
# A Clinical and Radiological Study to Evaluate the Safety and Efficacy of the PyroTITAN Humeral Resurfacing Arthroplasty (HRA) Device in a New Cohort of Patients after Product Re-Release

| | |
|---|---|
| PROTOCOL NO.: | T-HRA-003 |
| VERSION & DATE: | Version 5, 18-AUG-2017 |
| SUPERSEDED VERSION HISTORY: | Version 4, 13-SEP-2016 |
| SPONSOR: | Integra LifeSciences Corporation<br>311 Enterprise Drive<br>Plainsboro, NJ 08536, USA |

# TABLE OF CONTENTS

# INVESTIGATOR SIGNATURE

**Protocol Title:** **A Clinical and Radiological Study to Evaluate the Safety and Efficacy of the PyroTITAN Humeral Resurfacing Arthroplasty (HRA) Device in a New Cohort of Patients after Product Re-Release**

**Protocol Number:** T-HRA-003

**Date:**

**Superseded Version**: 13-SEP-2016

I have read and understand this protocol and agree to conduct the study as outlined herein. I will conduct the study in compliance with Good Clinical Practice and all applicable regulations specified in the country in which the study takes place.

In addition, I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and will discuss this material with them to ensure they are fully informed regarding the study.

_____
Investigational Site Name (Hospital/Practice)

_____ Date:_____
Site Principle Investigator Signature

_____
Printed Name of Site Principle Investigator

# REVISION HISTORY

| Version | Date | Reason for Update |
|---|---|---|
| 1.0 | 03-MAY-2016 | Initial version |
| 2.0 | 01-JUL-2016 | Section 4.3: Removed Exc. Criteria - Participated in the previous PyroTITAN HRA clinical study.<br>Section 4.3: Added Exc. Criteria - Women, who are pregnant or are planning to become pregnant.<br>Section 7.1.4 : Added all SAEs need to be reported |
| 3.0 | 19-JUL-2016 | Protocol Title Change |
| 4.0 | 13-SEP-2016 | ABBREVIATIONSs and ACRONYMS – added & defined TGA |
| 5.0 | 18-AUG-2017 | Protocol Synopsis: Study Sponsor contact information updated.<br>Section 4.2: Inclusion criteria # 2- changed to a two-year follow-up<br>Section 4.2: Inclusion criteria # 5- 21 years of age changed to 18 years of age<br>Section 4.3: Exclusion criteria #14- 21 years of age or over 75 changed to 18 years of age or over 85<br>Section 4.3: Exclusion criteria # 16- one year changed to two years<br>Section 6.3: Range of Motion- additional precisions added.<br>Section 7: Safety and Adverse Event section updated |

# ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| ADE | Adverse Device Effect |
| AE | Adverse Event |
| AP | Anterior Posterior |
| ASES | American Shoulder and Elbow Surgeon Score |
| Co-Cr | Cobalt Chrome |
| CRF | Case Report Form |
| CRO | Contract Research Organization |
| CV | Curriculum Vitae |
| DOB | Date of Birth |
| EC | Ethics Committee |
| eCRF | Electronic Case Report Form |
| GCP | Good Clinical Practice |
| HRA | Humeral Resurfacing Arthroplasty |
| ICF | Informed Consent Form |
| ICH | International Conference on Harmonization |
| ITT | Intent to Treat |
| LPLV | Last Patient Last Visit |
| PI | Principal Investigator |
| ROM | Range of Motion |
| SADE | Serious Adverse Device Effect |
| SAE | Serious Adverse Event |
| SOP | Standard Operating Procedure |
| TGA | Therapeutic Goods Administration |
| USADE | Unanticipated Serious Adverse Event |
| VAS | Visual Analog Score |
| WOOS | Western Ontario Osteoarthritis Score |

# PROTOCOL SYNOPSIS

| | |
|---|---|
| **Protocol Title:** | A Clinical and Radiological Study to Evaluate the Safety and Efficacy of the PyroTITAN Humeral Resurfacing Arthroplasty (HRA) Device in a New Cohort of Patients after Product Re-Release |
| **Protocol Number:** | T-HRA-003 |
| **Protocol Version:** | Version 5.0 |
| **Protocol Date:** | 18-AUG-2017 |
| **Study Sponsor:** | Integra LifeSciences Corporation<br>311 Enterprise Drive<br>Plainsboro, NJ 08536, USA |
| **Study Sponsor Contact:** | Derick Bermudez Lead Clinical Research Associate, Global Clinical Affairs Office: (+1) 512-852-3932<br>E-mail: Derick.Bermudez@integralife.com |
| **Registration Sponsor:** | PyroTITAN HRA system is registered in Australia under LMT Surgical Pty Ltd under ARTG Entry 273189 |
| **Product:** | PyroTITAN Humeral Resurfacing Arthroplasty (HRA) Shoulder System |
| **Objective:** | The objective of this study is to evaluate the 2-year post implantation survivorship of the PyroTITAN HRA device following the implementation of a new proof test to identify and eliminate devices with sub-standard mechanical integrity. The results will be compared to data collected in a prior study conducted before implementing the new proof test. |
| **Study Design:** | Post-market, non-randomized, open-label, observational clinical study with retrospective and prospective enrollment. |
| **Enrollment:** | One center in Australia will enroll up to 137 patients in this study |
| **Subject Criteria:** | **Inclusion Criteria:**<br>Patients of either sex will be included, if they:<br>1. Present (prospective cohort) or presented (retrospective cohort) for primary shoulder surface replacement or arthroplasty with any of the following diagnoses:<br>a. Osteoarthritis<br>b. Rheumatoid / Inflammatory Arthritis |

c. Post-traumatic arthritis.

d. Focal and large (Hill-Sachs) osteochondral defects.

2. Subject receives (prospective cohort) the PyroTITAN HRA device after the re-release of the product or received (retrospective cohort) the PyroTITAN HRA device after the re-release of the product and is enrolled in the study prior to their two-year follow-up visit.
3. Subject is able to or capable of providing consent to participate in the clinical investigation.
4. Subject agrees to comply with this protocol, including participating in required follow-up visits at the investigations site and completing study questionnaires.
5. Subject is at least 18 years of age and skeletally mature at the time of surgery.

**Exclusion Criteria**

Patients will be excluded from participation if they:

1. Has/had destruction of the proximal humerus to preclude rigid fixation of the humeral component.
2. Has/had insufficient bone quality as determined by intra-operative evaluation.
3. Has/had arthritis with defective rotator cuff.
4. Has/had had a failed rotator cuff surgery.
5. Has/had loss of musculature, neuromuscular compromise or vascular deficiency in the affected limb rendering the procedure unjustified.
6. Has/had evidence of active infection.
7. Present/presented with a condition of neuromuscular compromise of the shoulder (e.g., neuropathic joints or brachioplexus injury with a flail shoulder joint).
8. Are unwilling or unable to comply with a rehabilitation program or would fail to return for the postoperative follow-up visits prescribed by the protocol.
9. Are/were skeletally immature.
10. Has/had a known allergic reaction to PyroCarbon.
11. Has/had other conditions such as central nervous system disturbances, alcohol or drug addiction, etc. that may make effective evaluation of the joint replacement difficult or impossible.
12. Has/had known, active metastatic or neoplastic disease.

| | |
|---|---|
| | 13. Are/were taking > 10mg/day corticosteroids (e.g. prednisone) excluding inhalers, within 3 months prior to surgery.<br>14. Are/were under 18 years of age or over 85.<br>15. Require/required glenoid replacement.<br>16. Retrospective patients cannot be enrolled if they are two years or greater out from the index surgery.<br>17. Women, who are pregnant or are planning to become pregnant. |
| **Study Duration:** | Individual retrospective and prospective patients will be involved in the study for up to 60 months and will be evaluated at the following intervals:<br>1. Baseline/Screening; within 180 days prior to surgery<br>2. Surgery<br>3. 6 months ± 1 month,<br>4. 12 months ± 2 months<br>5. 24 months ± 2 months<br>6. 60 months ± 3 months<br>Patients enrolled retrospectively (i.e. before the protocol was initiated and prior to their two year follow-up visit) will be evaluated at the time-points listed above based on the date of the index surgery. Retrospective patients will be asked to consent to allow collection of information from the index surgery and any prior visits for inclusion in the database.<br>It is anticipated that subject accrual will be carried out over a twelve-month period but may take longer depending upon the availability of suitable subjects. The anticipated study duration to LPLV is six years, with an additional year to analyze and submit the study results making the total study duration approximately 7 years. |
| **Data Collection:** | The following data will be collected from the study population:<br>• Demographics and Medical History<br>• Surgical method<br>• Functional and patient reported assessments (ASES Score, Visual Analog Scale (VAS) for pain and satisfaction, Range of Motion (ROM), Western Ontario Osteoarthritis Score (WOOS), *Quick*DASH and Constant Score)<br>• Implant Survival |

| | |
|---|---|
| | • Complications and post-operative procedures on the affected joint<br>• Radiographic (X-rays) evaluation<br>• Device Related Adverse Events |
| **Outcome Parameters:** | **Primary outcome measures:**<br>• Assessment of device survival at the two year time-point<br>**Secondary outcome measures:**<br>• Absence of complications (device related Adverse Events), and post-op procedures on the affected joint including additional revision surgeries at 2-year and 5-year time-points.<br>• Assessment of the functionality of the PyroTITAN HRA Shoulder System through clinical assessments at 2-year and 5-year time-points. |
| **Statistical Analysis:** | The non-inferiority hypothesis will be evaluated using the Blackwelder approach based on the Intent-to-treat population. The approach is based on 95% confidence interval by comparing the interval limit to the pre-specified non-inferiority margin. |

# 1 INTRODUCTION

This document is a protocol for a human research study. This study is to be conducted according to International standards of Good Clinical Practice (International Conference on Harmonization ICHE6), any applicable government regulations and the Responsible Human Research Ethics Committee ("HREC") policies and procedures.

## 1.1 Background

With the increase of activity in younger patients, glenohumeral arthritis has also increased. These patients seek relief from pain but also require the ability to return to full or near participation in those recreational sports activities[1].Total shoulder arthroplasty, associated with reports of high rates of early glenoid wear, aseptic loosening, and the reduced return of full function is an effective solution for less active patients. Persistent pain related to glenoid arthrosis after hemiarthroplasty or humeral head resurfacing with metal components is often a barrier for many patients. Economic pressures require the implant system allow an efficient continuum of staged intervention while meeting increasing demands. The design must replicate anatomy; allow a range of treatment options including bone conservation, minimization of implant on bone wear, avoidance of a cemented polyethylene glenoid component when the glenoid is intact, and the staged addition of a glenoid implant or conversion to a full shoulder or to a reverse shoulder implant in those patients whose disease process continues to advance. Hemiarthroplasty and humeral head resurfacing (HRA) is indicated in those patients with an intact rotator cuff, a congruent glenoid, and no history of instability or subluxation where an alteration in humeral version is required or where a change in version, neck shaft angle or head height would be required after a nonunion or mal union of a fracture. HRA allows earlier intervention, restoration of function, higher patient satisfaction and the ability to stage the intervention to meet the patient needs.

## 1.2 Study Devices

### 1.2.1 Device Description

The PyroTITAN ™ HRA device is an anatomically designed, semi-constrained, monolithic device designed for resurfacing of the humeral head (hemi-shoulder). The system is designed for non-cemented (i.e. press-fit) fixation. Each device is boxed individually and delivered sterile for single use. The system incorporates twelve anatomically designed sizes.

The Pyro HRA device incorporates design features for replacing the damaged humeral head bearing surface and restoring normal anatomy with minimal bone resection. The stem is tapered with a cruciform shape to provide rotational as well as axial stability of the seated implant. System instrumentation is designed to offer precise implant preparation.

[1] Miller D. "Humeral Head Surface Replacement in the Young and Active Patient." *Operative Techniques in Sports Medicine;* 2008; 16(1): 32-36.

**Figure 1; the PyroTITAN Humeral Resurfacing Arthroplasty Device**

### 1.2.2 Regulatory Status

The PyroTITAN HRA system is registered in Australia under LMT Surgical Pty Ltd as the "Registration Sponsor" under ARTG Entry 273189.

Note: Although LMT Surgical Pty Ltd is the "Registration Sponsor" under ARTG Entry 273189, Integra LifeSciences is the Sponsor of this study.

## 1.3 Intended Use

The PyroTITAN HRA System is indicated for resurfacing of the humeral head due to arthritis (i.e. rheumatoid arthritis, osteoarthritis and some cases of osteonecrosis), mild or moderate humeral head deformity and/or limited motion, post-traumatic arthritis, focal and large (Hill-Sachs) osteochondral defects, and patients with an intact or reparable rotator cuff.

## 1.4 Preclinical Data

PyroCarbon has been shown to be much less damaging to cartilage and bone tissues than the Co-Cr alloys currently used for hemi-arthroplasty. Cook *et al* studied cartilage degradation in 45 canine acetabula after implantation of prostheses with articulating surfaces of PyroCarbon, Co-Cr alloy and titanium alloy for periods ranging from two weeks to 18 months[2]. Gross specimens and histological sections were compared with the non-operated (control) acetabulum of the same animal. Cartilage articulating with PyroCarbon exhibited significantly lower levels of gross wear, fibrillation, eburnation, glycosaminoglycan loss, and subchondral

[2] Cook S, Thomas K, Kester M. "Wear Characteristics of the Canine Acetabulum against Different Femoral Prosthesis." *Journal of Bone and Joint Surgery (British Volume);* 1989; 71(2): 189-197

bone change than with metallic surfaces. Survivorship analysis showed a 92% probability for cartilage articulating with PyroCarbon at 18 months, as compared to only a 20% probability of survival for cartilage with either of the metallic alloys.

Kawalec, Hetherington Melillo and Corbin investigated PyroCarbon and Co-Cr alloy as materials for hemi-arthroplasty in an animal model mimicking an arthritic joint[3]. PyroCarbon and Co-Cr alloy resurfacing implants were placed in the canine knee joint. The cartilage on the lateral side of the tibial plateau was abraded to create a full-thickness, arthritic type defect which exposed the subchondral bone. PyroCarbon and Co-Cr alloy implants were placed in the lateral femoral condyle in contact with the subchondral bone exposed by the cartilage defect and the joints evaluated after a period of one year. Histological examination of the tibial defects revealed a smooth bony surface for both implant groups. Microscopic surface cracks in the subchondral bone were present adjacent to the implants being seen in 14% of the PyroCarbon implants and in 100% of the Co-Cr alloy implants. Fibrocartilage regeneration was seen in 86% of the PyroCarbon implants and in 25% of the Co-Cr alloy implants. Kawalec and colleagues concluded that PyroCarbon implants were better tolerated as hemi- arthroplasty implants in the canine arthritic joint model than Co-Cr alloy implants.

Additionally, bone wear testing comparing a PyroCarbon radial head to a Co-Cr alloy radial head has been conducted. An axial load of 170 N, resulting in a contact pressure of 1.34 MPa, was applied to radial head test specimens rotated through a range of ± 13.5° using bovine serum as a lubricant. Although the original test protocol called for wear testing up to 5 million cycles, it was necessary to terminate the Co-Cr alloy test specimens at 500,000 cycles because of excessive bone loss. On the other hand, the PyroCarbon test specimens completed the 5 million cycle run out. The resultant bone wear depth for the Co-Cr alloy specimen after 0.5 million cycles was 2.25 mm while the PyroCarbon specimen resulted in a bone wear depth of 0.17 mm after 5 million cycles. Differential damage to the implant bearing faces was also observed. The surface finish of the PyroCarbon specimens was 0.032 µm prior to wear testing and 0.039 µm following 5 million wear cycles. The surface finish of the Co-Cr alloy specimen was 0.027 µm prior to wear testing and 2.06 µm following 0.5 million wear cycles. In conclusion, test results show that when articulating with bone, PyroCarbon results in significantly less damage when compared to the Co-Cr alloy.

The material provided above supports the contention that a PyroCarbon humeral head resurfacing will result in less damage to native joint tissues than the current Co-Cr alloy material and will result in better patient outcomes as compared to Co-Cr alloy when used as hemi-arthroplasty prosthesis.

## 1.5 Clinical Data to Date

An ongoing clinical study is being conducted outside the United States. To date, there is data available out to 4 years of follow-up which show overall continued improvement in pain, satisfaction, and range of motion. The study is ongoing and will follow patients out to ten years of follow-up. A higher than expected device fracture rate occurred on the study (4.2%) at the 2-year follow-up time point and enrollment was stopped to investigate the root cause of the fractures. It was determined that high angle loading was the cause of the fractures and the proof test used to identify sub-standard parts was not sufficient. Therefore a new

[3] Kawalec JS, Hetherington VJ, Melillo TC, Carbin H. “Evaluation of Fibrocartilage Regeneration and Bone Response at Full-Thickness Cartilage Defects in Articulation with Pyrolitic Carbon or Cobalt-Chromium Alloy Hemiarthroplasties.” *Journal of Biomedical Materials Research;* 1998; 41: 534-540

proof test was implemented to identify and eliminate devices with sub-standard mechanical integrity. The new proof test is conducted at a higher 60º inclination loading. The purpose of this study is to determine that clinical efficacy in the new cohort of patients is superior to that in the ongoing study.

# 2 OBJECTIVE OF THE CLINICAL INVESTIGATION

## 2.1 Primary Objective

To evaluate the 2-year post implantation survivorship of the PyroTITAN HRA device following the implementation of a new proof test to identify and eliminate devices with sub- standard mechanical integrity. The results will be compared to data collected in a prior study conducted before implementing the new proof test.

## 2.2 Secondary Objective(s)

The secondary objective of the study is to evaluate any other adverse events and overall clinical outcomes of the PyroTITAN HRA device in the new cohort at 2-year and 5-year post implantation time-points.

# 3 STUDY DESIGN

## 3.1 General Study Design

Post-Market, prospective and retrospective, non-randomized, open label observational clinical study.

## 3.2 Study Duration

Individual prospective patients will be involved in the study for 60 months and will be evaluated at the following intervals:

1. Baseline/Screening; within 180 days prior to surgery
2. Surgery
3. 6 months ± 1 month,
4. 12 months ± 2 months
5. 24 months ± 2 months
6. 60 months ± 3 months

Patients enrolled retrospectively (before the protocol was initiated and prior to their two year follow-up visit) will be evaluated at the time-points listed above based on the date of the index surgery. Retrospective patients will be asked to consent to allow collection of information from the index surgery and any prior follow-up visits for inclusion in the database.

It is anticipated that subject accrual will be carried out over a twelve-month period. Considering a year enrollment period, the anticipated study duration to LPLV is six years.

## 3.3 Study Endpoints

### 3.3.1 Primary Study Endpoints

The Primary Study Endpoint is:

- Assessment of device survival at the two year time-point

### 3.3.2 Secondary Study Endpoints

The Secondary Study Endpoints are:

- Absence of complications (device related Adverse Events), and post-op procedures on the affected joint including additional revision surgeries at 2-year and 5-year time-points.
- Assessment of the functionality of the PyroTITAN HRA Shoulder System through clinical assessments at 2-year and 5-year time-points.

# 4 SUBJECT POPULATION

## 4.1 Number of Subjects

Target enrollment in the study will be a total of 137 subjects. Anticipating a 10% lost to follow-up rate, 137 subjects will give us 123 evaluable subjects at the two year time-point.

## 4.2 Inclusion Criteria

Patients will be included if they:

1. Present (prospective cohort) or presented (retrospective cohort) for primary shoulder surface replacement or arthroplasty with any of the following diagnoses:
   a) Osteoarthritis
   b) Rheumatoid/Inflammatory arthritis
   c) Post-traumatic arthritis
   d) Focal and large (Hill-Sachs) osteochondral defects
2. Subject receives (prospective cohort) the PyroTITAN HRA device after the re-release of the product or received the PyroTITAN HRA device after the re-release of the product and is enrolled (retrospective cohort) in the study prior to their two-year follow-up visit.
3. Subject is able to or capable of providing consent to participate in the clinical investigation

4. Subject agrees to comply with this protocol, including participating in required follow-up visits at the investigational site
5. Subject is at least 18 years of age and skeletally mature at the time of surgery

## 4.3 Exclusion Criteria:

Subjects will be excluded from the study if they:

1. Has/had destruction of the proximal humerus to preclude rigid fixation of the humeral component
2. Has/had Insufficient bone quality as determined by intraoperative evaluation
3. Has/had arthritis with defective rotator cuff
4. Has/had a failed rotator cuff surgery
5. Has/had a loss of musculature, neuromuscular compromise or vascular deficiency in the affected limb rendering the procedure unjustified
6. Has/had evidence of active infection
7. Present/presented with a condition of neuromuscular compromise of the shoulder (e.g., neuropathic joints or brachioplexus injury with a flail shoulder joint)
8. Are unwilling or unable to comply with a rehabilitation program or would fail to return for the postoperative follow-up visits prescribed by the protocol.
9. Are/were skeletally immature.
10. Has/had a known allergic reaction to PyroCarbon
11. Has/had other conditions such as central nervous system disturbances, alcohol or drug addiction, etc. that may make effective evaluation of the joint replacement difficult or impossible.
12. Has/had known, active metastatic or neoplastic disease
13. Are/were taking > 10mg/day corticosteroids, excluding inhalers, within 3 months prior to surgery
14. Are/were under 18 years of age or over 85
15. Require/required glenoid replacement
16. Retrospective patients cannot be enrolled if they are two years or greater out from the index surgery
17. Women, who are pregnant or are planning to become pregnant.

## 4.4 Subject Recruitment, Screening and Informed Consent

Subjects will be recruited from the investigator and/or sub-investigator clinical practices and referring physicians. If advertisement will be performed for subject recruitment, it will be done as per the overseeing Ethics Committee's (EC) instructions. At the minimum, all information disseminated to subjects (handouts, brochures, participant information sheets and consent forms etc.) must be approved by the EC prior to use.

At each clinical site, all patients who potentially meet the study inclusion and exclusion criteria will be screened for eligibility.

A patient will be considered enrolled and a study subject once they have signed an informed consent and their study eligibility has been confirmed.

Informed consent must be obtained from each patient or authorized legal representative of the patient prior to participation in this protocol. Patients (or their legally authorized representative) who elect to enroll must be informed of the risks (and possible untoward effects of the devices) and the potential benefits, as well as the risks and benefits of the associated medical procedures. Alternative modes of treatment must be explained to the patient as well. Such information is provided in the Patient Informed Consent document.

## 4.5 Subject Withdrawal and Discontinuation

### 4.5.1 When and How to Withdraw Subjects

All subjects have the right to withdraw at any point during treatment without prejudice. It will be documented whether or not each subject completed the clinical study. If for any subject, study procedures or observations were discontinued, the reason(s) will be recorded and the Sponsor should be notified promptly. Reasons that a subject may discontinue participation in a clinical study may constitute one of the following:

- Subject withdrew consent
- Subject chooses to withdraw or is withdrawn due to an adverse experience
- Lost to follow-up
- Protocol violation
- Discontinuation of study by Sponsor

The Investigator can discontinue a subject at any time if it is considered medically necessary. Rationales for discontinuation of a subject for medical reasons include, but are not limited to, the following:

- Subject repeated non-compliance
- Medical reason or situation in which the subject is no longer under the care of the Investigator and unable to return for required study visits (e.g. subject moved out of the area).

### 4.5.2 Data Collection and Follow-up for Withdrawn Subjects

Every attempt should be made to collect follow-up information. The reason for treatment discontinuation or withdrawal from the study will be recorded in the source documents and on the CRF.

Before a subject is identified as lost-to-follow up, the site should make all reasonable efforts to contact the subject. These attempts must be documented. Subjects are considered lost to follow-up if there are three documented unsuccessful attempts to reach a study subject or after the subject fails to show up for three scheduled follow-up visits.

# 5 STUDY SCHEDULE

## 5.1 Screening / Baseline Visit

The subject will sign and date the Informed Consent (ICF) prior to any study-related procedures.

Once the ICF is signed, the Screening/Baseline assessments and procedures described below must be complete within a 180-day window before the surgery:

- Demographics and medical history
  - Gender
  - DOB
  - Height
  - Weight
  - Dominant side
  - Primary diagnosis
  - Date symptoms began
  - Presenting symptoms
  - Concomitant conditions
  - Disease specific concomitant medications
  - Surgical history of surgical shoulder
  - Surgical history of non-surgical shoulder
- Eligibility criteria
- X-ray evaluation:
  - AP Neutral
  - AP External Rotation
  - AP Internal Rotation
  - Axial Lateral (Scapular Y)
  - Axillary Lateral
- ASES Score
- Pain Visual Analog Scale (VAS)
- Range of Motion (ROM)
- Western Ontario Osteoarthritis Score (WOOS)
- *Quick*DASH
- Constant Score

For patients enrolled retrospectively, consent will be obtained to collect retrospective data on demographics and medical history in addition to any standard of care clinical assessments (if available) mentioned above. Retrospective patients must also meet documented eligibility requirements to be included in the study.

## 5.2 Surgical Procedure

Within 180 days of the Screening/Baseline visit, the subject will undergo the shoulder arthroplasty surgery.

Data of the following intra- /peri- operative assessments will be collected:

- Operative shoulder(s)
- Surgical approach
- PyroTITAN HRA components used (size, lot number)
- Concurrent Procedures (e.g. subscapularis tenotomy, glenoid reshaping, osteotomy of the tuberosity's, application of bone grafts, …)
- Soft Tissue Aspects (e.g. biceps tendon attachment preservation)
- Intraoperative complications
- Operative time

For patients enrolled retrospectively, data points outlined above will be collected if available in the medical record.

## 5.3 Follow-up Visits

Prospective subjects will undergo follow-up visits at 6 months (± 1 month) and 12 months (± 2 months), 24 months (± 2 months) and 60 months (± 3 months). Subjects enrolled retrospectively will undergo those follow-up visits listed above they have not already passed, based on the time from the index surgery. Retrospective subjects cannot be enrolled if they are two years or greater out from the index surgery.

Data from the following procedures/assessments will be collected at each of these visits:

- Assessment for device related adverse events
- Standard of care clinical assessment in conjunction with X-ray evaluation (below) to determine if implant fractured or is at risk of fracture
- X-ray evaluation: X-rays should be assessed for evidence of loosening, movement, wear, fracture of the implant and bone, and dislocation)
    - AP Neutral
    - AP External Rotation
    - AP Internal Rotation
    - Axial Lateral (Scapular Y)
    - Axillary Lateral

- ASES Score
- Visual Analog Scale (Pain and Satisfaction)
- Range of Motion
- Western Ontario Osteoarthritis Score (WOOS)
- *Quick*DASH
- Constant Score

For patients enrolled retrospectively, data points outlined above will be collected if available in their medical record (except for 24 months (± 2 months) and 60 months (± 3 months) which will be collected prospectively).

## 5.4 Unscheduled Visits

In some circumstances, subjects may return to the clinic for a visit that is out of the normal follow-up schedule. If the visit is related to the device, the Investigator should evaluate the patient according to the patient's clinical presentation and document the visit on appropriate "Unscheduled Visit" case report forms.

Data from the following assessments will be collected at each of these visits:

- Assessment for device related adverse events
- Standard of care clinical assessment to determine if implant fractured or is at risk of fracture
- X-ray evaluation: X-rays should be assessed for evidence of loosening, movement, wear, fracture of the implant and bone, and dislocation)
    - AP Neutral
    - AP External Rotation
    - AP Internal Rotation
    - Axial Lateral (Scapular Y)
    - Axillary Lateral
- ASES Score
- Pain and Satisfaction Visual Analog Scale
- Range of Motion
- Western Ontario Osteoarthritis Score (WOOS)
- *Quick*DASH
- Constant Score

## 5.5 Implant Revision or Removal

In case revision or removal of the implanted prosthesis or components thereof is required within the 60 months following the surgery, the following data of this surgical intervention will be collected:

- Type of intervention (revision, removal, re-operation or supplemental fixation)
- Reason for surgical intervention (device fracture, device migration, device loosening, new/increased pain, infection, etc.)
- Presence of wear particulate debris
- Device components removed or added

Furthermore, if removal is required every effort should be made to return the removed device along with any tissue from the structures surrounding the implant for histopathological examination. Tissue and device container and instructions for packaging will be provided to the site for the revision / removal surgery and the removed device/tissues will be shipped back to Integra.

Revision and removal cases will be recorded as adverse events, as detailed below, and subjects will exit the study after the revision/removal surgery. Subjects who require a revision should be followed per the site's standard of care.

## 5.6 Study Visit Schedule

A summary of study specific procedures and assessments at each of the study visits is shown below.

**Table 1: Schedule of study visits**

| Activity | Pre-Op (within 180days of surgery) | Surgery | 6 mons (± 1 mon) | 12 mons (± 2 mons) | 24 mons (± 2 mons) | 60 mons (± 3 mons) | Unscheduled visit |
|---|---|---|---|---|---|---|---|
| Informed Consent | X | | | | | | |
| Patient Eligibility | X | | | | | | |
| Demographics | X | | | | | | |
| Relevant Medical History & Diagnosis | X | | | | | | |
| Surgery Information | | X | | | | | |
| Clinical assessment of implant status | | X | X | X | X | X | X |
| Completion of X-Ray CRF | X | | X | X | X | X | X |
| ASES Score | X | | X | X | X | X | X |
| Visual Analog Scale for Pain | X | | X | X | X | X | X |
| Visual Analog Scale for Satisfaction | | | X | X | X | X | X |
| Range of Motion | X | | X | X | X | X | X |
| WOOS | X | | X | X | X | X | X |
| *Quick*DASH | X | | X | X | X | X | X |
| Constant Score | X | | X | X | X | X | X |
| Protocol Deviations | | as applicable | as applicable | as applicable | as applicable | as applicable | as applicable |
| Complications/Adverse Events | | X | X | X | X | X | X |
| Exit | | | | | | X (or p.r.n.) | |

# 6 STUDY PROCEDURES

All study procedures listed in this section will be completed preoperatively and postoperatively (6 months, 12 months, 24 months and 60 months).

## 6.1 ASES Score

The ASES Shoulder Score is a functional outcome tool that has been validated for various shoulder conditions (Leggin et al., 1999). This form is commonly used during the clinical process. The ASES Shoulder Score form consists of questions pertaining to patients' satisfaction, function and pain as related to the shoulder. The participant will take between 10 to 15 minutes to complete the test. If the subject requests assistance or a phone consultation is done, completion of the form will be completed with minimum or no assistance from the coordinator. The coordinator can clarify a question but will not influence the participant.

The participant will provide the best possible answer for that day.

## 6.2 Visual Analog Scale

The Visual Analog Scale (VAS) form assesses pain, shoulder pain and satisfaction as it relates to the effected shoulder. The subject completed form requests the subject marks the response on a line scale with a single slash. The form will be completed at each testing session. Completion of the form will be completed with minimum or no assistance from the coordinator. The coordinator can clarify a question but will not influence the participant.

The participant will provide the best possible answer for that day.

## 6.3 Range of Motion

For each subject at all study visits record the angle achieved for each of the range of motions listed below:

### 6.3.1 Flexion

Flexion is when the arm is moving in a straightforward and upward motion. Normal range of motion for flexion of the shoulder joint is 170 to 180 degrees. The motion starts at 0 degrees, or neutral, which is when the arms are at the side of the body with palms facing forward. 180 degrees is when the arms are straight overhead and elbows are by the ears. Anything beyond 180 degrees is considered hyperflexion.

### 6.3.2 External Rotation

External rotation occurs when the lower arm rotates outward, away from the body while the elbow remains at the side. Normal range of motion for external rotation is 90 to 100 degrees. For external rotation, 0 degrees is when the upper arm is at the side with the elbows bent 90 degrees. The lower arm is parallel to the floor, and the palm of the hand points toward the midline.

### 6.3.3 Internal Rotation

Internal rotation occurs when the lower arm moves inward, toward the body while the elbow remains at the side. Normal range of motion for internal rotation is 80 to 90 degrees. For internal rotation, 0 degrees is when the upper arm is at the side with the elbows bent 90 degrees and the palms facing back. The lower arm is parallel to the floor, and the hand is pointing to the highest point of spinal anatomy reached.

### 6.3.4 Abduction

Abduction is when the arm is moved outward from the side of the body. Normal range of motion for abduction of the shoulder joint is 170 to 180 degrees. The motion starts at 0 degrees, which is when the arms are at the side of the body with palms facing forward. 180 degrees is when the arms are straight overhead and elbows are by the ears.

### 6.3.5 Adduction

Adduction is moving the limb closer to or across the body. Normal range of motion for adduction is 45 degrees. The motion starts at 0 degrees or neutral, which is when the arms – arm is abducted to 90 degrees, elbow is bent at 90 degrees, forearm is parallel to the floor (i.e. palm down), starting position is with the elbow pointing forward.

### 6.3.6 Internal Rotation at 90 Degrees Abduction

Arm is abduction to 90 degrees, elbow is bent at 90 degrees, bending the arm upwards.

### 6.3.7 External Rotation at 90 Degrees Abduction

Arm is abducted to 90 degrees, elbow is bent at 90 degrees, bending the arm downwards.

## 6.4 Western Ontario Osteoarthritis Score (WOOS)

The WOOS Score is a quality of life questionnaire that has been validated for various shoulder conditions. The WOOS Score form consists of 4 components, Physical Symptoms, Sports/Recreation/Work, Lifestyle, and Emotions pertaining to the patients' satisfaction, function and pain as related to the shoulder. The subject will take between 10 to 15 minutes to complete the form. If the subject requests assistance completing the form, the coordinator can clarify a question but will not influence the subject.

The subject will provide the best possible answer for that day.

## 6.5 The *Quick*DASH Outcome Measure

The *Quick*DASH Outcome Measure is a validated self (patient) reported questionnaire designed to measure physical function and symptoms in people with any of the several musculoskeletal disorders in the joints in the upper limb. The *Quick*DASH is a shorter version of the DASH score (Disabilities of the Arm, Shoulder and Hand) has 30 questions

whereas the *Quick*DASH has 11 questions designed to measure function and symptoms in patients.

### 6.6 Constant Score

The Constant Murley Score is a 100-point scale composed of individual parameters. These parameters define the level of pain and the ability to carry out the normal daily activities of the patient. The test is divided into four subscales: pain (15 points), activities of daily living (20 points), strength (25 points) and range of motion (40 points). Subjective findings of patients are responsible for 35 points and objective measures are responsible for the remaining 65 points.

The specific method to measure strength using a spring balance is as follows:

- A spring balance is attached distal on the forearm
- Strength is measured with the arm in 90 degrees abduction, full extension of the elbow and the palm of the hand in pronation
- The patient is asked to maintain this position for 5 seconds
- The patient is asked to repeat this 3 times immediately after another
- The average pound (lb) or kilogram (kg) is noted

The measurement should be pain free. If pain is involved the patient gets 0 points, the same if the patient is unable to achieve 90 degrees of elevation.

## 7 SAFETY AND ADVERSE EVENTS

For the purpose of this study, an adverse event is defined as any medical condition or event for which the subject seeks medical attention that, in the physician's opinion has an association with the medical device or operative procedure. Adverse events may be mild, moderate or severe. All device-related adverse events are transcribed from source documentation onto an Adverse Event eCRF. **For the purposes of this study, only AEs (Serious and Not Serious) that are possibly, probably and related to the device and/or study procedure are to be recorded.**

### 7.1 Adverse Event Definitions

#### 7.1.1 Adverse Event (AE)

An AE is any untoward medical occurrences, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in a clinical investigation subject, user or other persons related to the investigational medical device..

### 7.1.2 Adverse Device Effect (ADE)

An ADE is an adverse event related to the use of an investigational medical device (this definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device; or any event resulting from use error or from intentional misuse of the investigational medical device).

### 7.1.3 Serious Adverse Device Effect (SADE)

An SADE is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event (see below).

### 7.1.4 Serious Adverse Events (SAE)

A SAE is any AE that; results in death, results in a life threatening illness or injury, requires inpatient or prolongation of existing hospitalization, results in a permanent impairment of a body structure or a body function, requires a medical or surgical intervention to prevent a life-threatening illness or injury or permanent impairment to a body structure or a body function, or leads to a fetal distress, fetal death or congenital anomaly/birth defect. Only SAEs considered causally related to the study device and/or study procedure must be recorded and reported (if applicable) by the investigator.

**INCIDENT:**

Any malfunction or deterioration in the characteristics and/or performance of a device, as well as any inadequacy in the labelling or the instructions for use which, directly or indirectly, might lead to or might have led to the death of a patient, or user or of other persons or to a serious deterioration in their state of health."
A serious deterioration in state of health can include:

a) Life-threatening illness

b) Permanent impairment of a body function or permanent damage to a body structure

c) A condition necessitating medical or surgical intervention to prevent a) or b) (Examples: Clinically relevant increase in the duration of a surgical procedure. A condition that requires hospitalization or significant prolongation of existing hospitalization)

d) Any indirect harm as a consequence of an incorrect diagnostic or IVD test results when used within manufacturer´s instructions for use

e) Foetal distress, foetal death or any congenital abnormality or birth defect

**NOTIFICATION:**

The registration owner LMT Surgical Pty Ltd will report to TGA, within the required time period.

Integra LifeSciences will report, as applicable, to any other national notified bodies as required by the applicable regulations.

### 7.1.5 Adverse Event Relationship

The relationship of AEs to the study devices and/or study procedures will be categorized according to the following definitions:

- **Not Related:** the AE is due to an underlying or concurrent illness or the effect of another device, drug or intervention and is not related to the study device. The AE has no temporal relationship to the investigational device or an alternate etiology is likely.
- **Possibly Related:** the AE occurred in a reasonable time period relative to implantation of the investigational device, which makes a causal relationship possible, but an alternative etiology is equally or less likely compared to the potential relationship to the investigational device.
- **Probably Related:** the AE occurred in a reasonable time period relative to implantation of the study device, and another etiology is unlikely or significantly less likely, which makes a causal relationship probable
- **Related:** the AE occurred in a reasonable time period relative to implantation of the investigational device and has a known relationship to the device.

**For the purposes of this study, only AEs that are possibly, probably and related to the device and/or study procedure are to be recorded.**

### 7.1.6 Unanticipated Serious Adverse Device Effect (USADE)

An unanticipated serious adverse device effect (USADE) is defined 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, the current risk analysis report or product labeling.

#### 7.1.6.1 Device Deficiencies and Subsequent Surgical Interventions

For the purposes of the study Device Deficiencies are defined as inadequacies of a medical device (PyroTITAN HRA) with respect to its identity, quality, durability, reliability, safety or performance.

Note: Device deficiencies include malfunctions, use errors, and inadequate labelling.

All subsequent interventions at the implant location will be recorded and categorized according to the following definitions:

- **Revision:** a procedure that adjusts or in any way modifies or removes part of the original implant configuration, with or without replacement of a

component. A revision may also include adjusting the position of the original configuration.

- **Removal:** a procedure where all of the original system configuration are removed with or without replacement.
- **Re-operation:** any surgical procedure at the location of the index surgery site that does not remove, modify or add any component to the system.
- **Supplemental fixation:** a procedure in which additional instrumentation not under study is implanted (e.g., supplemental placement or of a rod/screw system or a plate/screw system).

### 7.1.7 Anticipated Adverse Events:

As with any type of surgical procedure, there are certain risks or complications associated with shoulder resurfacing. The following list represents the most commonly reported complications and adverse events associated with surgery and shoulder replacement.

Potential risks associated with any surgery may include:

- Pain
- Bleeding
- Blood clots
- Infection
- Swelling
- Damage to surrounding blood vessels
- Damage to surrounding tissues or nerves
- Death

Potential risks associated with any shoulder replacement may include:

- Implant loosening
- Implant movement
- Implant wear
- Allergic reaction to wear debris or implant materials
- Implant fracture
- Implant failure (including need to take the implant out)
- Bone fracture
- Shoulder dislocation
- Shoulder pain

- Loss of shoulder function

## 7.2 Adverse Event Severity Determination:

All Adverse Events must be classified using mild, moderate, or severe to determine the level of severity of the AE as it relates to the evaluation of patient safety through the full course of the AE from initial reporting to the end of study for each patient who participates in this clinical study.

| ADVERSE EVENT SEVERITY | |
|---|---|
| **Mild** | An event that is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities |
| **Moderate** | An event that is sufficiently discomforting to interfere with normal everyday activities |
| **Severe** | An event that prevents normal everyday activities |

## 7.3 Principal Investigator's Responsibilities in Adverse Event Reporting:

- The PI will record adverse events and observed device deficiencies as specified in Section 7.1 together with an assessment of the events and/or deficiency.
- Report to the Sponsor, within 5 business days of learning of the event, all serious adverse events and device deficiencies that could have led to a serious adverse device effect
- Report to the Ethics Committee serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or the Ethics Committee policies and procedures
- Supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event

## 7.4 Sponsor's Responsibilities in Adverse Event Reporting:

- The Sponsor will review the investigator's assessment of recorded adverse events. In case of a disagreement between the Sponsor and the PI's assessment of the seriousness and relationship to the device, the Sponsor shall communicate both options to the Ethics Committee
- The Sponsor will review all device deficiencies and determine whether they could have led to a serious adverse device effect. In case of a disagreement between the Sponsor and the PI's assessment of the seriousness and relationship to the device, the Sponsor shall communicate both options to the Ethics Committee
- The Sponsor will ensure reporting to the Ethics Committee by the PI or designee of all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the Ethics Committee

- The Sponsor, with LMT Surgical Pty Ltd the registration owner, will decide and execute on reportability to regulatory authorities, within the time period required by the national regulations. This will include all serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by national regulations.
- The Sponsor will ensure that the Ethics Committee and regulatory authorities are informed of significant new information about the clinical study

## 7.5 Potential Benefits

Participation in the study may offer no benefit to subjects. Subjects may experience the same benefit as with any shoulder arthroplasty surgery. Participation in this study may allow investigators and the study Sponsor to find better materials and techniques to help patients in the future who need shoulder arthroplasty.

## 7.6 Risk Mitigation

To minimize the potential risks, the study procedures will be conducted by trained orthopedic surgeons with experience and training with the study devices. All adverse events that occur on the study will be collected and monitored. All confidential subject information will be kept confidential and access to the data limited to appropriate clinical personnel.

## 7.7 Changes to the Study Protocol

Changes to the protocol must receive both Sponsor and the investigator's EC approval before they are initiated. Any protocol change initiated without Sponsor and the investigator's EC approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study subjects, must be reported to the Sponsor as soon as possible, and to the investigator's EC as per the EC's procedure.

## 7.8 Protocol Deviations

Any protocol deviations must be clearly documented on the Protocol Deviation Case Report Form, identifying the deviation type and explanation of the circumstances for the deviation. It is the responsibility of the Investigator to report protocol deviations, to the Sponsor and the reviewing IEC as required in their guidelines

### 7.8.1 Investigator Reporting: Notifying the EC

Investigators are responsible for safety reporting to their EC in accordance with the EC's reporting requirements and timelines. Copies of each report and documentation of EC notification and receipt shall be kept in the investigator's study file and copies sent to the Sponsor for the trial master file.

## 7.9 Medical Monitoring

It is the responsibility of the Investigators to oversee the study safety at their site. This safety monitoring will include careful assessment and appropriate reporting of adverse

events as noted above. Safety monitoring by the Investigator will include a regular assessment of the number and type of adverse device events.

A Medical Monitor (physician) at Integra will also review all reportable AEs/SAEs including grading, toxicity assignments, protocol violations/deviations, as well as all other safety data and activity data observed in the ongoing clinical trial. The Sponsor's Medical Monitor will assist the Investigators upon their request with discussions of patient eligibility, management and protocol deviations, adverse events evaluation and trend analysis. Additionally, any device deficiencies that may occur on the study will be carefully investigated. The Medical Monitor has the ability to close enrollment to the study at any time he/she feels the study is putting subjects at unreasonable risk e.g. type and/or rate of device deficiencies.

Further details on medical monitoring for this study will be outlined in a study specific safety plan.

# 8 STATISTICAL ANALYSIS

## 8.1 Statistical Considerations

A detailed statistical analysis plan will be developed prior to the final database lock. The statistical analysis of the data derived from this study will be performed using SAS version 9.2 or higher.

All data collected in this study will be documented using summary tables and patient data listings. Continuous variables will be summarized using descriptive statistics, specifically the mean, median, standard deviation, minimum, and maximum. Categorical variables will be summarized by frequencies and percentages.

## 8.2 Analysis Population

The statistical analyses will be performed on an intent-to-treat (ITT) basis, i.e. all patients implanted will be included, and all patients' data will be analyzed.

The analyses will also be performed on per-protocol population, i.e. the subset of the patients in the ITT that are compliant with requirements of the Clinical Study Protocol, meeting all inclusion criteria and not meeting any exclusion criteria. This population is defined for use in supportive analyses.

## 8.3 Baseline Characteristics

Baseline demographics and clinical characteristics will be summarized.

## 8.4 Primary Endpoint

### 8.4.1 Study Hypothesis

The study hypothesis is to test whether the 2-year success (i.e. no fractures) rate in the investigational PyroTITAN HRA group is non-inferior to the reference rate at 95.8%. This study will be considered successful if the upper bound of the two-sided

95% confidence interval for the success rate difference is less than the non-inferiority margin of 4.5%.

***Primary Non-inferiority (efficacy) Hypothesis***

The primary non-inferiority hypothesis is formulated as:

**$H_0$: $P_0 - P_T \geq \delta$ (inferiority)**

**$H_a$: $P_0 - P_T < \delta$ (non-inferiority)**

The variables are defined as follows:

$P_T$ = 24-month success rate in the PyroTitan HRA group

$P_0$ = reference 24-month success rate from CP-HRA-002 study

$H_0$ = null hypothesis that the success rate in the investigational group is inferior to the reference rate

$H_a$ = alternative hypothesis that that the success rate in the investigational group is non-inferior to the reference rate

$\delta$ = non-inferiority margin pre-specified to be 0.045.

## 8.5 Sample Size Determination and Adjustment

The non-inferiority hypothesis will be evaluated using the Blackwelder approach[4] based on the Intent-to-treat population. The approach is based on 95% confidence interval[5] by comparing the interval limit to the pre-specified non-inferiority margin. The non-inferiority will be claimed if the upper 95% confidence bound of ($P_0 - P_T$) is less than $\delta$.

The success rate for the study device is unknown for this population but there is no reason to believe that it would be less than reference rate. Therefore, for a conservative success rate of 95.8% of the study device is used in the study. The non-inferiority margin $\delta$ of -0.045 is chosen in the study. 123 subjects are required to achieve 100(1 – $\beta$) % =80% power to detect non-inferiority at the Significance level of $\alpha = 0.05$. With 10% lost to follow-up, the total sample size needed is 137.

## 8.6 Primary Endpoint Analysis

A two-sided 95% confidence interval for the device survival will be calculated. The null hypothesis will be rejected if the upper limit of the two-sided 95% confidence of treatment is less than 4.5%. Time-to-event curves for device survival will be estimated using the Kaplan-Meier technique. For analysis of device survival, deaths due to other causes will be regarded as censored observations.

## 8.7 Secondary Endpoint Analysis

The secondary endpoints are the occurrence of device related adverse events and outcomes of clinical assessments at 2-year and 5-year time-points. Data from these assessments will be summarized using descriptive statistics.

[4] Blackwelder WC. “Proving the Null Blackwelder Hypothesis.” *Controlled Clinical Trials;* 1982: 3: 345-353
[5] Bristol DR. “Clinical Equivalence.” *Journal of Biopharmaceutical Statistics;* 1999; 9:4: 549-561

## 8.8 Description of Study Endpoints

### 8.8.1 Primary Endpoint

The primary outcome measure is the assessment of device survival at the 2-year time-point.

### 8.8.2 Secondary Endpoints

The secondary endpoints are:

- Absence of complications (device related Adverse Events), and post-op procedures on the affected joint including additional revision surgeries at 2-year and 5-year time-points.
- Assessment of the functionality of the PyroTITAN HRA Shoulder System through clinical assessments at 2-year and 5-year time-points..

### 8.8.3 Safety Endpoint

The occurrence of device related adverse events and serious adverse events at 2-year and 5-year time-points.

## 8.9 Subject Disposition and Follow-up Accounting

The disposition of all subjects who sign an ICF will be provided. The number of subjects screened, enrolled, completed, and discontinued during the study, as well as the reasons for all discontinuations will be summarized, for all centers combined and each center separately. Disposition and reason for study discontinuation will also be provided as a by- subject listing.

# 9 DATA HANDLING AND RECORD KEEPING

## 9.1 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the country in which the study takes place.

## 9.2 Study Registration

This research will be registered on the website http://clinicaltrials.gov/

## 9.3 Source Documents

Investigators are responsible for obtaining and maintaining complete patient health information in the medical record for each subject and each assessment (source documents). Source data includes all information in original records and certified copies of original records of clinic findings, observations or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source

documents (e.g., hospital records, clinic and office charts, memoranda, dispensing records, subject questionnaires, clinic evaluation transcriptions, operative notes, x-rays, radiology reports, blood collection and shipment records, research subject files, etc.). In some cases, source document forms are developed to capture study data that is not normally part of the medical record e.g. patient questionnaires. Every data point that is found in the eCRF and submitted to the Sponsor must have a corresponding source document in the patient record(s) that provides detailed evidence of the assessment. In some cases, case report forms are considered source documents when the data is either obtained by the health care professional doing the assessment or when completed as part of subject recorded assessment.

The patient questionnaires will be kept in patient's files and are a source document by themselves.

The Sponsor, its agents, the Ethics Committee and regulatory authorities (when applicable) will be provided direct access to source documents for the purpose of verifying and evaluating the clinical data submitted to the Sponsor by the investigator on eCRFs.

## 9.4 Case Report Forms

The study electronic Case Report Form (eCRF) is the primary data collection instrument for the study. All data requested on the eCRF must be recorded. All missing data must be explained. If a space on the eCRF is left blank because the procedure was not done or the question was not asked, enter "N/D". If the item is not applicable to the individual case, enter "N/A". Any data recorded on source documents specifically developed for the study should be printed legibly in black or blue ink.

An electronic Case Report Form will be completed for each subject enrolled into the clinical study. Each Investigator is responsible for the accuracy of the information entered on the eCRFs. Each Investigator is required to electronically approve (e-sign) the electronic CRFs, serving as attestation of the Investigator's responsibility for ensuring that all clinical data entered on the eCRFs are complete, accurate and authentic.

## 9.5 Records Retention

It is the investigator's responsibility to retain study essential documents in accordance with the site's SOPs, and as specified in the Clinical Research Agreement.

Records to be retained by the Investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g., subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study).
- Signed protocols and protocol amendments
- Study personnel signature log
- Monitoring logs
- Correspondence to and from the Sponsor, designee and EC
- Investigator and sub-investigator CVs

- Signed informed consent
- Serious adverse event reports
- Ethics Committee approval and re-approval letters
- Other documents pertaining to the conduct of the study

Irrespective of the language on record retention in the Clinical Research Agreement, record retention shall not be less than:

- 2-years after the formal discontinuation of the clinical study and final study report.

It is the responsibility of the Sponsor to inform the investigator/institution as to when these documents no longer need to be retained.

### 9.6 Clinical Data Management

The Sponsor and/or designated CRO will be responsible for the processing and quality control of the data. Data management will be carried out as described in the Sponsor's standard operating procedures (SOPs) for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines in the country in which the study is conducted (e.g., ICH E6 GCP, and local regulations where applicable) and the Sponsor's SOPs as well as provisions of the study-specific Data Management Plan.

## 10 STUDY MONITORING, AUDITING AND INSPECTING

### 10.1 Study Monitoring Requirements

In an effort to fulfill the obligations outlined in ICH guidelines, which requires the Sponsor to maintain current personal knowledge of the progress of a study, the Sponsor's designated monitor will visit the center(s) during the study as well as maintain frequent communication. The Investigator will permit the Sponsor and/or designated CRO to monitor the study as frequently as is deemed necessary and provide access to medical records to ensure that data are being recorded adequately, that data are verifiable and that protocol adherence is satisfactory.

Frequency and extent of monitoring will be detailed in the Sponsor's Monitoring Plan.

### 10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the EC, the Sponsor, government regulatory bodies, and Institution's 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.

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

# 11 STUDY FINANCES

This study is funded by the Sponsor, Integra LifeSciences Corporation. Any conflicts of interest with participating investigators will be appropriately disclosed. Any stipends or payments made to study subjects will be in accordance with governing EC and will be disclosed in the informed consent form. Study payments will be made to the investigational site based on study staff time to conduct the research activities (enroll patients, obtain ICF, schedule visits, complete clinical visits, enter study data). The standard of care assessments conducted during the follow-up visits (x-rays, other clinical assessments) will not be paid for by the Sponsor, as these standard of care assessments are covered or paid for as any other follow-up visit for shoulder replacement patients. The Sponsor will pay for study staff time to administer and conduct the following assessments during the follow-up visits:

- Patient travel reimbursement
- Coordinator time for retrospective data collection for patients who consent and were implanted prior to study initiation
- Radiographic (X-ray) evaluation at 24 months and 60 months
- ASES
- The Constant Score
- The WOOS Score
- The *Quick*DASH questionnaire
- Range of Motion (ROM)
- Assessment of adverse events

# 12 CLINICAL STUDY REPORTS AND PUBLICATIONS

Clinical Study Reports will be prepared according to the Integra's Standard Operating Procedures (based on ISO 14155:2011(E)) at the 2-year and 5-year time-points. They will include the study objectives, the methodology, statistical analysis and raw data listings, and the conclusions of the study. They will also include all the AEs that occurred during the study and data concerning all the patients included in the study up to the time point being reported. They will be submitted to the Investigators for acknowledgement and signature.

The intention is to publish the results of the study at both the 2-year and 5-year time points, when all subjects have completed their respective visits and the data has been reviewed and analyzed. Unless specifically agreed in the study contract(s) Investigator(s) may not publish the results referent to their group of subjects until the study in its entirety has been submitted for publication. Any publication will adhere to the standards of the applicable journal(s) or professional societies.

The Investigator or the Sponsor may not submit for publication, nor present the results of this project, before all other parties have been given the opportunity, within sixty (60) days or period agreed to in the study contract, to review and comment on the manuscript to be published. The Investigator(s) may not submit the results of the study for publication, without the Sponsor's prior permission.