant, anchors to secure the scaffold to the underlying tendon and PEEK anchors to secure implant to the bone) is indicated for the management and protection of tendon injuries which there has been no substantial loss of tendon tissue.

		China, United Kingdom, Germany, Switzerland, France, Canada, Australia, Netherlands, Japan New Zealand: The REGENETEN Bioinductive Implant System (compromised of disposable instruments, a resorbable collagen implant, anchors to secure the scaffold to the underlying tendon and PEEK anchors to secure implant to the bone) is indicated for the management and protection of rotator cuff tendon injuries which there has been no substantial loss of tendon tissue.
6.1.1.1 Investigational Product(S), Description	Old IFU versions	*Updated IFU version in table format.* The IFUs may be updated periodically, in which case, the latest version will be used as a guide.
6.3.1 Labelling of Investigational Product	The REGENETEN Bioinductive Implant System is an investigational product in China. Addition labels will be included on the commercial packaging to specify that the product is for clinical trial use only in order to meet regulatory requirements for use of investigational devices. In the United States, Singapore and Hong Kong the REGENETEN Bioinductive Implant System is a commercial product and will be used as cleared/licensed. Product labeling will be the same as per standard commercial packaging. In Europe, Canada, Australia and New Zealand the REGENETEN Bioinductive Implant System is a product that will be cleared/registered before study enrollment. The product	The REGENETEN Bioinductive Implant System is an investigational product in China. Addition labels will be included on the commercial packaging to specify that the product is for clinical trial use only in order to meet regulatory requirements for use of investigational devices. In the United States, Singapore, Hong Kong, Europe, Canada, Australia and New Zealand, the REGENETEN Bioinductive Implant System is a commercial product and will be used as cleared/licensed. Product labeling will be the same as per standard commercial packaging. In Japan, the REGENETEN Bioinductive Implant System is a product that will be cleared/registered

	will only be used either through market approval and/or special access approval. For China only, labels on the REGENETEN Bioinductive Implant System contain the following information in addition to standard commercial packaging: • Study number, • Clinical Investigation Use Only.	before study enrollment. The product will only be used either through market approval and/or special access approval. For China only, labels on the REGENETEN Bioinductive Implant System contain the following information in addition to standard commercial packaging: • Study number, • Clinical Investigation Use Only. Any regulatory status updates that may impact labeling requirements moving forward will be managed via TMP-CD-18-01 Investigational Products/Ancillary Products/Supplies Protocol.
6.5 Surgical Technique	The REGENETEN System should be used according to the surgical technique and IFUs provided with the investigational device List of outdated IFUs follow	The REGENETEN System should be used according to the surgical technique and IFUs provided with the investigational device per Section 6.1.1.1 *(removed list of outdated IFUs)*
7.1 Subject Population	Up to 300 subjects will be enrolled into the study in up to 20 sites in the United States, Canada, United Kingdom, France, Switzerland, Germany, China, Singapore, Hong Kong, Australia and New Zealand:	Up to 300 subjects will be enrolled into the study in up to 30 sites in the United States, Canada, United Kingdom, France, Switzerland, Germany, China, Singapore, Hong Kong, Australia, New Zealand, Japan and Netherlands
7.2 Inclusion Criteria	Subjects with a diagnosis of a symptomatic primary or recurrent (revision repair subject group), large or massive tear (≥ 3 cm AP/ML as	Subjects with a diagnosis of a symptomatic primary or recurrent (revision repair subject group), large or massive tear (≥ 3 cm AP/ML) of

	measured on MRI and confirmed on arthroscopy using a calibrated probe) of the supraspinatus and/or infraspinatus tendons amenable to repair.	the supraspinatus and/or infraspinatus tendons amenable to repair. For screening purposes, a ≥ 2 cm AP/ML tear as measured on MRI will be eligible to proceed to the operative visit but will have to be confirmed as ≥ 3 cm on arthroscopy using a calibrated probe to proceed.
7.3 Exclusion Criteria	Subject who is pregnant or breast feeding.	Subjects who are pregnant or breast feeding.
7.3 Exclusion Criteria	Subjects who are currently involved in any litigation relating to the index shoulder	Subjects who are currently involved in any litigation or workers compensation claims.
7.3 Exclusion Criteria	Subject that meets the definition of a Vulnerable Subject per ISO14155:2011 Section 3.44.	Subject that meets the definition of a Vulnerable Subject per ISO14155:2020 Section 3.44.
7.5 Informed Consent	Before conducting any study related procedures, informed consent shall be obtained from all participating subjects according to ISO14155:2011 guidelines or applicable NMPA requirements in China.	Before conducting any study related procedures, informed consent shall be obtained from all participating subjects according to ISO14155:2020 guidelines or applicable NMPA requirements in China.
8.1 Study Design	This clinical trial is supporting the registration of a medical device in China and will support the post market clinical follow up in Europe, Australia and New Zealand after market approval and reimbursement to relevant countries and therefore is required to follow the requirements of relevant regulations issued by NMPA, MHRA, EMA, TGA, Medsafe, HealthCanada or FDA. Study duration is planned to take approximately 42 months (18-month enrollment and 24-month follow-up).	This clinical trial is supporting the registration of a medical device in China and will support the post market clinical follow up in Europe, Australia and New Zealand after market approval and reimbursement to relevant countries and therefore is required to follow the requirements of relevant regulations issued by NMPA, PMDA, MHRA, EMA, TGA, Medsafe, HealthCanada or FDA. Study duration is planned to take approximately 48 months (24-month enrollment and 24-month follow-up).

	For primary hypothesis a total of up to 260 subjects (130 ARCR augmented with REGENETEN; 130 ARCR alone) and additionally up to 40 revision repair subjects if applicable, for sub-group analysis are planned to be included in up to 20 study sites.	For primary hypothesis a total of up to 260 subjects (130 ARCR augmented with REGENETEN; 130 ARCR alone) and additionally up to 40 revision repair subjects if applicable, for sub-group analysis are planned to be included in up to 30 study sites.
8.1.1 Study Flowchart	Original Flowchart	The flow diagram has been updated to have the randomization process after performing repair and to include process for patients requiring re-operation. Title updated to Study Flowchart-Main Arms
8.1.2 Study Flowchart	NA	Created new flowchart for Revision Repair Group
8.3.2 Secondary Endpoints	-Constant Murley (except at 3 months) -Pain VAS score frequency at 2 & 6 weeks - MRI Tendon Findings in ARCR augmented with REGENETEN versus ARCR alone postoperatively at 3, 6, 12 and 24 months - Retear: Divided into symptomatic and asymptomatic	-Constant Murley -Pain VAS score frequency updated to include baseline, 2 weeks, 6 weeks, 3 months and 6 months - MRI Tendon Findings in ARCR augmented with REGENETEN versus ARCR alone postoperatively at Baseline, 2 weeks, 6 weeks, 12 months and 24 months ~~- Retear: Divided into symptomatic and asymptomatic~~
8.4.1	In this study, subjects will be enrolled at multiple sites, utilizing up to 20 sites globally.	In this study, subjects will be enrolled at multiple sites, utilizing up to 30 sites globally.
8.4.2	A randomization number will be assigned only when subject has signed the ICF and satisfied all study eligibility criteria.	Randomization will occur and a treatment will be assigned only when subject has signed the ICF and satisfied all study eligibility criteria.

9.1.1-1 Study Procedures by Visit	Schedule of Event: Demographics/Medical History Return to Work Questionnaire Constant Murley VAS Pain Score X-Ray and MRI to confirm eligibility criteria must be within 6 months of surgery	Schedule of Event: Demographics/Medical History/BMI Return to Work Questionnaire: marked for screening visit as there is baseline info being collected here Constant Murley added to 3 month visit VAS Pain Score: added for baseline, 3 months and 6 months. X-Ray and MRI to confirm eligibility criteria must be within 12 months of surgery
9.1.2 Screening (Baseline) Visit 1 (Day -60 to Day-1)	4. Other Demographic information 5.Obtain MRI and X-Ray (must be within 6 months of surgery) 13. Instruct the subject to return for the Operation Visit on the scheduled date.	4. Other demographic information updated to include BMI 5. Obtain MRI and X-Ray (must be within 12 months of surgery). The tear size measurement may be provided by the radiography report or as determined by the Investigator. 13. Have the subject complete Work Status for Return to Work Questionnaire 14. Have the subject complete VAS pain questionnaire. 15. Instruct the subject to return for the Operation Visit on the scheduled date.
9.1.6		Added the following:

Postoperative Follow-up Visit 5 (3 Months [91 ± 15 days)	*No VAS and Constant-Murley Questionnaire*	2. Have the subject complete VAS pain score 3. Complete the Constant-Murley Questionnaire (Physician/Examiner completed portion) 6. Have the subject complete the subjective part of Constant-Murley Questionnaire. *The rest of the activities re-numbered automatically.*
9.1.7 Postoperative Follow-Up Visit (6 Months [182 ± 30 days])	*No VAS*	Added the following: 2. Have the subject complete VAS pain score *The rest of the activities renumbered automatically.*
9.2.10 Return to Work Questionnaire	1. Where you working before surgery? Y/N a. If yes, what was your job and does your job require heavy lifting? 2. Have you returned to work? Y/N a. If yes, how long after your operation did you return to work or if you couldn't get back to work was there a particular reason? 3. Have you been able to return to the job you did before your injury/surgery (doing the same activities)? Y/N	1. Were you working before surgery? Y/N a. If yes, what was your job type and b. the nature of your work? 2. Have you returned to work? Y/N a. If yes, how long after your operation did you return to work b. if you couldn't get back to work was there a particular reason? 3. Have you been able to return to the job you did before your surgery (doing the same activities)? Y/N

	4. If RTW, did you feel ready to go back to work or did you have to take further time off due to shoulder pain or weakness? Y/N a. If so, how long?	a. If No, is there a particular reason you couldn't return to the same activities? 4. If RTW, did you feel ready to go back to work physically ? Y/N 5. Since returning to work, did you have to take further time off due to shoulder pain or weakness? Y/N a. If so, how long?
9.2.12 Imaging Examinations	The Baseline MRI must occur within 6 months of enrollment into this study.	The Baseline MRI must occur within 12 months of enrollment into this study.
9.2.12 Imaging Examinations	The following reviewer assessments will be performed for all MRIs collected post-OP throughout the study (for endpoint analysis): • Sugaya score • Goutallier grading • Total tendon thickness, tendon length • Retear: Divided into symptomatic and asymptomatic • Size of retear (anteroposterior [AP]/mediolateral [ML]) • Shape of retear All MRI assessments are detailed in the Image Review Charter. All imaging data will be stored in electronic Digital Imaging and Communications in Medicine (DICOM) format at the site until they	The following reviewer assessments will be performed for all MRIs collected post-OP throughout the study (for endpoint analysis): • Sugaya score • Goutallier grading • Total tendon thickness, tendon length ~~• Retear: Divided into symptomatic and asymptomatic~~ • Size of retear (anteroposterior [AP]/mediolateral [ML]) • Shape of retear All MRI assessments are detailed in the Image Review Charter. All imaging data will be stored in electronic Digital Imaging and Communications in Medicine (DICOM) format at the site until they

	are no longer needed in case further evaluation by an independent centralized reviewer is requested by NMPA, MHRA, EMA, TGA, Medsafe, HealthCanada, or FDA.	are no longer needed in case further evaluation by an independent centralized reviewer is requested by NMPA, PMDA, MHRA, EMA, TGA, Medsafe, HealthCanada, or FDA.
10.4.1 Analysis of Primary Endpoint	The following hypotheses will be tested to establish the rate of operations in the ARCR augmented with REGENETEN group is strictly no worse (lower) than the ARCR alone (standard of care) group: H0: $\mu - \mu_0 \leq 0$ Ha: $\mu - \mu_0 > 0$ In the stated hypothesis, μ represents the rate of retear for those patients which received Regeneten and μ0 represents the rate of retear for the standard of care group. A one-sided t-test with alpha = 0.025 will be used to evaluate the hypothesis and the corresponding 95% CIs will also be presented. As a further analysis of the primary endpoint, the time taken for retear to occur will be assessed as a survival endpoint for both treatment groups in order to compare the trend of incidence of retear over time. Analysis will be carried out using the PP population as the primary analysis population with the FAS population used for sensitivity analysis.	To test whether ARCR augmented with REGENETEN is superior to ARCR alone, the null hypothesis is that the retear rate of the ARCR augmented with REGENETEN group is not better than, or the same as, the retear rate of the ARCR alone group (standard of care): H0: $\mu - \mu_0 \geq 0$ H1: $\mu - \mu_0 < 0$ In the stated hypothesis, μ represents the rate of retear for those patients which received REGENETEN and μ0 represents the rate of retear for the standard of care group. A binary variable of success/failure will be created to fit a logistic model adjusting for differences in baseline characteristics. As a further analysis of the primary endpoint, the time taken for retear to occur will be assessed as a survival endpoint for both treatment groups in order to compare the trend of incidence of retear over time. Analysis will be carried out using the FAS and PP population.

10.4.2 Analysis of Secondary Endpoints	MRI analysis will be conducted by an external vendor at 3, 6, 12 and 24 months and will be presented appropriately for continuous or categorical variables.	MRI analysis will be conducted by an external vendor at baseline, 3, 6, 12 and 24 months and will be presented appropriately for continuous or categorical variables.
10.6 Interim Analyses	A formal interim analysis will be conducted once the subjects reach the 6-month and 1 year follow-up visits to assess how the relative performance of the two treatments differ over time.	A formal interim analysis will be conducted once 50% of the planned subjects reach the 6-month follow-up visit to assess how the relative performance of the two treatments differ over time.
17. Statements of Compliance	This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki and ISO14155:2011 Clinical investigation of medical devices – Good Clinical Practice (GCP) [37, 38, 46], and all applicable local Singapore, Hong Kong, China, United Kingdom, Germany, Switzerland, France, Canada, United States, Australia and New Zealand regulations.	This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki and ISO14155:2020 Clinical investigation of medical devices – Good Clinical Practice (GCP) [37, 38, 46], and all applicable local Singapore, Hong Kong, China, United Kingdom, Germany, Switzerland, France, Canada, United States, Australia, New Zealand, Japan and Netherlands regulations.
20. References	25. Smith+Nephew. REGENETEN Bioinductive Implant IFU. Jan2018 ed.; Rev C. 26. Smith+Nephew. REGENETEN Tendon Marker IFU. Jan2018 ed.; Rev D. 27. Smith+Nephew. REGENETEN Tendon Stabilizing Guide IFU. Jan2018 ed.; Rev E. 28. Smith+Nephew. REGENETEN Manual Placement Instruments IFU. Jan2018 ed.; Rev B.	48. Smith+Nephew. REGENETEN Bioinductive Implant IFU. refer to 6.1.1.1 for current version. 49. Smith+Nephew. REGENETEN Tendon Marker IFU. refer to 6.1.1.1 for current version. 50. Smith+Nephew. REGENETEN Tendon Stabilizing Guide IFU. refer to 6.1.1.1 for current version. 51. Smith+Nephew. REGENETEN Manual Placement Instruments IFU. refer to 6.1.1.1 for current version.

	29. Smith+Nephew. REGENETEN Tendon Anchors IFU. Jan2018 ed.; Rev D. 30. Smith+Nephew. REGENETEN Bone Anchors IFU. Feb2018 ed.; Rev G. 31. Smith+Nephew. REGENETEN Bioinductive Implant Placement Cannula IFU. Feb2018; RevC.	52. Smith+Nephew. REGENETEN Tendon Anchors IFU. refer to 6.1.1.1 for current version. 53. Smith+Nephew. REGENETEN Bone Anchors IFU. refer to 6.1.1.1 for current version. 54. Smith+Nephew. REGENETEN Bioinductive Implant Placement Cannula IFU. refer to 6.1.1.1 for current version
21.1.1 Protocol Amendments General Purpose	N/A	This amendment has been completed to update the inclusion criteria, visit schedule, correct some errors in statistical section and perform administrative changes. The total number of sites have also been increased to reflect the challenges of recruiting for this indication.
21.1.2 Rationale	N/A	Added table of rationale for changes made *(refer to actual section)*
21.1.3 Effect on Study Status	N/A	The changes made with this protocol amendment allows the study to improve recruitment by expanding the patient pool in the screening stage so as not to miss large tears that appear smaller on MRI as well as increase in number of sites that can recruit to the study. Some changes were also added to reflect the patient reported outcomes that need to be collected at each visit. Finally, the statistical section has been updated to reflect that the study is an superiority study and has continuous variables.

		The database will be updated according to the new protocol once approved.
21.1.4 Details of Protocol Amendment	N/A	*Added this table detailing changes made between the two versions*
21.1.5 Approval/Notification	N/A	These updates will be submitted for REC/IRB approval. The changes will only be implemented after REC/IRB approval confirmation.
21.2	• Smith+Nephew. REGENETEN Bioinductive Implant IFU. Jan2020 ed.; Rev C. • Smith+Nephew. REGENETEN Manual Placement Instruments IFU. Jan2018 ed.; Rev B. • Smith+Nephew. REGENETEN Tendon Anchors IFU. Jan2018 ed.; Rev D. • Smith+Nephew. REGENETEN Bone Anchors IFU. Feb2018 ed.; Rev G. • Smith+Nephew. REGENETEN Bioinductive Implant Placement Cannula IFU. Feb2018; RevC. • Smith+Nephew. REGENETEN Tendon Marker IFU. Jan2018 ed.; Rev D. • Smith+Nephew. REGENETEN Tendon Stabilizing Guide IFU. Jan2018 ed.; Rev E	Updated to be consistent with current versions and to reflect there are three generations of device that are in use in the study.
21.5 Principal Investigator Obligations	PRINCIPAL INVESTIGATOR OBLIGATIONS (ISO14155:2011)	PRINCIPAL INVESTIGATOR OBLIGATIONS (ISO14155:2020) *Further references to 2011 version updated to 2020 elsewhere in the section*

General comment: the protocol template was also updated over-all to include all the changes from TMP-CD-05 Rev A to current Rev D.1.

21.1.5 Approval/Notification

These updates will be submitted for REC/IRB approval. The changes will only be implemented after REC/IRB approval confirmation.

21.2 INSTRUCTIONS FOR USE

	Gen 3.5 US	Gen 3.5 Intl	Gen 3.0
Part	IFU Version	IFU Version	IFU Version
Bioinductive Implant	02/2020 10601445 Rev. D	02/2020 10601447 Rev. B	02/2020 10601401 Rev. C
Tendon Anchors	01/2019 10601404 Rev. B	02/2020 10601391 Rev. C	02/2020 10601391 Rev. C
Bone Anchors	01/2019 10601405 Rev. B	02/2020 10601392 Rev. C	02/2020 10601392 Rev. C
Tendon Stabilising Guide	10/2018 10601407 Rev. A	02/2020 10601394 Rev. C	02/2020 10601393 Rev. C

21.3 EQUIPMENT AND SPECIAL INSTRUCTIONS

Clinical study sites and PIs should properly manage the surgical tools, investigational devices and test equipment in accordance with regulations of applicable guidelines and trial protocol. The clinical study sites and the PIs cannot use and permit the use of the investigational devices and test equipment for any purpose other than the implementation of this trial, and will follow applicable guidelines, trial protocol and any instructions given by the Sponsor regarding any operation, maintenance or storage of the investigational devices and test equipment. Upon termination or expiration of this Agreement, according to the Sponsor's choice, all unused investigational devices and test equipment should be returned to the Sponsor or be disposed according to the written instructions of the Sponsor.

21.4 HEALTH ECONOMIC OUTCOME MEASURES/ QUALITY OF LIFE MEASURES

For reimbursement and health economic evidence following data will be collected additionally to endpoint related data, where possible:

1. Hospital length of stay including readmission, number of specialist clinic or physician, physiotherapy visits.
2. Unit costs of procedures or resource utilization where possible

21.4.1 Reoperation:

1. Hospital readmissions (number of patients readmitted post-surgery and reasons for readmissions)
2. Number of specialist clinic or physician, physiotherapy visits

21.4.2 Unit costs of resource use where possible

Type of cost	Cost for	Specification/ Examples	Source of unit costs
Direct cost to the healthcare system or the patient	Primary care consultations	General practitioner, medical specialist, physiotherapist, chiropractor etc	Relevant National Reference costs
	Secondary care consultations	Inpatient, emergency department, and outpatient services	Relevant National Reference costs
	Diagnostic tests	MRI, CT scan, and X-ray	Relevant National Reference costs

	Pharmaceutical treatment	Analgesic, NSAIDs, tramadol, (just as examples)	Relevant National Reference costs
	Transportation	Travel expenses for the patient	Mileage allowance according to the relevant country
	Reoperation	Type of surgery, implant costs, material costs	Relevant National Reference costs
Indirect cost	Absenteeism	Absence from work	Mean wage according to Statistics of relevant country
	Presenteeism	Reduced productivity at work due to rotator shoulder pain	Mean wage according to Statistics of relevant country

21.5 PRINCIPAL INVESTIGATOR OBLIGATIONS (ISO14155:2020)

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, safety, and well-being of the subjects 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 subjects 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 ISO14155:2020.
      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 subjects; procedures for recruiting subjects 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 subject'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 subjects 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 subject'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 subjects 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 subject 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 subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject; except when special circumstances for emergency treatments apply (see below)

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 subject'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 subject's decision to participate throughout the clinical investigation

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

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

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

vi. Provide ample time for the subject 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 subject is unable to provide him or herself, and

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

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

i. Subject needing legally authorized representatives: informed consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation (e.g., infant, child, or juvenile, seriously ill or unconscious subject, 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. Subject unable to read or write: informed consent shall be obtained through a supervised oral process if a subject 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 subject 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 subject is not possible because of the subject's medical condition, the informed consent of the subject's legally authorized representative, if present, shall be requested.
2. When it is not possible to obtain prior informed consent from the subject, and the subject's legally authorized representative, is not available, the subject may still be enrolled if a specific process has been described in the protocol.
3. Arrangements shall be made to inform the subject or legally authorized representative, as soon as possible, about the subject's inclusion in the clinical investigation and about all aspects of the clinical investigation.
4. The subject 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 subject without obtaining informed consent of the subject or his/her legally authorized representative only when the following conditions are fulfilled: the prospective subject 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 subject 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 subject. 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 subject (or the subject's legally authorized representative):
   i. Description and purpose
   ii. Potential benefits
   iii. Risks and inconveniences or the subject and, when applicable, for any embryo, fetus 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 subject's continued participation shall be made available to the subject.
   xi. Statement indicating that, upon the subject's approval, the subject's personal physician will be informed of the subject'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 subject
   iii. A statement declaring that discontinuation at any time incurs no penalty for the subject
   iv. A statement with regard to the possible consequences of withdrawal

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

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

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

g. New information: if new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects 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 subjects. The Principal Investigator shall

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

g. if appropriate, subjects 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 subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation, and

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

21.6 RESPONSIBILITIES OF CLINICAL TRIAL INSTITUTION AND INVESTIGATOR (CFDA CHINA FOOD AND DRUG ADMINISTRATION)

- Article 59 Before accepting a clinical trial, the clinical trial institution shall assess relevant resources according to the characteristics of the investigational medical device to determine whether to accept that clinical trial.
- Article 60 The clinical trial institutions shall properly keep the clinical trial records and basic documents as per the agreement with the sponsor.
- Article 61 The investigator who is responsible for the clinical trial shall meet the following conditions:

  (1) Having the professional technical titles and qualifications of deputy chief physician, associate professor and associate investigator in the clinical trial institution;

  (2) Having the expertise and experience required by the investigational medical device, and having accepted relevant training if necessary;

  (3) Familiar with the material and literatures related to the clinical trial required and provided by the sponsor;

  (4) Competent to coordinate, control and make use of the personnel and equipment to carry out the trial, and to deal with adverse events and other associated events that may be incurred by in the investigational medical device;

  (5) Familiar with relevant state laws and regulations and this GCP.

- Article 62 Before the clinical trial, the medical device clinical trial management department of the clinical trial institution shall coordinate with the sponsor to submit the application to the ethics committee and submit relevant documents according to the regulations.
- Article 63 The investigator shall ensure that the relevant working personnel involved in the trial are familiar with the principles, scope of application, product performance, operating methods, installation requirements and technical specifications of the investigational medical device, understand the pre-clinical study data and safety data of the investigational medical

device, and master the prevention and emergency treatment methods for possible risks in the clinical trial.

- Article 64 The investigator shall ensure that all clinical trial participants are fully aware of the clinical trial protocol, relevant provisions, characteristics of the investigational medical device and the respective responsibilities in the clinical trial, that sufficient subjects who meet the selection criteria in the clinical trial protocol are involved in the clinical trial and that the time decided in the agreement is sufficient to safely implement and complete the clinical trial in accordance with relevant regulations during the trial period.
- Article 65 The investigator shall ensure that the investigational medical device is used only for the subjects of the clinical trial and shall not charge any fees.
- Article 66 The investigator shall strictly follow the clinical trial protocol and shall not deviate from the protocol or make a substantive change of plan without the consent of the sponsor and the ethics committee or the approval of China Food and Drug Administration in accordance with the regulations. However, when immediate treatment is needed in the face of emergencies such as direct danger to the subjects, the written report can be provided afterwards.
- Article 67 The investigator is responsible for recruiting subjects and talking with them or the guardians. The investigator shall explain to the subjects the details of the investigational medical device and details about the clinical trial, inform the subjects of possible benefits and known and foreseeable risks, and obtain signed and dated informed consent forms from the subjects or the guardians.
- Article 68 The investigators or other personnel involved in the trial shall not force or induce subjects to participate in the trial by any improper means.
- Article 69 If any unexpected adverse event incurred by the investigational medical device is found during the clinical trial, the investigator shall modify relevant content of the informed consent form with the sponsor, and the affected subjects or the guardians shall re-sign the modified informed consent form after it is reviewed and approved by the ethics committee in accordance with the relevant working procedures.

- Article 70 The investigator is responsible for making medical decisions related to the clinical trial. When any adverse event related to the clinical trial occurs, the clinical trial institution and the investigator shall ensure that the subjects are in a timely manner provided with adequate treatment and solution. When the subjects develop complications which require treatment, the investigator shall promptly inform the subjects of the situation.
- Article 71 If any serious adverse event in the clinical trial occurs, the investigator shall immediately give appropriate treatment measures to the subjects, at the same time report in writing to the relevant medical device clinical trial management department of the clinical trial institution, and notify the sponsor through the department by a written notice. The medical device clinical trial management department shall report in writing to the corresponding ethics committee and the local food and drug administration department and the competent health and family planning department of the province, autonomous region or municipality where the clinical trial institution is located within 24 hours. For death events, the clinical trial institution and the investigator shall provide the ethics committee and the sponsor with all the information needed.
- Article 72 The investigator shall record all the adverse events occurred and the device defects found during the clinical trial and analyze the cause of the event together with the sponsor, form a written analysis report, give the opinion of continuing, suspending or terminating the trial, and report to the ethics committee for review through the medical device clinical trial management department of the clinical trial institution.
- Article 73 The investigator shall ensure that the clinical trial data is accurately, completely, clearly and promptly entered in the case report form. The case report form shall be signed by the investigator; any change in the data shall be signed and dated by the investigator and meanwhile clear and identifiable original records shall be kept.
- Article 74 The clinical trial institution and the investigator shall ensure that the data, documents and records formed in the clinical trial are authentic, accurate, clear and secure.
- Article 75 The clinical trial institution and the investigator shall be subject to the supervision and verification of the sponsor and supervision of the ethics committee and shall provide all

required records related to the trial. The clinical trial institution and the investigator shall cooperate with the inspectors during the inspections assigned by the food and drug administration department and the competent health and family planning department.

- Article 76 Where the clinical trial institution and the investigator find that the risk exceeds the potential benefit, or the result obtained is enough to judge the safety and effectiveness of the investigational medical device and therefore the clinical trial needs to be suspended or terminated, they shall notify the subjects, ensure that the subjects are properly treated and followed up, and report and provide a detailed written explanation in accordance with the regulations. If necessary, they shall report to the local food and drug administration department of the province, autonomous region and municipality.

  When receiving a notice from the sponsor or the ethics committee to suspend or terminate the clinical trial, the investigator shall inform the subjects promptly and ensure that the subjects are properly treated and followed up.
- Article 77 Where the sponsor violates relevant regulations or requires the change of the trial data and conclusions, the clinical trial institution and the investigator shall report to the local food and drug administration departments of the province, autonomous region and municipality or China Food and Drug Administration.
- Article 78 Upon the completion of the clinical trial, the investigator shall ensure that the records and reports are completed. At the same time, the investigator shall also ensure that the number of investigational medical devices received is consistent with that of the used, discarded or returned devices, and ensure that the remaining investigational medical devices are properly handled, recorded and documented.
- Article 79 The investigator may, according to the needs of the clinical trial, authorize corresponding personnel to recruit subjects, communicate with the subjects, record the clinical data and manage the investigational medical device. The investigator shall carry out relevant training and form the corresponding document for the personnel authorized.