ORTHOSPACE

InSpace™ Clinical Investigational Plan

Study Title:	A prospective, single blinded, multi-center, randomized, controlled, pivotal study to assess the safety and effectiveness of the InSpace™ device for treatment of full thickness Massive Rotator Cuff Tears
Version No:	Version 4.0
Version Date:	**March 26, 2018**
Study Device:	**InSpace™ Device**
[redacted] **NCT No.:**	NCT02493660[redacted]
Sponsor:	Ortho-Space Ltd. [redacted]
Sponsor's Contact Person:	Heather Neill, VP Clinical Operations

Confidentiality Statement:

The information contained in this Clinical Investigational Plan is provided to you in confidence, for review by you, your staff and an applicable regulatory authority or institutional review committee. It is understood that this information may not be disclosed to any other party, in any form, without prior authorization from Ortho-Space Ltd., except to the extent necessary to obtain informed consent from the persons on whom the medical device may be used.

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STUDY PROTOCOL SIGNATURE PAGE

Confidentiality Statement:

This Clinical Investigational Plan (CIP) contains privileged or confidential information, which is the property of the Sponsor. Information may not be disclosed to a third party without written authorization from the Sponsor.

Regulatory Statement:

This study will be conducted according to the protocol, the US Code of Federal Regulations 21 CFR Part 50, 54, 56, and 812, the ethical principles originating from the Declaration of Helsinki, and Good Clinical Practice (GCP) as defined in ICH E6, and the ICH Guidelines. All aspects of this study will be conducted in accordance with all national, state, and local laws of the pertinent regulatory authorities.

Investigator's Statement:

I understand the protocol *"*A prospective, single blinded, multi-center, randomized, controlled, pivotal study to assess the safety and effectiveness of the InSpace™ device for treatment of full thickness Massive Rotator Cuff Tears."

I agree to conduct this study in accordance with the design and specific provisions of the protocol in this CIP, the Clinical Study Research Agreement, and all applicable regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

I agree to ensure the rights, safety, and well-being of the subjects involved in the study.

I agree to await Institutional Review Board (IRB)/Research Ethics Board (REB) approval of the CIP and Informed Consent Form (ICF) before initiating the study, to obtain informed consent prior to subject enrollment in the study, to collect and record data as required by this CIP and corresponding Case Report Forms (CRF), to prepare Annual, Final, and Adverse Events (AE) Reports as required, and to maintain study documentation for the period of time required.

I agree to maintain responsibility for all medical devices under investigation.

Investigator's Printed Name:	
Investigator's Signature:	Date of Signature:

STUDY SYNOPSIS

Title	A prospective, single blinded, multi-center, randomized, controlled, pivotal study to assess the safety and effectiveness of the InSpace™ device for treatment of full thickness Massive Rotator Cuff Tears
Short Title	InSpace device
Protocol Number	CLD-OR-010
Study Design	Prospective, single blinded, multi-center, randomized, controlled, pivotal
Study Duration	48 months total (approximately 24 month enrollment + 24 month follow-up)
Study Center(s)	Up to 20 clinical sites (US and Canada)
Number of Subjects	184 subjects
Objectives	Primary: • To evaluate the safety and effectiveness of the InSpace device as a primary surgical treatment for full thickness massive rotator cuff tears Secondary: • Change in clinical outcomes compared to baseline
Study Population	Male and female ≥ 40 years of age presenting with a full thickness massive rotator cuff tear (MRCT)
Study Treatment	Group I: InSpace device
Control Treatment	Group II: Partial Repair
Randomization Scheme	Subjects will be assigned by a 1:1 schema
Route of Administration	Arthroscopic surgical implantation of the InSpace device
Endpoints:	Primary Composite Endpoint • WORC improvement of 275 points by Week 6 from pre-operative baseline and maintained at Month 12 • ASES improvement of 6.4 points by Week 6 from pre-operative baseline and maintained at Month 12 • No subsequent secondary surgical interventions (SSSI) in the index shoulder through Month 12 • Absence of Serious Adverse Device Effects (SADEs), through Month 12 Secondary Endpoints: Clinical endpoints • Composite endpoint component-level success for WORC compared to baseline

	• Composite endpoint component-level success for ASES compared to baseline • Change in Western Ontario Rotator Cuff Index (WORC) questionnaire scores from baseline • Change in American Shoulder and Elbow Surgeons (ASES) from baseline • Change in Constant Murley Shoulder Outcome Score from baseline • Change in EuroQOL five dimensions questionnaire (EQ-5D-5L) from baseline • Change in Visual Analogue Scale (VAS) scores from baseline • Change in Range of Motion (ROM) from baseline • Composite endpoint success at Month 24 Imaging endpoints will include reading of MRI scans conducted at • Week 6 post treatment to assess (Group I: InSpace device [includes only subjects enrolled under Protocol V3.0, May 1, 2017]): i. device location in the sub-acromial space • Month 12 post treatment to assess (all randomized subjects): i. the device residuals (Group I – InSpace only) the shoulder joint and surrounding tissue condition (Group I: InSpace device and Group II: Partial Repair)

TABLE 1: STUDY FLOWCHART AND FOLLOW-UP ASSESSMENTS

Procedure	Screening/ Baseline	Surgery	Post-Treatment Follow-up Evaluation					
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	Days - 45 to -1	Day 0	Day 10 ± 6 d	Wk 6 ± 7 d	M 3 ± 14 d	M 6 ± 14 d	M 12 ± 1 m	M 24 ± 2 m
Informed Consent	X[1]							
Pregnancy Test (if applicable)		X[2]						
Medical History	X							
Demographics	X							
Subject Eligibility Criteria Verification	X	X						
Subject Randomization		X[3]						
Subject Treatment		X[5]						
Magnetic Resonance Imaging (MRI)	X[4]			X[6]			X[7]	
Western Ontario Rotator Cuff Index (WORC)	X		X	X	X	X	X	X
American Shoulder and Elbow Surgeons (ASES)	X		X	X	X	X	X	X
EuroQOL five dimensions questionnaire (EQ-5D-5L)	X		X	X	X	X	X	X
Constant-Murley Shoulder Outcome Score	X			X	X	X	X	X

Visual Analogue Scale (VAS)	X		X	X	X	X	X	X
Adverse Events		X	X	X	X	X	X	X
Concomitant Medications Review	X	X	X	X	X	X	X	X

1. Must occur prior to any study-specific procedures.
2. If applicable, a pregnancy test, urine or blood, will be performed no earlier than 2 days before the scheduled surgery.
3. Interactive web randomization performed after intra-operative inclusion confirmed.
4. Pre-operative MRI taken within 9 months of enrollment.
5. Subject will be blinded to treatment assignment until end of study.
6. MRI to all study treatment arm subjects (Group I: InSpace device [includes only subjects enrolled under Protocol V3.0, May 1, 2017])at Week 6 per Imaging Acquisition guidance (provided in Appendix H)
7. MRI to all randomized subjects as per imaging Acquisition guidance (provided in Appendix C).

1 BACKGROUND INFORMATION

1.1 Introduction

Rotator cuff tears (RCTs) are amongst the most common orthopaedic condition in adults. The incidence of rotator cuff tears increases in frequency with age (Lehman, 1995) and is often associated with degeneration of the tendons (Matava, 2005). Full thickness tears of the rotator cuff are among the most common sources of pain and dysfunction in the shoulder (Bunker, 2002). Approximately 18 million Americans self-reported shoulder pain in 2005. By 2030, over 20% of the US population will be over 65, with that the prevalence of rotator cuff disorders are expected to increase over the next two decades (AAOS, 2013).

RCTs are classified by the size of the tear (Matthews, 2006), the presence of tendon retraction, chronicity of the injury (Coleman, 2003; Liu, 2011) and the amount of muscle atrophy and degree of fatty degeneration (Harryman, 1991; Goutallier, 2007; Encalada-Diaz, 2011). Tears may range in severity from partial to massive.

Massive tears, commonly defined as a tear is greater than 5 centimeters in diameter (Cofield, 1985) are frequently associated with pain, weakness, and functional disability (Jost, 2006; Gartsman, 1997). Furthermore, these massive tears have demonstrated unfavorable outcomes following conservative care, necessitating surgical intervention.

Although technically challenging, complete primary repair of the massive tear may be achieved through open or arthroscopic procedures (Mellado, 2005). When a patient has pain and weakness in the setting of a massive tear which may not be amenable to complete repair, there are a variety of potential treatment options (Elhassan, 2008). These options may include conservative management (e.g., physical therapy) (Walch, 2005), simple decompression and debridement with or without biceps tenotomy (or tenodesis), subscapular nerve release, biologic augmentation, tendon transfer, partial repair, and reconstruction with hemiarthroplasty or reverse shoulder arthroplasty (Encalada-Diaz, 2011; Moser, 2007; Aurora, 2007; Goldberg, 2008; Cuff, 2008; Berth, 2010). A thorough history and physical examination are important to establish the diagnosis and determine the most appropriate treatment. The treatment algorithm is largely

based on the patient's level of function, age, comorbidities, size and quality of remaining rotator cuff (Tonino, 2009).

Arthroscopic partial repair, as advocated by Burkhart et al. (Burkhart, 1997) attempts to restore function and provide pain reduction. This approach involves surgical repair utilizing anchors or suture placement and requires a protracted period of recovery in order to protect the repair. Biomechanical studies have supported such partial repair approaches (Hsu, 2011; Burkhart, 1997).

Nevertheless, repair of massive tears is often followed by re-tears, additional muscular degeneration, and diminished clinical results over time (Galatz, 2004). Given this, there remains a need to evaluate potential alternatives which may prove effective in the treatment of full thickness massive rotator cuff tears.

The study device, the InSpace™ device, is an inflatable biodegradable balloon that is deployed arthroscopically into the subacromial space, acting as a spacer, in patients with full thickness massive RCTs. The temporary lowering of the humeral head during spacer inflation may additionally provide improved balance between the subscapularis anteriorly and the infraspinatus posteriorly, permitting better deltoid activation and compensation. The use of the InSpace device may be a simple and less invasive alternative that has the potential to provide comparable safety and effectiveness profile to the current, well-established technique of arthroscopic partial repair.

The purpose of this study is to evaluate the safety and effectiveness of the InSpace device as a primary surgical treatment for full thickness massive rotator cuff tears. Secondary aims include evaluating additional clinical outcomes and imaging.

1.2 Device Name and Intended Use

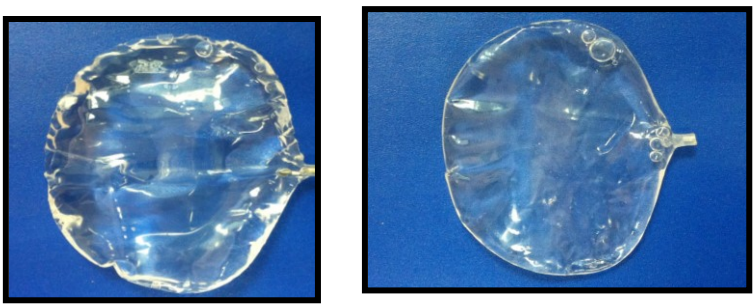
The InSpace device under investigation is a biodegradable balloon spacer provided by Ortho-Space Ltd. The InSpace device is indicated for the treatment of patients with massive, full-thickness torn rotator cuff tendons due to trauma or degradation with mild to moderate gleno-humeral osteoarthritis.

1.3 Investigational Device

The InSpace system components are single-use, supplied sterile and ready for use upon removal from their package *(Figure 1)*.

The Biodegradable, Inflatable Spacer [(Balloon) – InSpace device] is a single use, biodegradable, inflatable spacer (balloon) implant *(Figure 2)*.

FIGURE 2:

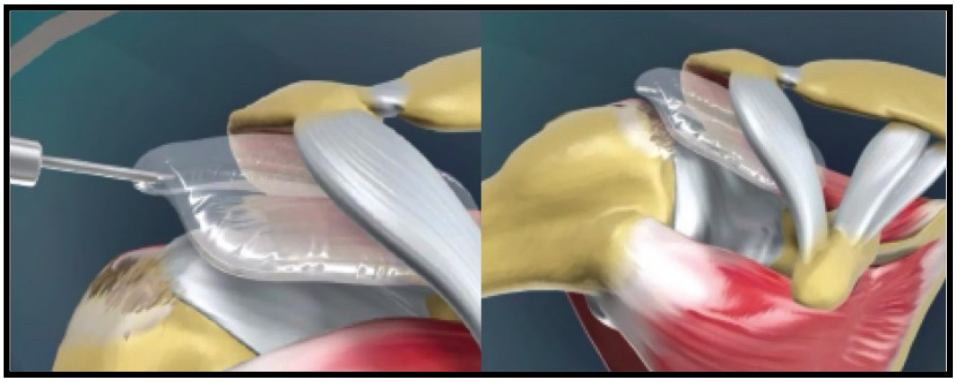


[redacted]

Through an arthroscopic procedure, following standard debridement/ASD of the shoulder, the Deployer is placed in-situ and the InSpace device is positioned in the sub-acromial space between the humeral head and the acromion. [redacted]. In this position, the InSpace device fills the space created by the removal of the bursa thus allowing smooth gliding without friction of the humeral head against the acromion *(Figure 3)*.

The InSpace device degrades within 12 months, a period that may conform well to the rehabilitation timeframe following a rotator cuff arthroscopic procedure.

FIGURE 3: ILLUSTRATION OF THE INSPACE DEVICE PLACED IN THE SUB-ACROMIAL SPACE



The InSpace device has three optional sizes and volume specifications *(Table 2)*.

TABLE 2: INSPACE DEVICE SIZE AND ASSOCIATED VOLUMES

[redacted]

[redacted]

[redacted]

1.5 Mode of Action

The following section describes the mode of action of the InSpace device and is supported by in-vitro, animal, and human clinical studies.

Following a standard diagnostic arthroscopy, the InSpace device is positioned, [redacted], in the sub-acromial space between the humeral head and the acromion.

[redacted]

(i.e. reverse total shoulder arthroplasty). This mode of action may lead to an enhanced quality of life.

2 OVERVIEW OF INVESTIGATIONAL PLAN

This is a non-inferiority, prospective, single blinded, multi-center, randomized, controlled, pivotal study evaluating the safety and effectiveness of the InSpace device as a primary surgical treatment for full thickness MRCT in comparison to Partial Repair of a full thickness MRCT performed during an arthroscopic procedure. The primary effectiveness endpoint is a composite endpoint consisting of four pre-specified components where each component must achieve success by Month 12. In addition, a complete Month 24 analysis will be submitted at the conclusion of the study.

2.1 Objectives

2.1.1 Primary Objectives

- To evaluate the safety and effectiveness of the InSpace device as a primary surgical treatment for full thickness massive rotator cuff tears

2.1.2 Secondary Objectives

- Change in clinical outcomes compared to baseline

2.2 Endpoints

2.2.1 Primary Composite Endpoint

- WORC improvement of 275 points by Week 6 from pre-operative baseline and maintained at Month 12
- ASES improvement of 6.4 points by Week 6 from pre-operative baseline and maintained at Month 12
- No subsequent secondary surgical interventions (SSSI) in the index shoulder through Month 12
- Absence of Serious Adverse Device Effects (SADEs), through Month 12

2.2.2 Secondary Endpoints

- Clinical endpoints:
  - Composite endpoint component-level success for WORC compared to baseline

- Composite endpoint component-level success for ASES compared to baseline
- Change in Western Ontario Rotator Cuff Index (WORC) questionnaire scores from baseline
- Change in American Shoulder and Elbow Surgeons (ASES) from baseline
- Change in Constant-Murley Shoulder Outcome Score from baseline
- Change in EuroQOL five dimensions questionnaire (EQ-5D-5L) from baseline
- Change in Visual Analogue Scale (VAS) scores from baseline
- Change in Range of Motion (ROM) from baseline
- Composite endpoint success at Month 24

- Imaging endpoints will include reading of MRI scans conducted at
  - Week 6 post treatment to assess (Group I: InSpace device [includes only subjects enrolled under Protocol V3.0, May 1, 2017]):
    - device location in the sub-acromial space
  - Month 12 post treatment to assess (all randomized subjects):
    - the device residuals (Group I – InSpace only)
    - the shoulder joint and surrounding tissue condition (Group I: InSpace device and Group II: Partial Repair)

2.2.3 Safety Assessment

Safety will be evaluated by type, frequency, severity, and relatedness of adverse events to study treatment and control treatment.

3 PROTOCOL

3.1 Study Design

This is a non-inferiority, prospective, single blinded, multi-center, randomized, controlled, pivotal study. The study is designed to evaluate the safety and effectiveness of the InSpace device as a primary surgical treatment for a full thickness MRCT in comparison to Partial Repair of a full thickness MRCT performed during an arthroscopic procedure.

The study will enroll 184 subjects presenting with a full thickness MRCT. These 184 subjects will be randomized 1:1, producing approximately 92 subjects randomized to the

Study Treatment: Group I- InSpace device and 92 randomized to the Control Treatment: Group II – Partial Repair.

Pharmacoeconomic data such as the subject's bills relating to the surgical procedure (i.e., operating room time, length of stay, medications, research center visits, rehabilitation and other related procedural costs) will be collected at the follow-up visits, if applicable. In addition, procedural and diagnostic codes, and reimbursement information may be collected. Analysis of these data should allow a comparison of the net costs and net benefits of the study treatment to the control treatment. These economic endpoints will not be included in the data set for FDA submission because they do not relate to device safety or effectiveness.

3.2 Subject Recruitment and Screening

Subjects will be voluntarily recruited from the Principal Investigator or Sub-Investigator population and/or referring physicians.

Subjects who present with a full thickness MRCT will be screened to determine if they meet all inclusion and no exclusion criteria. If all entry criteria are achieved, the subject will be eligible to participate in the study. All general and indication-specific entry criteria must be met prior to study entry.

All potential subjects screened for eligibility will be listed on the Screening and Enrollment Log. The Screening and Enrollment Log will document the date of screening, the results of screening, and the primary reason for excluding the subject (e.g., does not satisfy eligibility criteria or subject declined).

Subjects who are eligible to enter the study will be provided with an Institutional Review Board (IRB) or a Research Ethics Board (REB) approved Informed Consent Form (ICF) for review and signature. Each subject will have a physical exam of the index shoulder that incorporates a medical history and injury etiology. Diagnosis of the rotator cuff tear will be confirmed with MRI acquired within 9 months of enrollment.

3.3 Study Blinding

The Investigator and surgical attendees will be unblinded to the treatment assignment due to the nature of the surgical procedure and post-op rehabilitation process.
The subject will remain blinded to the treatment assignment until completion of the study.
See section 5.4 for *Unblinding Procedures.*

3.4 Study Duration and Follow-up

The anticipated study duration is 48 months, which includes an approximate 24 month enrollment period and 24 month follow-up period.

Subjects will be assessed pre-operatively and at Day 10, Week 6, and Months 3, 6, 12, and 24 post-operatively. At each follow-up visit, a shoulder examination will be performed, subject questionnaires will be administered, and Adverse Events (AEs) and concomitant medication will be reviewed, if applicable. All study treatment arm subjects (Group I: InSpace device [includes only subjects enrolled under Protocol V3.0, May 1, 2017]) will receive an MRI at Week 6 to assess device location.
At Month 12 post-operatively, all randomized subjects will complete a MRI scan of the treated shoulder.

The Study Flowchart and Follow-Up Assessments table (Table 1) outlines study procedures and timelines.

3.5 Randomization

Centralized randomization will be performed, and subjects will be randomly assigned to one of the following groups by a 1:1 schema:

- Group I: InSpace device
- Group II: Partial Repair

3.6 Selection of Subjects

Subjects who meet all of the following criteria will be voluntarily recruited by participating Investigators:

3.6.1 Inclusion Criteria

Subjects MUST meet ALL of the following criteria to be included in the study:

1. The subject has signed the IRB/REB approved Informed Consent Form (ICF) specific to this study prior to enrollment
2. Is male or female ≥ forty (40) years of age
3. Positive diagnostic imaging by MRI within 9 months of enrollment of the index shoulder indicating a full thickness MRCT:
    a. measuring ≥ 5 cm in diameter (Cofield classification)
    b. involving ≥ two tendons
4. Functional deltoid muscle and preserved passive range of motion on physical examination
5. Documented VAS score of >30 mm pain
6. Failed non-operative treatment of at least 4 months from the initial treatment to include one or all of the following:
    a. Oral analgesics
    b. Anti-inflammatory medication (e.g., ibuprofen, naproxen)
    c. Corticosteroid injection(s)
    d. Physical therapy
    e. Activity modification
    f. Rest (sling used)
7. Must be able to read and understand the approved Informed Consent Form (written and oral)
8. Must be in general good health (as determined by the Investigator) based on screening assessments and medical history
9. Must be independent, ambulatory, and can comply with all post-operative evaluations and visits.

3.6.1.1 Intra-operative Inclusion Criteria

Subjects MUST meet the following criteria to be randomized in the study:

- Full thickness tear
- Tear size ≥5 cm in diameter (Cofield classification)
- Tear involving ≥ two tendons

3.6.2 Exclusion Criteria

Subjects will be excluded from the study, if they meet ANY one (1) of the following criteria:

1. Known allergy to the device material (copolymer of PLA and -ε-caprolactone)
2. Evidence of the following conditions:
    a. severe gleno-humeral or acromiohumeral arthritis
    b. full thickness cartilage loss as seen on MRI
    c. history within the past 5 years of anterior or posterior shoulder subluxation or dislocation as determined by history, examination or radiographic findings
    d. pre-existing deltoid defect or deltoid palsy
    e. major joint trauma, infection or necrosis
    f. partial thickness tears of the supraspinatous
    g. fully reparable rotator cuff tear [Tear of less than 5 cm in diameter (or < 4 cm^2) with retractable tendon that can be fully repaired]
    h. known neurovascular compromise
    i. complete deltoid muscle palsy
    j. traumatic muscle tears of the pectoralis or deltoid
3. The subject requires concomitant:
    a. subscapularis repair
    b. labral repair of any type
4. Previous surgery of the index shoulder in the past 1 year, excluding diagnostic arthroscopy
5. The subject's condition is bilateral and rotator cuff repair is scheduled or to be scheduled over the course of this study for the contra lateral shoulder
6. Major medical condition that could affect quality of life and influence the results of the study (e.g. HIV or other immunosuppressive conditions, active malignancy in the past 5 years, acute MI, CVA, etc.)
7. The subject has documented evidence of a history (e.g., liver testing) of drug/alcohol abuse within12 months of enrollment
8. The subject's condition represents a worker's compensation case
9. The subject is currently involved in a health-related litigation procedure

10. Females of child-bearing potential who are pregnant or breastfeeding or plan to become pregnant during the course of the study
11. Concurrent participation in any other investigational clinical study one month prior to enrollment or during the entire study period
12. The subject has implanted metallic devices (e.g., cardiac pacemakers, insulin pumps, nerve stimulators), medically implanted clips or other electronically, magnetically or mechanically activated implants that would contraindicate undergoing a MRI scan of the index shoulder
13. The subject has claustrophobia that would inhibit their ability to undergo a MRI scan of the index shoulder
14. The subject is physically or mentally compromised (e.g., currently being treated for a psychiatric disorder, senile dementia, Alzheimer's disease, etc.), to the extent that the Investigator judges the subject to be unable or unlikely to remain compliant to follow-up
15. The subject is receiving prescription narcotic pain medication for conditions unrelated to the index shoulder condition
16. The subject currently has an acute infection in the area surrounding the surgical site.
17. Baseline WORC score less than 420.

3.6.2.1 Intra-operative Exclusion Criteria

Subjects will not be randomized and will be terminated from the study if they meet **any one (1)** of the following intra-operative exclusion criteria:

- Rotator cuff is/presents with:
    - fully reparable with adequate tissue quality (equivalent to Goutallier stage 1 or 2)
    - partial thickness tear of the supraspinatous
    - evidence of significant osteoarthritis
- The subject requires concomitant:
    - subscapularis repair
    - labral repair of any type

- Coracoacromial ligament functional deficiency is identified
- Partial repair requires any type of grafting for enhancement of the partial repair procedure

3.7 Early Withdrawal of Subjects

3.7.1 When and How to Withdraw Subjects

Subjects may voluntarily withdraw from the study at any time for any reason. The Investigator(s) may elect at any time to withdraw a subject from the study for any reason unrelated to the study if such a decision is in the subject's best medical interest. Subjects who experience an AE may also voluntarily withdraw or be withdrawn if deemed in the subject's best medical interest. Subjects with a secondary surgical intervention to the index shoulder will also be discontinued in the study. If a subject discontinues the study prematurely or is withdrawn by the Investigator(s), data collected up to the time of withdrawal will be used, if applicable, for analysis. The primary reason for termination or discontinuation will be documented on the End of Study case report form (CRF). Subjects who are withdrawn following randomization for any reason from the study will not be replaced.

3.7.2 Data Collection and Follow-up for Withdrawn Subjects

Subjects who withdraw consent and refuse to complete the follow-up assessments, fail to adhere to protocol requirements, or die during the follow-up phase will be considered end of study at that time. Attempts will be made to retrieve any follow-up data, in particular, regarding possible AEs at the time of study discontinuation. If the Investigator(s) reports a subject as lost to follow-up, the Clinical Research Associate (CRA) will ensure that the designated study staff has documented the reason(s) this occurred and has ensured that every attempt was made by the Investigator(s) to contact the subject to determine subject status. Appropriate documentation will consist of at least two documented attempts at contact via telephone, followed by an attempt to contact via a registered US/Canada post letter.

3.7.3 Study Site Termination

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

- Failure of the Investigator to enroll subjects into the study at an acceptable rate;
- Failure of the Investigator to comply with Food and Drug Administration (FDA) and Health Canada (HC) regulations, the International Conference on Harmonization (ICH) guidelines, IRB/REB policies and procedures;
- Knowingly submitting false information from the study site to the Sponsor or its designee, IRB/REB, and/or regulatory body(s), as applicable; or
- Insufficient adherence to protocol requirements.

Study termination will be performed in compliance with the Sponsor's standard procedures.

3.8 Prior and Concomitant Therapy

Information on concomitant medications used will be recorded on the Concomitant Medication CRF. Any ongoing medication used by the subject within 4 months of enrollment will be considered concomitant medication (e.g., aspirin, Tylenol, vitamins, dietary supplements, etc). Any changes in medication must be noted on the Concomitant Medication CRF.

Any other investigational drug or approved therapy for investigational use is not permitted during study participation.

3.9 Study Interventions – Full Thickness MRCT

A diagnostic arthroscopic evaluation will be conducted to confirm the diagnosis of full thickness MRCT. Once intra-operative eligibility is confirmed, the subject will be randomized to receive one of the following treatments:

- Group I – InSpace device
- Group II – Partial Repair

3.9.1 Clinical and Functional Assessments

All subjects will be clinically evaluated by the Investigator or a qualified individual noted on the Delegation of Authority (DOA) log. Clinical and functional assessments will be measured as noted below:

- Western Ontario Rotator Cuff Index (WORC): a subject self–report questionnaire that is a disease-specific Quality of Life Measurement Tool specifically designed to

evaluate quality of life in persons with pathology of the rotator cuff. It is comprised of 21 items in 5 domains (i.e., physical symptoms, sports and recreation, work, lifestyle, emotions).

- American Shoulder and Elbow Surgeons (ASES): a subject self-report questionnaire and Investigator assessment questionnaire. The subject portion collects information on pain (i.e., 5 questions plus a VAS), instability (using a VAS) and activities of daily living (i.e., 10 questions). The MCID for the ASES has been determined to be 6.4 points, which is the value that is associated with the patient's perception of meaningful change (Michener LA, 2002). The Investigator assessment portion documents ROM, signs, strength, and instability.
- Constant-Murley Shoulder Outcome Score: performed by the Investigator or designee to assess the shoulder and determine at minimum the ROM, external rotation and internal rotation, and power score.
- EuroQOL five dimensions questionnaire (EQ-5D-5L): a subject self-report questionnaire to measure health-related quality of life (HRQOL). It consists of 5 questions capturing the subject's current health across five dimensions (i.e., mobility, self-care, usual activities, pain/discomfort and anxiety/depression). It also includes a numerical visual analogue scale (EQ-VAS).
- Visual Analogue Scale (VAS): a subject self-report questionnaire to measure pain. The patient marks on the line the point that they feel represents their perception of their current state. The amount of pain that a patient feels ranges across a continuum from none to an extreme amount of pain.

3.9.2 Magnetic Resonance Imaging (MRI)

At Week 6 post-operatively, all study treatment arm subjects (Group I: InSpace device [includes only subjects enrolled under Protocol V3.0, May 1, 2017]) will receive an MRI to assess device location.

Week 6 post-operative MRI assessments will consist of reads completed by an un-blinded radiologist(s)

- Group I: InSpace device
    - to assess the device location in the sub-acromial space

At Month 12 post-operatively, all randomized subjects will complete a MRI scan of the treated shoulder.

Month 12 post-operative MRI assessments will consist of reads completed by blinded radiologist(s).

The following MRI scans reads will be performed at Month 12 for the Study

- Group I: InSpace device
    - to assess the device residuals at Month 12 post treatment
    - to assess the shoulder joint and surrounding tissue condition at Month 12 post treatment
- Group II: Partial Repair
    - to assess the shoulder joint and surrounding tissue condition at Month 12 post treatment

3.9.3 Ultrasound

The first fifteen (15) study treatment arm subjects received an ultrasound to measure device position. Ultrasound was performed at Visit 3, 4 and 5 post implantation. The ultrasound series is now complete.

3.10 Visit Summary

3.10.1 Visit 1: Screening/Baseline (days - 45 to - 1)

All potential subjects screened for eligibility will be listed on the Screening and Enrollment Log. The Screening and Enrollment Log will document the date of screening, the results of screening, and the primary reason for excluding the subject (e.g., does not satisfy eligibility criteria or subject declined).

Qualified subjects who agree to participate in the study will be required to sign an IRB/ REB approved ICF. After signing the IRB/ REB approved ICF, study subjects will undergo study-specific procedures and the following activities will be performed.

- **Clinical Assessment:**

Data collected will include but not be limited to:

- Confirm written informed consent, prior to any screening procedures
- Eligibility criteria verification (inclusion/exclusion criteria)

- Medical and surgical history
- Previous non-operative treatment
- Demographics (e.g., age, sex, date of birth, height, weight)
- Work status, living environment, nicotine use
- Concomitant medication, if applicable
- Mechanism of injury, if applicable
- Screening number assignment
- Confirm Visit 2 (surgery) scheduled within 45 days after screening

- **Evaluation Assessment:**

Data collected will include, but is not limited to:

- Constant-Murley Shoulder Outcome Score
- ASES

Each subject will be asked to complete the following subject self-report questionnaires following the shoulder examination:

- WORC
- EQ-5D-5L
- ASES
- VAS

Pre-operative imaging includes (within 9 months of enrollment):

- MRI

3.10.2 Visit 2: Surgery: (day 0)

If the Investigator(s) discovers the presence of a condition at the time of the procedure that would render the subject ineligible for study participation, the subject should be considered as an intra-operative failure and be discontinued from the study. The subject should receive the standard of care as determined by the Investigator(s).

The primary reason for termination or discontinuation will be documented on the End of Study CRF.

If the subject continues to meet eligibility criteria the information collected will include, but not be limited to:

- Date of surgical procedure
- Randomization assignment
- Anesthesia type, time
- Operating room times, procedure times
- Product related information
- AEs

- Concomitant medications

For females of child-bearing potential, a pregnancy test, urine or blood, will be performed no earlier than 2 days before the scheduled surgical procedure, if applicable.

3.10.2.1 Intra-operative Procedure

- **Randomization**
  - If the subject continues to meet all of the intra-operative inclusion and none of the intra-operative exclusion they will be randomized to receive one of the following:
  - **Group I: InSpace Device**
  - **Group II: Partial Repair**

- **Intra-operative Inclusion Criteria**

Subjects MUST meet the following criteria to be randomized in the study:

- Full thickness tear
- Tear size ≥5 cm in diameter (Cofield classification)
- Tear involving ≥ two tendons

- **End of Study – Intra-operative Exclusion**

  Subjects will not be randomized and be considered end of study if they meet **any one (1)** of the following intra-operative exclusion criteria:

  - Rotator cuff is/presents with:
    - fully reparable with adequate tissue quality (equivalent to Goutallier stage 1 or 2)
    - partial thickness tear of the supraspinatous
    - evidence of significant osteoarthritis
  - The subject requires concomitant:
    - subscapularis repair
    - labral repair of any type
  - Coracoacromial ligament functional deficiency is identified
  - Partial repair requires any type of grafting for enhancement of the partial repair procedure

In case of intra-operative failure the subject will **not** be randomized into the study and will **not** be counted as a recruited subject (will be replaced with a new subject).

3.10.3 Visit 3: Day 10 Follow-Up (+/- 6 days)

- **Admission/Discharge information**
    - Length of stay
- **Evaluation Assessment:**

Data collected will include, but is not limited to:

- ASES - Shoulder examination
- AEs, if applicable
- Concomitant medication, if applicable
    - Any changes in concomitant medication

Each subject will be asked to complete the following subject self-report questionnaires following the shoulder examination:

- WORC
- EQ-5D-5L
- ASES
- VAS

3.10.4 Visit 4: Week 6 Follow-Up (+/- 7 days)

- **Evaluation Assessment:**

Data collection and procedures will include but not be limited to:

- Constant-Murley Shoulder Outcome Score
- ASES - Shoulder examination
- AEs, if applicable
- Concomitant medication, if applicable
    - Any changes in concomitant medication
- Compliance with Post-operative Rehabilitation Guideline

Each subject will be asked to complete the following subject self-report questionnaires following the shoulder examination:

- WORC
- EQ-5D-5L
- ASES
- VAS

Post-operative imaging includes:

- Week 6 MRI scan to all study treatment arm subjects (Group I: InSpace device [includes only subjects enrolled under Protocol V3.0, May 1, 2017])

3.10.5 Visit 5: Month 3 Follow-Up (+/- 14 days)

- **Evaluation Assessment:**

Data collection and procedures will include but not be limited to:

- Constant-Murley Shoulder Outcome Score
- ASES - Shoulder examination
- Assessment of evidence of infection (warmth, swelling, skin changes)
- AEs, if applicable
- Concomitant medication, if applicable
    - Any changes in concomitant medication

Each subject will be asked to complete the following subject self-report questionnaire following the shoulder examination:

- WORC
- EQ-5D-5L
- ASES
- VAS

3.10.6 Visit 6: Month Follow-Up (+/-14 days)

- **Evaluation Assessment:**

Data collection and procedures will include but not be limited to:

- Constant-Murley Shoulder Outcome Score
- ASES - Shoulder examination
- Assessment of evidence of infection (warmth, swelling, skin changes)
- AEs, if applicable
- Concomitant medication, if applicable
    - Any changes in concomitant medication

Each subject will be asked to complete the following subject self-report questionnaires following the shoulder examination:

- WORC
- EQ-5D-5L
- ASES
- VAS

3.10.7 Visit 7: 12 Month Follow-Up (+/-1 month)

- **Evaluation Assessment:**

Data collection and procedures will include but not be limited to:

- Constant-Murley Shoulder Outcome Score
- ASES - Shoulder examination
- Assessment of evidence of infection (warmth, swelling, skin changes)
- AEs, if applicable
- Concomitant medication, if applicable
    - Any changes in concomitant medication

Each subject will be asked to complete the following subject self-report questionnaires following the shoulder examination:

- WORC
- EQ-5D-5L
- ASES
- VAS

Post-operative imaging includes:

- Month 12 MRI scan to all randomized subjects (Both Arms)

3.10.8 Visit 8: Month 24 Follow-Up (+/-2 months)

- **Evaluation Assessment:**

Data collection and procedures will include but not be limited to:

- Constant-Murley Shoulder Outcome Score
- ASES - Shoulder examination
- Assessment of evidence of infection (warmth, swelling, skin changes)
- AEs, if applicable
- Concomitant medication, if applicable
    - Any changes in concomitant medication

Each subject will be asked to complete the following subject self-report questionnaires following the shoulder examination:

- WORC
- EQ-5D-5L
- ASES
- VAS

3.10.9 Optional Follow-Up Visit, Unscheduled Visit Procedures

Subjects that have pre-scheduled surgical visits not involving the index or contralateral shoulder (e.g., gallbladder removal, knee arthroscopy), and subjects that have additional visits beyond the study-scheduled visits and within the standard of care do not need documentation, unless associated with an AE (e.g., generalized AE or device/treatment-related AE).

3.10.10 Post-operative Rehabilitation Guideline

Recommended guidelines for post-operative rehabilitation are included for consistency in procedures across all study sites (Appendix I).

3.11 Receiving, Storage, Dispensing and Return of Investigational Product

3.11.1 Receipt and accountability

The InSpace device will be shipped directly to each study site from Ortho-Space Ltd., or designated affiliate.

The Principal Investigator is responsible for ensuring that accurate records are maintained for the receipt and dispensing of all investigational devices, including dates and number of investigational devices received, to whom dispensed (subject-by-subject accounting), and accounts of any investigational devices accidentally or deliberately destroyed. Upon receipt of the shipment, inventory will be performed and an accountability log completed and signed by the person accepting the shipment. The designated study staff will count and verify that the shipment contains all the items noted on the shipment inventory list.

Any damaged or unusable investigational device in a given shipment will be documented. The Investigator or designee must notify the Sponsor of any damaged or unusable investigational devices supplied to the investigator's site. Peel-off labels on the InSpace device package are to be placed in the chart / source documents. These records must be readily available for inspection by the Sponsor or designee (if applicable) during routine site monitoring visits and are open to regulatory authority inspection at any time. The Investigator may dispense investigational devices(s) only to subjects who have enrolled in the study and have signed the IRB/REB approved ICF.

3.11.2 Storage

Until use, the InSpace device should be stored in a secured, clean, and dry area with a maintained temperature of 0-29°C (32-84.2°F) degrees.

3.11.3 Dispensing of Investigational Device

One (1) InSpace device will be implanted per subject according to the randomization assignment. It may be necessary to dispense three (3) InSpace devices to the operating room due to sizing availability. Reconciliation will be performed to document date used or destroyed, subject assignment, and investigational device balance. This reconciliation will be documented on the accountability log, signed and dated by the study staff. Any discrepancies noted will be documented, investigated, and resolved.

3.11.4 Return or Destruction of Investigational Product

Unless otherwise specified, all unused investigational devices must be saved for accountability purposes and returned to the Sponsor or designated affiliate. A copy of the accountability log must be forwarded to the Sponsor or designated affiliate with the returned or defaced investigational devices (as applicable).

4 STATISTICAL ANALYSIS

This section presents general information about statistical considerations and concepts such as randomization, stratification, statistical power, sample size, and a brief discussion on analysis methodology, as well as some data conventions. Detailed descriptions of the statistical analysis methods and data conventions will be in a separate document; i.e., the Statistical Analysis Plan (SAP).

4.1 Treatment Groups

The following treatment groups will be assessed:

Arm	Description
Study Treatment	Group I: InSpace device
Control Treatment	Group II: Partial Repair

4.2 Description of Study Endpoints

4.2.1 Primary Composite Endpoint

The primary composite endpoint has four components as follows:

- WORC improvement of 275 points by Week 6 from pre-operative baseline and maintained at Month 12
- ASES improvement of 6.4 points by Week 6 from pre-operative baseline and maintained at Month 12
- No subsequent secondary surgical interventions (SSSI) in the index shoulder through Month 12
- Absence of Serious Adverse Device Effects (SADEs), through Month 12

The first component of the composite endpoint is a clinical measure. WORC is a validated and reliable disease-specific quality of life index that assesses multiple domains with twenty-one (21) questions from five (5) domains that are scored with use of a 100-mm VAS. The total score ranges from 0 to 2100, with higher scores indicating a worse outcome. Results from Kirkley et al. (2003) and Ekeberg et al. (2010) have established a minimal important change of less or equal to 275 WORC points. In this study, we use the mean difference for a component of the composite endpoint with success declared when a 275-point improvement from pre-operative baseline is achieved by Week 6 and maintained at Month 12.

The second component is an improvement in pain and function. The American Shoulder and Elbow Surgeons Assessment Form (ASES) was developed as a standardized assessment of shoulder function (Richards RR, 1994). The ASES patient self-reported section, consists of 2 dimensions: pain and activities of daily living (function). The pain score is determined from a single pain question, and the function score from the sum of 10 questions specific to activities of daily living. In this study, for a component of the composite endpoint we use the mean difference with success declared if a 6.4-point improvement in the ASES computed score from pre-operative baseline is achieved by Week 6 and maintained at Month 12. This aligns with the ASES MCID determined by Michener et al. (2002).

The third component is the absence of any subsequent secondary surgical interventions (SSSI) in the index shoulder through Month 12.

The fourth component is the Absence of Serious Adverse Device Effects (SADEs), through Month 12.

4.2.2 Secondary Endpoints

Clinical Endpoints:

- Composite endpoint component-level success for WORC compared to baseline
- Composite endpoint component-level success for ASES compared to baseline
- Change in Western Ontario Rotator Cuff Index (WORC) questionnaire scores from baseline. Mean and percent changes as well as the corresponding standard deviations will be calculated.
- Change in American Shoulder and Elbow Surgeons (ASES) from baseline. Mean changes and standard deviations will be calculated.
- Change in Constant-Murley Shoulder Outcome Score from baseline. Mean changes and standard deviations will be calculated.
- Change in EuroQOL five dimensions questionnaire (EQ-5D-5L) from baseline. Mean changes and standard deviations will be calculated.
- Change in Visual Analogue Scale (VAS) scores from baseline. Mean changes and standard deviations will be calculated.
- Change in Range of Motion (ROM) from baseline. Mean changes and standard deviations will be calculated.
- Composite endpoint success at Month 24
  - Imaging endpoints will include reading of MRI scans conducted at:
    - Week 6 post treatment to assess (Group I: InSpace device [includes only subjects enrolled under Protocol V3.0, May 1, 2017]):
      - device location in the sub-acromial space
    - Month 12 post treatment to assess (all randomized subjects):
      - the device residuals (Group I – InSpace only)
      - the shoulder joint and surrounding tissue condition (Group I: InSpace device and Group II: Partial Repair)

4.2.3 Safety Assessments

Safety will be assessed by monitoring the Adverse Events and tolerance post treatment, as detailed in SAFETY AND ADVERSE EVENTS section of this protocol.

Safety will be evaluated by type, frequency, severity, and relatedness of adverse events to study treatment and control treatment.

4.2.4 Radiographic Assessments

In the first year after surgery, the radiological assessment of the rotator cuff will serve as a supportive marker to establish the efficacy for the study success (based on the clinical evaluation of the index shoulder).

Shoulder MRI will be conducted per imaging acquisition guidance (Appendix C) in the following visits:

- Visit 1 (Screening/Baseline): All Subjects (Both Arms): Pre-operative baseline MRI scan within 9 months of enrollment.
- Visit 7 (12 Month Follow-Up): All Subjects (Both Arms):

Group I: InSpace device

- to assess the device residuals at 12 months post implantation
- to assess the shoulder joint and surrounding tissue condition at 12 months post implantation.

Group II: Partial Repair

- to assess the shoulder joint and surrounding tissue condition at 12 months post implantation.

Additionally, at Week 6 all study treatment arm subjects (Group I: InSpace device [includes only subjects enrolled under Protocol V3.0, May 1, 2017]) will receive an MRI to assess the device location in the sub-acromial space.

Shoulder MRI will be conducted per imaging acquisition guidance (Appendix H) in the following visit:

- Week 6 (Group I: InSpace device [subjects enrolled under Protocol V3.0, May 1, 2017])

In addition, at any stage during the follow up period, if deemed necessary by the Investigator, (due to clinical symptoms such as suspected infection, suspected device displacement associated with deterioration in shoulder function or symptomatic re-tear of the repaired rotator cuff) shoulder radiography (X-Ray), ultrasound or MRI may be performed to confirm shoulder condition or any surgery associated adverse effects. Imaging results will be assessed by independent certified radiologist.

4.3 Hypotheses

The null hypothesis is that there is at least a 10% disadvantage in the composite success percent for InSpace vs. Partial Repair Control while the alternative hypothesis is that there is less than a 10% disadvantage for InSpace (P_T) vs. Partial Repair Control (P_C).

H_0: $P_T - P_C \leq -10\%$

versus

H_A: $P_T - P_C > -10\%$.

The non-inferiority design allows a penalty-free test for superiority in the event that non-inferiority is established (one-sided $p \leq 0.025$). Non-inferiority will rule out the 10% non-inferiority margin favoring InSpace while superiority will need to rule out a 0% margin favoring InSpace.

This sequential hypothesis testing has the Type I error rates for both the non-inferiority and superiority controlled at one-sided 2.5% Type 1 error with superiority to be tested after non-inferiority as:

H_0: $P_T \leq P_C$

versus

H_A: $P_T > P_C$,

4.4 Sample Size Determination and Rationale

A total of 184 subjects (92 subjects per group) will be randomized to ensure that at least 166 subjects (83 subjects per group) complete the study; it is assumed that 10% will be excluded. The hypothesis testing will be one-sided with 2.5% Type I error to test non-

inferiority with 80% power. The null hypothesis of a 10% absolute disadvantage vs Partial Control will be tested against a 10% absolute advantage vs. Partial Control for the purpose of sample size justification.

Table 1.A.1 displays the sample size for various surgical control success percents ranging from 50% to 62.5% for the composite endpoint; this will be adjusted at the interim analysis. The 50% success percent is the worst case and will decrease as the success rate deviates from 50%; the sample size would increase to 180 from 166.

Table 1.A.1: Lower 97.5% confidence limit to rule out 10% N-I margin for success % differences: 80% power

	1	2	3
Partial Repair success %, P_C	0.500	0.600	0.625
InSpace success % expected, P_T	0.600	0.700	0.725
Lower limit for $P_T - P_C$, LL	-0.100	-0.100	-0.100
Power (%)	80	80	80
n per group	90	85	83

Table 1.A.2 presents the corresponding InSpace success percents that would achieve statistical significance to rule out a 10% disadvantage. For 166 completers, a 3.8-4.2% InSpace advantage is needed (Columns 1-2).

Table 1.A.2: Lower 97.5% confidence limit to rule out 10% N-I margin for success % difference: One-sided p=0.025

	1	2	3
Partial Repair success %, P_C	0.500	0.600	0.625
InSpace success % expected, P_T	0.538	0.641	0.6667
Lower limit for $P_T - P_C$, LL	-0.100	-0.100	-0.100
n per group	90	85	83

Table 1.A.3 presents the corresponding InSpace success percents that would achieve superiority. A 14-14.2% InSpace advantage is needed (Columns 1-2).

Table 1.A.3: Lower 97.5% confidence limit to establish superiority for success % difference: One-sided p=0.025

	1	**2**	**3**
Partial Repair success %, P_C	0.500	0.600	0.625
InSpace success % expected, P_T	0.642	0.74	0.764
Lower limit for $P_T - P_C$, LL	0.000	0.000	0.000
n per group	90	85	83

4.5 Randomization

This is a non-inferiority prospective, single blinded, multi-center, randomized, pivotal study. The randomization will be central and use a mixed block size with a 1:1 ratio of study treatment group to control treatment group.

An individual independent of the study execution team will develop the randomization schedule. Subjects who have met all of the inclusion and none of the exclusion criteria, who have provided written informed consent will be randomly assigned to the study treatment group or the control treatment group based on this randomization schedule. The randomization assignment will be made through an Interactive Web Randomization System (IWRS).

4.6 Stratification and Site Blocking

Stratification is used to assure a within-stratum-balanced distribution of subjects between the two groups. Prior to randomization, subjects will be stratified based on gender and site.

4.7 Blinding

4.7.1 Study Blinding

The study will remain blinded until all subjects complete the Month 12 evaluation. The Month 12 report will contain all effectiveness results including clinical, imaging, and safety data.

4.7.2 Subject Blinding

Subjects will be blinded to treatment assignment until the completion of the study. All efforts will be made to keep the subject blinded through Month 24. Should a subject undergo subsequent arthroscopy for recurrent or new symptoms, withdraw from the study, or be terminated from the study, the blinded assignment will be revealed to the subject and the Investigator will provide care as standard and usual.

4.8 Interim Analysis (IA)

An Interim Analysis (IA) will be conducted when approximately 80 per-protocol subjects (~40 per treatment group) have been randomized and completed the Month 12 post-treatment follow-up. Only subjects completing the Month 12 post-treatment follow-up, including early withdrawals, will be included in the interim analysis.

The procedures for this IA will be based on a standard operating procedure (SOP) that has a well-established firewall to protect the integrity of the study, and the Type I Error rate will be adjusted to maintain the Trial-wise Error rate. The IA will be performed by an unblinded statistician, who is not otherwise associated with the conduct of this study. The IA will be conducted under the auspices of an independent Data Safety Monitoring Board (DSMB).

The objectives of this initial IA are to apply a promising zone methodology to make the following decisions:

- Re-assess sample size to evaluate the sample size estimations, which will serve in the planning of the remaining study. An unblinded statistician will conduct the power analyses.
- Assess futility of continuing the study based on the interim data.

The study will not be stopped for superiority.

4.8.1 Procedures for Interim Analysis

- Cutoff dates for collection of CRFs, data cleaning, database lock and analysis is established based on an estimated target date of the 80th treated subject per protocol completing the Month 12 post treatment follow up.
- All data received by the cutoff date is entered, validated, queries generated and resolved or pending queries documented.
- The database is locked for the IA.
- The locked database is saved in a drive to which only the unblinded statistician responsible for the IA has access.

Using this data, the unblinded statistician will prepare safety summaries and calculate the following metrics for the primary endpoint:

1. Composite success percents (P_t and P_c) at Month 12.

2. The dropout rate at the time of the IA.
3. The Conditional Power (CP) Analysis of the study at the time of the IA (Chen, 2004). (The method for this calculation is provided in the paragraph below).
4. The revised sample size requirement based on this IA (The rule and method for sample size recalculation and p-value adjustment are provided below).

4.8.2 Conditional Power Calculation

The CP will be calculated according to the below formula (Chen, 2004) using the Month 12 success percents for the study treatment group to control treatment groups

$$CP\ (f_1,z_1) = \Phi\ \{\ z_1 / \sqrt{f_1\ (1-f_1)}\ -\ z_\alpha / \sqrt{(1-f_1)}\ \}$$

Where:

- $CP(f_1,z_1)$ is the conditional power at the IA
- **Φ{.}** is the cumulative distribution function of a standard Normal distribution ($\mu=0$, $\sigma^2 = 1$)
- f_1 is the fraction of patients enrolled and used in the IA before decision of increasing the sample size
- z_α is the upper α bound for standard Normal distribution
- z_1 is the standardized Normal, since the primary endpoint is based on proportions the z-score will be obtained from the following formula:

$$z_1 = ((p_t - p_c - \delta)/\sqrt{((p_t(1-p_t)/n_t) + (p_c(1-p_c)/n_c))}$$

Where:

- p_t = the Composite success percent at Month 12 for the subjects in the study treatment group
- p_c = the Composite success percent at Month 12 for the subjects in the control treatment group
- $pt(1-p_t)$ = the standard deviation for the subjects in the study treatment group
- $pc(1-p_c)$ = the standard deviation for the subjects in the control treatment group
- n_t = the number of subjects in the study treatment group used in the IA
- n_c = the number of subjects in the control treatment group used in the IA
- t = the InSpace group
- c = the Control group

The resulting CP will be used to determine whether the sample size needs to be increased or remain unchanged.

4.8.3 Rules and Method for Increasing Sample Size

Rules:

- If the conditional power at the time of the interim analysis is < 10% then the study will be terminated for futility.
- If the conditional power is >= 10% but <36%, then the sample size will not be increased and the study will continue based on the original sample size.
- If the conditional power is >= 36% and less than 80%, then the sample size will be adjusted to retain the original power of 80% or doubling the sample size, whichever is the smallest.
- If the conditional power is >= 80%, then the study will continue as is.

The sample size may also be adjusted to reflect the Partial Repair control success percent.

If the dropout rate is >10% for reasons other than safety or effectiveness, then the sample size will be increased accordingly to ensure that the PP accrual target is met.

Regardless of the size of the CP, the study sample size will not be reduced.

Data Provided to DSMB:

The DSMB will receive a statistical report, the details on the content of the report is described in the DSMB charter.

Stopping Rule:

The study will not be stopped for superiority.

Information Provided to Sponsor by Data Safety Management Board (DSMB):

The DSMB will make recommendations to the Sponsor on the futility and sample size adjustment and any safety concerns.

Type I Error Rate Adjustment:

The overall Type I error rate will be one-sided 2.5%, which is equivalent to two-sided 5%. There will be no Type I error rate adjustment as there is no intention to stop the study for efficacy benefit. In addition, the sample size is planned to be increased when the interim conditional power is promising and this will protect the Type 1 error (Mehta, Pocock – 2000).

4.9 Effectiveness Analyses

The primary effectiveness analysis will be conducted after all recruited subjects have reached their primary endpoint at the Month 12 post treatment. This analysis will evaluate the primary endpoint at Month 12, plus all available imaging and key safety data; results will be presented according to unblinded treatment group. This initial report will be used to submit the primary results of the study.

All subjects will be followed out to Month 24 to extend all analyses through Month 24 for the end of study analysis. Upon study completion, the analysis for the secondary endpoints will be conducted and reported inclusive of all available imaging and safety data. This subsequent report will be used to submit the final results of the study, including the Month 12 and Month 24 post treatment assessments.

4.10 General Statistical Considerations

All collected study data will be presented in subject data listings. Statistical analyses will be performed using SAS® version 9.3 or later. Descriptive statistics (n, mean, standard deviation, median, minimum and maximum) will be calculated by treatment group for continuous variables. Frequencies and percentages will be presented by treatment group for categorical variables.

4.11 Analysis Populations

4.11.1 Intent-to-Treat Population

The Intent-to-Treat population is defined as all randomized subjects who have had at least one post treatment efficacy assessment analyzed as treated.

The ITT analysis population will be used as the primary analysis population supportive of superiority and will also be used to generate all other effectiveness endpoints in support of superiority and to confirm non-inferiority.

4.11.2 Per Protocol Population

The per-protocol analysis set (PP) includes all subjects in the ITT analysis set without any major protocol deviations.

Given that this is a non-inferiority analysis, the PP analysis population will be used as the primary analysis population supportive of non-inferiority and will also be used to generate all other effectiveness endpoints in support of non-inferiority and to confirm superiority.

4.11.3 Safety Population

The Safety population is defined as all randomized subjects who underwent the study surgical procedure (i.e., InSpace device or Partial Repair). This population will be used for the analysis of safety parameters.

4.11.4 Covariates

For efficacy analyses, gender will be used as a covariate in the primary endpoint analysis models while gender and the baseline covariate will be used as covariates in secondary effectiveness endpoint analyses.

4.11.5 Missing Data

For efficacy evaluation data points, SAS PROC MI will be used to deal with missing data; the method will be detailed in the Statistical Analysis Plan (SAP) for the study.

4.11.6 Multiple Comparisons and Multiplicity

For the primary endpoint, non-inferiority hypotheses will be tested at Month 12 for the primary endpoint first and then for two first-ranked secondary endpoints (WORC and ASES). Type I error will be controlled by requiring significant (one-sided $p \leq 0.025$) for non-inferiority testing to achieve an extended claim in the following pre-defined order using the non-inferiority margins specified in the SAP:

- Mean WORC change from pre-operative baseline is non-inferior at Week 6 and maintained at Month 12 for the InSpace device.
- Mean ASES change from pre-operative baseline is non-inferior at Week 6 and maintained at Month 12 for the InSpace device.

Superiority will also be tested if non-inferiority is proven penalty-free per claim using one-sided $p \leq 0.025$ since the alternative hypothesis of superiority is a subset of the alternative hypothesis of non-inferiority. Thus, each endpoint, for which non-inferiority is

sequentially established, will then be tested for superiority; the inability to reach superiority for a specific endpoint will not terminate the sequential testing plan.

There are no further multiple comparisons involving time or endpoints to impact the overall Type I error.

4.12 Statistical Methods

A SAP will be developed and approved before the interim analysis database is locked. The SAP will present the detailed statistical methodology to be used in analyzing the efficacy and safety data from this study.

All the effectiveness endpoints will be analyzed using both the ITT (primary for superiority and secondary for non-inferiority) and PP (primary for non-inferiority and secondary for superiority) populations. The PP population will be primary to test non-inferiority while the ITT population will be primary to test superiority. The ITT population analyses will not be performed if less than 5% of the ITT population is excluded or did not use the randomized treatment. The ITT analysis will be performed using the randomized treatment assigned while the PP analyses will be performed using the actual treatment used. All safety analysis will be conducted using the safety population according to the actual study treatment.

All primary and secondary endpoints will be tested using one-sided 97.5% confidence intervals. All primary and secondary analyses will be repeated for the ITT population.

All data collected will be summarized according to the variable type:

- **Continuous data summaries comparing treatment groups will include:**
    - Number of observations, mean, standard deviation, median, and minimum and maximum values.
    - Unpaired t-tests for the mean changes from baseline for each secondary outcome at each nominal visit.
    - Generalized Estimating Equation (GEE) analysis (SAS PROC MIXED) analysis including the respective baseline covariate, age, gender, treatment, visit, and visit-treatment interaction.

- **Categorical data summaries will include:**
    - Frequency counts and percentages.

4.12.1 Subject Disposition

The disposition of all subjects who sign an ICF will be provided. The numbers of subjects screened, randomized, completed, and discontinued during the study, as well as the reasons for all post-treatment discontinuations will be summarized by treatment group. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

4.12.2 Demographic and Baseline Characteristics

Demographic and baseline characteristic data will be summarized descriptively and/or presented as a by-subject listing for the Safety population and Per Protocol populations.

4.12.3 Protocol Deviations

The deviations occurring during the clinical study will be summarized and/or presented as a by-subject listing.

4.12.4 Prior and Concomitant Medications

Concomitant medications will be summarized separately for the Safety and Per Protocol populations. All prior and concomitant medications recorded in the case report form will be coded to the drug substance level (i.e., generic term) using the most recent version of WHO Drug. Descriptive summaries, by treatment group, will be prepared using the coded term. All prior, continuing, and new medications recorded in the case report form will be listed.

4.12.5 Primary Endpoint Analysis

The primary analysis will be a logistic regression model for Month 12 success with age, gender, and treatment as the model covariates for the PP and ITT populations using the composite endpoint. The method of Firth (Firth, 2013) will be used to compute unbiased percent estimates of the composite endpoint for each treatment group from the logistic regression model odds ratio estimate.

The same approach will be used for the Month 24 analysis using the PP and ITT populations.

4.12.6 Secondary Endpoint Analyses

Endpoint-specific Generalized Estimating Equation (GEE) models (SAS PROC MIXED) will be used to further evaluate the secondary endpoints for non-inferiority and superiority using the PP and ITT populations. The non-inferiority margins (δ) will be prospectively defined in the AP. The method will be provided in detail in the SAP for the study.

Additionally, the composite endpoint at Months 12 and 24 except requiring: (1) no subsequent secondary surgical interventions (SSSI) in the index shoulder, and (2) no Serious Adverse Device Effects (SADEs) will be performed with multiple time point iterations determining when WORC and ASES clinical improvements threshold are achieved. The method will be provided in detail in the Statistical Analysis Plan (SAP) for the study.

4.12.7 Other Outcome Analyses

The following descriptive analyses will further support publications comparing the InSpace device with Partial Repair control as per the original SAP. Unpaired t-tests and one-sided 97.5% confidence intervals will be computed at Weeks 6 and 12 as well as at Months 6, 12, and 24 for the PP and ITT populations:

- Change from baseline in the mean and mean percent WORC scores
- Change from baseline in the mean and mean percent American Shoulder and Elbow Surgeons (ASES)
- Change from baseline in the mean and mean percent Constant-Murley Shoulder Outcome Score
- Distribution change from baseline in the EuroQOL five dimensions questionnaire (EQ-5D-5L)
- Change from baseline in the mean and mean percent Visual Analogue Scale (VAS) scores from baseline
- Change from baseline in the mean and mean percent Range of Motion (ROM)
- Composite endpoint success at Month 24

4.12.8 MRI

MRI findings will be summarized descriptively. At Month 12 post-treatment, shoulder joint and surrounding tissue condition for both InSpace and Partial Repair will be described . In addition, the device residual will be evaluated for the InSpace group at

Month 12. At Week 6, the device location in the sub-acromial space will be described for the InSpace group only (Group I: InSpace device [includes only subjects enrolled under Protocol V3.0, May 1, 2017]).

4.12.9 Safety Analyses

All safety assessments will be tabulated and no hypothesis testing will be conducted in this analysis. For continuous variables data, will be summarized by treatment group using n, mean, standard deviation, median, minimum and maximum values. For categorical variables, data will be summarized by treatment group using frequency and percentage.

The Safety population will be used for all analyses of safety. All safety parameters will be presented descriptively and as data listings.

4.12.9.1 Adverse Events / Adverse Device Effects

Adverse Events will be coded using most recent version of MedDRA. Treatment Emergent AE's (TEAE) are defined as events with an onset on or after the subject randomization. TEAEs will be summarized by treatment group, System Organ Class, and preferred term. The following TEAE summaries will be provided:

- Overall TEAEs
- TEAEs by severity grade
- TEAEs by relationship to study device.

Related AEs (ADEs) will also be presented. In addition, separate summaries of SAEs and SADEs will also be presented.

The total number of subjects with at least one AE/ADE and the number of AEs/ADEs will be derived. If more than one AE/ADE with the same preferred term occurs within a subject during the study period, they will be counted only once for that subject using the worst reported severity and causal relationship to the intervention. AEs/ADEs will also be tabulated versus worst severity and worst relationship to the intervention.

Symptoms recorded before administration of intervention will only be presented in listings.

5 SAFETY AND ADVERSE EVENTS

5.1 Definitions

5.1.1 Adverse Event

An AE can be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a study device, whether or not considered related to the study device.

5.1.1.1 Expected Adverse Events

Expected Adverse Events include:

- Post-operative fever
- Hematoma
- Localized pain
- Increase in shoulder pain
- Sensation decrease at incision site
- Inflammation
- Infection
- Prolonged surgery time due to device breakage or malfunction

5.1.2 Adverse Device Effect

ADEs are AEs caused by or related to the device.

5.1.3 Serious Adverse Events

Events are classified as serious if they meet any of the following criteria (in accordance with the recommendations of ICH [Federal Register, October 7, 1997, Vol. 62, No. 194, pp 52239-45]):

- Results in death,
- Is life-threatening (NOTE: the term "life-threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability/incapacity,
- Is a congenital anomaly/birth defect

Additionally, events are classified as serious if they meet any of the following criteria:

- Requires intervention to prevent permanent impairment/damage, or
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse device effect when, based upon appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

5.1.4 Unanticipated Adverse Device Effect (United States)

An Unanticipated Adverse Device Effect is described as any serious adverse effect on health or safety or any life-threatening problem or death caused by or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects (21 CFR 812.3(s)).

5.1.5 Reportable Incident (Canada)

According to the Canadian Medical Devices Regulations (Sections 59 and 81), a reportable incident is any incident that:

(a) is related to a failure of the device or a deterioration in its effectiveness, or any inadequacy in its labeling or in its the directions for use; and

(b) has led to the death or a serious deterioration in the state of health of a patient, user or other person, or could do so were it to recur.

5.2 Recording of Adverse Events and Incidents

At each contact with the subject, the Investigator or designee must seek information on AEs through questioning. Information on all AEs should be recorded immediately in the source document and in the appropriate AE module of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded in the source document, though should be grouped under one diagnosis.

All AEs occurring during the study must be recorded in standard medical terminology. The clinical course of each event should be followed until resolution, stabilization, or until it

has been determined that the study intervention or study participation is not the cause. All unresolved AEs should be followed by the Investigator until the events are resolved, the subject is lost to follow-up, through the end of the study, or until it has been determined that the study intervention or participation is not the cause (whichever timing occurs first). Any Serious Adverse Event (SAE) that occurs until thirty (30) days after the study and is considered to be related to the study device or study participation should be recorded and reported immediately.

5.3 Reporting

5.3.1 Adverse Event Reporting Period

The study period during which AEs must be reported is defined as from the initiation of any study treatment or randomization through the end of the study intervention follow-up.

5.3.2 Reporting Adverse Events

Any AE (clinical sign, symptom, or disease) temporally associated with the use of this study device, whether or not considered related to the study device, shall be documented on the AE CRF, except those physical assessment findings that are considered to be clinically insignificant.

All AEs meeting the above noted criteria reported by the subject or observed by the Investigator will be individually listed. The description of the event (confirmed diagnosis, if available), date of onset, date of resolution, severity and relationship to study device, action taken, outcome, and seriousness will be reported.

The Investigator will evaluate all AEs as follows:

- ***CTCAE Grade (Intensity) Assessment***

The guidelines outlined in CTCAE v4.03 will be used for assessing the intensity of the event. The general guidelines for assessing the AE grade appear below. Full guidelines may be obtained at http://evs.nci.nih.gov/ftp1/CTCAE.

Table 3: CTCAE v4.03 General Guidelines

Grade	Description
Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL†.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.‡

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

†Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

‡Unlike the AE outcome assessment (see Section 13.3.2), a subject may have more than one Grade 5 event.

-Common Terminology Criteria for Adverse Events (CTCAE), v4.03: June 14, 2010

- ***Causality Assessment***

AEs will be assigned a relationship (causality) to the study treatment or surgical procedure. The Investigator will be responsible for determining the relationship between an AE and the study treatment/surgical procedure. The type of event, organ system affected, and timing of onset of the event will be factors in assessing the likelihood that an AE is related to the study treatment/surgical procedure. Relationship of AEs to study treatment will be classified as follows:

- Not Related: Any reaction that does not follow a reasonable temporal sequence from administration of the study device AND that is likely to have been produced by the subject's clinical state or other modes of therapy administered to the subject.
- Related: A reaction that follows a reasonable temporal sequence from administration of the study device or control surgical procedure AND that follows a known response pattern to the suspected device/surgical procedure.

- ***Action Taken as a Result of the Event***

The action taken in terms of treatment provided will be as either: none, medication administered, therapy administered, surgery, study treatment unblinded, or other (with a specification).

- ***Outcome Assessment***

The outcome of the event will be assessed as either: resolved, resolved with sequelae, ongoing, lost to follow-up or death. Only one AE per subject is allowed to have an outcome assessment as "death." If there are multiple causes of death for a given subject, only the primary cause of death will have an outcome of death.

5.3.3 Reporting Serious Adverse Events and Incidents

For any **SAE** the Principal Investigator must notify the Sponsor's Medical Monitor, within 24 hours of becoming aware of the event and send the completed Serious Adverse Event/Unanticipated Adverse Device Effect (SAE/UADE) Report to the Sponsor's Medical Monitor within 48 hours. In addition, all IRB/REB reporting requirements will be followed.

The Principal Investigator shall make an accurate and adequate report of any **SAEs or Unanticipated Adverse Device Effects (UADE)**. The Principal Investigator shall document any such report on the appropriate CRF and fax/email any initial or follow-up report to the Sponsor's Medical Monitor and to the IRB/REB (as applicable) that has reviewed and continues to review the study.

- **Pre-existing Condition:**

  A pre-existing condition, other than the condition being treated, is one that is present at the start of the study. A pre-existing condition is recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study.

- **General Physical Assessment Findings:**

  At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the end of the study, any new clinically significant findings/abnormalities that meet the definition of a SAE must be recorded and documented as a SAE.

- **Post-study Serious Adverse Event:**

All unresolved SAEs should be followed by the Investigator until the events are resolved, the subject is lost to follow-up, through the end of the study, or until it has been determined that the study intervention or participation is not the cause (whichever timing occurs first). At the last scheduled visit, the Investigator should instruct each subject to report any subsequent event(s) until thirty (30) days after study completion that the subject or the subject's personal physician believes to be related to participation in the study. The Investigator should notify the Sponsor's Medical Monitor of any death or SAE occurring at any time after a subject has discontinued or terminated study participation that is related to the study.

- **Hospitalization, Prolonged Hospitalization, or Surgery:**

  Any medical conditions that occurs after randomization and results in hospitalization or prolonged hospitalization should be documented and reported as a SAE unless specifically instructed otherwise in this protocol. Any condition responsible for surgery should be documented as a SAE if the condition meets the criteria for a SAE.

  Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as a SAE in the following circumstances:

  - Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition.
  - Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the Investigator (e.g., secondary post-operative hemorrhage).

5.3.3.1 Investigator Reporting: Notifying the Sponsor

Any SAE or UADE must be reported to the Sponsor's Medical Monitor via telephone, fax, or email within 24 hours of becoming aware of the event:

SPONSOR'S MEDICAL MONITOR CONTACT INFORMATION

[redacted]

[redacted]

[redacted]

Within 48 hours after the initial report, the Investigator must provide further information to the Sponsor's Medical Monitor on the SAE or UADE in the form of a written narrative. This should include a copy of the completed SAE/UADE Report Form and any other related diagnostic information that will assist in the understanding of the event. Significant new information on ongoing SAEs should be provided promptly to the Sponsor's Medical Monitor. All identifiable reference to the subject except for the subject screening number will be redacted from any report sent to the Sponsor's Medical Monitor.

5.3.3.2 Investigator Reporting: Notifying Health Canada

Investigators are responsible for reporting device related serious adverse events and incidents to Health Canada within 72 hours. The Investigator shall assist the Sponsor in generating a preliminary report within 10 days, containing preliminary observations, a course of action for the investigation, and a timeline for a final report (Section 60 of the Medical Device Regulations).

5.3.3.3 Investigator Reporting: Notifying the IRB/REB

Investigators are responsible for safety reporting to their IRB/REB. Investigators are responsible for complying with their IRB/REB's reporting requirements for SAEs, though they must notify their IRB/REB within 10 working days of becoming aware of the event for any potential UADEs (21 CFR 812.150(a)(1)). The Investigator shall assist the Sponsor in generating the report of the UADE evaluation within 10 days after the Sponsor first receives notice of the effect. (21 CFR 812.46(b), 812.150(b)(1)).

5.3.3.4 Reporting Deaths

The following describes the Investigator reporting requirements in the event of a death, considered a SAE, which occurs during the course of a study:

- Notify the Sponsor's Medical Monitor within 24 hours of becoming aware of the event,
- Provide the completed SAE/UADE Report Form to the Sponsor's Medical Monitor within 48 hours of the event,

- Notify the IRB/REB of the death per IRB/REB reporting requirements.

Should the Investigator determine the death to be device-related and unanticipated, it is considered an UADE, and the following Investigator reporting requirements should be followed:

- Notify the Sponsor's Medical Monitor within 24 hours of becoming aware of the event,
- Provide the completed SAE/UADE Report Form to the Sponsor's Medical Monitor within 48 hours of the event,
- Notify the IRB/REB of the death per IRB/REB reporting requirements, but no later than 10 days of becoming aware of the event

5.3.4 Informed Consent Violation Reporting

If the Investigator uses the study device without obtaining informed consent, the Investigator shall report such use to the Sponsor and the reviewing IRB/REB within 5 working days after the use occurs (21 CFR 812.150(a)(5)).

5.3.5 Protocol Deviation Reporting

The Investigator shall notify the Sponsor and the reviewing IRB/REB of any deviation from the protocol to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred (21 CFR 812.150(a)(4)). All other deviations from the protocol will be reported on the appropriate CRF and reported to the IRB/REB, if required. Every effort shall be made to comply with the requirements of the protocol to avoid deviations.

5.3.6 Progress Reports

The Investigator shall submit Progress Reports on the study to the Sponsor and the reviewing IRB/REB at regular intervals, but in no event less often than yearly (21 CFR 812.150(a)(3)).

5.3.7 Final Report

The Investigator shall, within 3 months after termination or completion of the study or the Investigator's part of the study, submit a Final Report to the Sponsor and the reviewing IRB/REB (21 CFR 812.150(a)(6)).

5.4 Unblinding Procedures

Data are to remain blinded per protocol throughout the study. However, unblinding of subjects by the DSMB, data manager and/or statisticians may occur in the event of a SAE that is deemed related to the study intervention. If time permits, the Investigator should make every attempt to contact the Sponsor and/or Medical Monitor before unblinding any subjects' treatment. For emergent unblinding, appropriate study personnel must contact the Sponsor and the Medical Monitor as soon as possible after the incident to report the details surrounding the emergency unblind and to receive instruction on follow-up procedures.

5.5 Data Safety Monitoring Board

The Data and Safety Monitoring Board (DSMB) consists of a group of individuals (including independent Statistician and at least one independent Senior Orthopedic Surgeon experienced with the study indication), appointed by the Sponsor or its designee, with pertinent expertise that will review accumulated data at the interim analysis from the study. The DSMB advises the Sponsor regarding the continuing safety of subjects and those yet to be voluntarily recruited to the study, as well as the continuing validity and scientific merit of the study. Unblinded data reviewed by the DSMB will be kept confidential and protected from inadvertent or inappropriate access by the Sponsor or its designee. Following review of data generated from the interim analysis, the DSMB may advise the Sponsor to continue, redesign, or stop the study.

5.6 Study Stopping

The Sponsor may terminate the study at any study site, at any time, for any of the following reasons:

- 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
- Recommendation made by the DSMB
- Administrative decision

5.7 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her study site. Safety monitoring will include careful assessment and appropriate reporting of AEs. Medical monitoring will include a regular assessment of the number and type of SAEs.

5.8 Assessment of Risks and Benefits

Any surgical procedure poses a potential risk, and the procedures undertaken as part of this study are no exception. There are always risks associated with any surgery or treatment and associated anesthesia, including death.

These risks have been minimized by establishing strict inclusion/exclusion criteria to assure only appropriate surgical candidates participate in the study. A diagnostic arthroscopy will be used to confirm that all inclusion criteria and no exclusion criteria are met. In addition, only trained surgeons with expertise in sports medicine and expertise in performing arthroscopic shoulder procedures will participate in this study.

All study participants may benefit from having frequent physician visits and close observation. Additionally, the results of this study may benefit both physicians treating subjects and subjects diagnosed with full thickness MRCTs by generating data regarding the safety and outcome of the procedure.

Subjects will be advised of the potential risks and benefits associated with this study in the IRB/REB approved ICF.

5.8.1 Risks of Procedure

Possible risks that may occur post-operatively with an arthroscopic treatment for a full thickness MRCT procedure are identified as follows:

- Deltoid detachment
- Stiffness
- Frozen shoulder

- Joint effusion
- Tendon re-tear
- Hematoma
- Adhesions or arthrofibrosis
- Hemarthrosis
- Loss of motion
- Localized pain
- Sensation decrease at incision site
- Inflammation
- Wound infection
- Wound drainage
- Fever
- Synovitis
- Treatment failure due to rehabilitation non-compliance
- Swelling and bruising
- Nerve injury
- Tendon Injury
- Delayed wound healing
- Vascular injury
- Conversion to mini-open or open procedure
- DVT
- PE
- General risks associated with surgery and anesthesia (i.e., dizziness, fainting, difficulty breathing)

5.8.2 Risks of Study Device

Anticipated study device-related risks are identified below:

- Tissue response to the implant
- Re-operation of the index shoulder
- Device displacement from the sub-acromial space
- Prolonged surgery time due to device breakage or malfunction

5.8.3 Benefits of Study Device

Potential benefits of the study device include:

- Reduction of shoulder pain
- Improved quality of life
- Ability to return to activities of daily life following short rehabilitation.

6 DATA HANDLING AND RECORD KEEPING

6.1 Confidentiality

All information and data concerning subjects or their participation in this study will be considered confidential and handled in compliance with the ICH E6 and all applicable regulations including the requirements of the Federal and Provincial Data Protection regulations, and additionally the Personal Information Protection and Electronic Documents Act (PIPEDA 2000). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

Only authorized personnel, the Sponsor or its designee, and applicable regulatory bodies will have access to these confidential files. All data used in the analysis, reporting, and publication of this study will be maintained without identifiable reference to the subject. The HIPAA (Health Insurance Portability and Accountability Act) authorization adds to protections already provided by the elements of ICF and may be contained within the ICF document or as a separate document. The HIPAA document informs the subject that they can withdraw authorization to use data or samples not already submitted to the Sponsor or its designee and that the request must be in writing. If the subject allows samples to be used after withdrawal from the study, this permission may be withdrawn at a later date. The HIPAA authorization specifies who may review confidential medical information and to whom test results will be submitted. It also describes that test results obtained solely for research will not be part of a subject's medical record.

In the event that a subject revokes authorization to collect or use PHI, the Investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (i.e., that the subject is alive) at the end of their scheduled study period.

6.2 Source Documents

Source data is all information, original records of clinical findings, observations, or other activities in a study necessary for the reconstruction and evaluation of the study. Source data are contained in source documents. Examples of source documents include, but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, subject's diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, subject files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the study.

The following data may be recorded directly in the CRF, which will then be considered as source data:

- WORC
- VAS
- ASES
- EQ-5D-5L
- VAS
- Imaging observations

6.3 Case Report Forms

The CRF is an integral part of the study and subsequent reports. The CRF provided by the Sponsor must be used to capture all study data recorded in the subject's medical record. The CRF must be kept current to reflect subject status during the course of the study. Only a subject screening number will be used to identify the subject. The Investigator must keep a separate log of subject names and medical record numbers (or other personal identifiers). After obtaining written source document information from each subject at each visit, the study site will enter the data into the CRF (paper or electronic). The monitor is responsible for performing on-site monitoring at regular intervals throughout the study to verify adherence to the protocol and applicable regulations on the conduct of clinical research as well as to ensure completeness, accuracy, and consistency of the data entered in the CRF. At the study site, the monitor must have access to subject medical records, study-related records, and written source documentation needed to verify the entries on the CRFs. Final monitored and/or audited CRFs will be available at all times, unless specified in writing to the Sponsor. These CRFs must be reviewed and verified for accuracy by the Principal

Investigator and signed off (via electronic and/or paper signature). A copy of the final CRFs will remain at the Investigator's study site at the completion of the study.

6.4 Data Management

Data management and handling will be conducted according to the study specific Data Management Plan in accordance with applicable guidelines.

6.5 Records Retention

Investigators are required to maintain all study documentation, including CRFs, ICFs, and adequate records for the receipt and disposition of the investigational device according to the regulatory requirements and/or until notified by the Sponsor that the records may be destroyed. If the Principal Investigator retires, relocates, or for other reasons withdraws from the responsibility of keeping the study records, custody must be transferred to a person who will accept responsibility. The Sponsor must be notified in writing of the name and address of the new custodian.

7 STUDY MONITORING, AUDITING, AND INSPECTING

A monitor, whether an employee of the Sponsor or its designee, has the obligation to follow this study closely. In doing so, the monitor will visit the study sites at periodic intervals, in addition to maintaining necessary contact. The monitor will maintain current personal knowledge of the study through observation, review of study records and source documentation, and discussion of the conduct of the study with the Investigator and study staff. 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. The Sponsor audit reports will be kept highly confidential.

7.1 Study Monitoring

Monitoring of study progress and conduct will be ongoing. The study will be monitored throughout its active phase. The first monitoring visit during the active phase of the study will occur shortly after the first subject has been enrolled into the study at any particular study site. Subsequent monitor visits will occur as the frequency of enrollment dictates.

Monitoring of study activity will be performed using several approaches (i.e., on-site, off-site EDC). The study data to be 100% monitored includes, but is not limited to the following: endpoints, SAE, randomization, consent, inclusion and exclusion criteria. The Investigator will allocate adequate time for such monitoring activities. The Investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study-related facilities (e.g., pharmacy, operating room, etc) and has adequate space to conduct the monitoring visit. All data recorded during the study will be available for audit against source data and for compliance with GCP (21 CFR Parts 11, 50, 54, 56, 812, ICH E6) and specific protocol requirements. The Principal Investigator will be responsible for the following:

- Monitoring study conduct to ensure that the rights and well-being of subjects are protected;
- Monitoring accuracy, completion, and verification of source documents; and
- Monitoring study conduct to ensure study compliance with the protocol/amendment(s), GCP, and applicable regulatory requirements.

7.2 Auditing and Inspecting

The Investigator will permit study-related monitoring, audits, and inspections by the IRB/REB, the Sponsor, government regulatory bodies, and institution compliance and quality assurance groups of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data, etc.). The Investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, operating room, etc.).

Participation as an Investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable institution compliance and quality assurance offices.

8 ETHICAL CONSIDERATIONS

This study will be conducted according to the protocol, the US Code of Federal Regulations 21 CFR Part 50, 54, 56, and 812, the ethical principles originating from the Declaration of Helsinki, and Good Clinical Practice (GCP) as defined in ICH E6, and the

ICH Guidelines. All aspects of this study will be conducted in accordance with all national, state, and local laws of the pertinent regulatory authorities.

The decision of the IRB/REB concerning the conduct of the study will be made in writing to the Investigator and a copy of this decision will be provided to the Sponsor before commencement of this study. The Investigator should provide a list of IRB/REB members or an IRB/REB assurance number to the Sponsor.

8.1 Protocol Amendments

All protocol amendments must be submitted to the regulatory authorities and the IRB/REB, as required. A protocol amendment is generated by the Sponsor. The Investigator(s) is notified of the changes. The amended and/or revised protocol cannot be implemented until IRB/REB and/or regulatory authority approval is received, as required. Protocol revisions that impact on subject safety, the scope of the study, or affect the scientific quality of the study must be approved by the regulatory authorities and submitted to the IRB/REB for approval before implementation of such revisions to the conduct of the study.

The Sponsor may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be subsequently notified. In the event of a protocol revision, the ICF may require revisions, which must also be approved by the IRB/REB.

8.2 Informed Consent

All subjects for this study will be provided an IRB/REB approved ICF describing this study and providing sufficient information for subjects to make an informed decision about participation in this study. This consent form will be submitted with the Clinical Investigational Plan (CIP) for review and approval by the regulatory authority. The approved ICF will be submitted to the IRB/REB for the study. The formal consent of a subject, using the IRB/REB approved ICF, must be obtained prior to any study participation. The consent form must be signed by the subject and the Investigator and/or designated study staff obtaining the consent. A copy of the signed and dated ICF must be given to the subject, and the consent process must be documented in the source

documentation. Before recruitment and enrollment, each prospective subject will be given a full explanation of the study, allowed to read the approved ICF, and be provided with ample time and the opportunity to ask any questions that may arise. Once all questions have been answered and the Investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing the ICF. As part of the consent process, each subject must consent to direct access to his/her medical records for study-related monitoring, auditing, IRB/REB review, and regulatory inspection. If an amendment to the protocol changes the subject participant schedule or activity or increases the potential risk to the subject, the ICF must be revised and submitted to the IRB/REB and regulatory authority for review and approval. The revised ICF must be used to obtain consent from a subject currently enrolled in the study if he/she is affected by the amendment, as deemed necessary by the reviewing IRB/REB. The revised ICF must be used to obtain consent from any new subjects who are enrolled into the study after the date of the IRB/REB approval.

9 INVESTIGATOR TRAINING

9.1 Investigator Training

The Sponsor will select only Investigator(s) with extensive experience in performing arthroscopic shoulder procedures. Training on the protocol will be provided prior to the start of the study. The protocol and instructions on how to complete the study documentation will be reviewed with the Investigator(s) and their study personnel at the Site Initiation Visit. All Investigators will be required to attend the initial investigator meeting that will include training on an inanimate shoulder model. Additionally, a field clinical trainer (Sponsor employee or designee) will attend at minimum the initial surgical procedure(s), as deemed necessary, under the supervision of the Investigator.

9.2 Training of Study Staff

The Investigator will ensure that appropriate training relevant to the study is given to the medical, nursing and other staff involved and that new information of relevance to the performance of this study is forwarded to the staff involved.

10 PUBLICATION PLAN

Authorship and contents of the publication shall be discussed between each Principal Investigator at the study site participating in this study and the Sponsor. The Sponsor shall serve as the coordinator of multi-center study disclosures and, in the event of a disagreement among the Investigators, the Sponsor shall determine, in its sole discretion, the resolution of any such dispute. The Sponsor shall be furnished copies of any proposed multi-center publication or disclosure, including, without limitation, disclosures in papers or abstracts or at research seminars, lectures, professional meetings, or poster sessions, at least 90 days prior to the proposed date for submission for publication or disclosure. During such 90-day period, the Sponsor shall have the right to review and require modification of such publication to assure the accuracy of the contents thereof and to delete Sponsor Confidential Information therefrom. In addition, upon the Sponsor's written request during the foregoing 90-day period, the proposed submission for publication or disclosure shall be delayed for a period not to exceed ninety (90) days from the date of such request to permit the Sponsor to file patent applications or to otherwise seek intellectual property protection related to information contained in such publication or disclosure.

It is also agreed that no presentations or publications will be authorized individually or by subgroups participating in the study without the consent of the Sponsor prior to publication of the pooled data; provided, however, that in no event shall any Institution or Investigator involved in this study be restricted from submitting a publication independently after the expiration of 365 days from the completion of the multi-center study.

11 INSTITUTIONAL REVIEW BOARD / RESEARCH ETHICS BOARD

Before initiation of the study, the Investigator must obtain approval of the protocol, ICF, CRFs, and any advertisement for subject recruitment from an IRB/REB complying with the provisions specified in 21 CFR Part 56 or ICH GCP, as applicable, and pertinent government regulations.

A copy of written IRB/REB approvals of the protocol, ICF, CRFs, and any advertising for subject recruitment (if applicable) must be provided to the Sponsor or its designee prior to initiation of the study. The approval letter must be signed by the IRB/REB chairman or

designee, identify the IRB/REB name and address, identify the protocol by title and/or protocol number, and include the date that approval was granted. The letter must also contain a statement that the IRB/REB complies with the requirements in 21 CFR Part 56 for a study conducted under ICH or GCP, as applicable.

The Investigator is responsible for obtaining continued review of the clinical research or submitting periodic progress reports, in accordance with applicable regulations, at intervals not exceeding one year or otherwise specified by the IRB/REB.

12 REFERENCES

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