A Multi-center Outcomes Clinical Study of the PyroTITAN™ HRA Shoulder Implant in Humeral Head Resurfacing

Study ID Number: CP-HRA-002
Protocol Date: 27-May-2013
Amendment 1
Revision 2

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APPROVAL OF PROTOCOL

Title	A Multi-center Outcomes Clinical Study of the PyroTITAN™ HRA Shoulder Implant in Humeral Head Resurfacing
EudraCT	Not Applicable
Protocol N°	CP-HRA-002
Version	Revision 2
Date	27-May-2013

Sponsor

Stan Harris — *Date:*

Senior Director of Clinical Affairs — *Signature:*

Principal Investigator

Date:

Signature:

VERSION	DATE	REASON FOR UPDATE
Amendment 1	27-May-2013	Change of 3, 4 and 8 year timepoints to site visit Inclusion criteria change from 18 to 21 years

TITLE	A Multi Center Outcomes Clinical Study of the PyroTITAN™ HRA Shoulder Implant (Ascension Orthopedics, Austin TX) in Humeral Head Resurfacing
SPONSOR	Ascension Orthopedics, Inc
OBJECTIVES	*The primary objective is to determine success of the PyroTITAN ™ HRA Shoulder Prosthesis* as defined by no revisions, no device related complications requiring surgical replacement and freedom from chronic dislocation. The secondary objectives of this investigation are to evaluate the functionality, and radiographic performance of the PyroTITAN™ HRA Shoulder prosthesis.
INDICATION	Subjects with shoulder replacement conditions associated without rotator cuff deficiencies, fractures or tumors.
CLINICAL INVESTIGATION DESIGN	This post market clinical investigation plan is for a multi-centre prospective, non-randomized, non-comparative, open investigation.
NUMBER OF SUBJECTS	It is anticipated that a total of 387 subjects may be enrolled. It is anticipated that a minimum of 20 subjects will be recruited at each investigational site.
TARGET POPULATION	Subjects who have presented at an investigation centre with a shoulder pathology justifying shoulder resurfacing that are not showing signs of associated rotator cuff deficient conditions and who have a functioning glenoid.
LENGTH OF CLINICAL INVESTIGATION	Subjects included in the clinical investigation will return for follow-up visits at first post op visit 3 month (1 – 120 days), 6 months and 1, 2, 3, 4, 5, 8 and 10 years post-treatment. The recruitment period is estimated as 48 months with anticipated investigation duration of 168 months.
PERFORMANCE	Primary endpoint: absence of device related complications resulting in revision or removal of components. Secondary endpoints: To demonstrate postoperative functionality and radiographic performance at 2, 3, 4, 5, 8 and 10 years post treatment, as compared with pre-treatment results through: • ASES Score improvement • Patient satisfaction • WOOS • Constant Score • EQ-5D Quality of Life Questionnaire • Radiographic success (X-Ray and MRI)
SAFETY	Adverse events will be recorded and reported appropriately throughout the investigation to assess safety.

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2.0 Subject Management Table

VISIT INTERVAL	Pre-Op <=180 days Prior to Surgery Day	Day of surgery	1st Post-Op (1–120 days) 3 Mo Follow Up	Post-Op 6 mo Follow Up	Post-Op 12 mo Follow Up	Post-Op 24 mo Follow Up	Post-Op 36 mo Follow Up	Post-Op 48 mo Follow Up	Post-Op 60 mo Follow Up	Post-Op 96 mo Follow Up	Post-Op 120 mo Follow Up
VISIT	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11
	Screening	Surgery	Post Op	Post Op	Post Op	Post Op	Post Op	Post Op	Post Op	Post Op	Post Op
X-Ray Evaluation	X		X	X	X	X	X	X	X	X	X
MRI Evaluation*	X		X		X	X	X	X	X	X	X
Informed Consent	X										
Inclusion / Exclusion Criteria Worksheet	X										
Medical History	X										
Constant Score	X		X	X	X	X	X	X	X	X	X
WOOS Score	X		X	X	X	X	X	X	X	X	X
EQ-5D Evaluation	X		X	X	X	X	X	X	X	X	X
ASES Score Evaluation	X		X	X	X	X	X	X	X	X	X
Visual Analog Scare for Satisfaction			X	X	X	X	X	X	X	X	X
Visual Analog Scale for Pain	X		X	X	X	X	X	X	X	X	X
Operative Detail		X									
Adverse Event**		X	X	X	X	X	X	X	X	X	X
Subject Withdrawal Forms(as needed)**		X	X	X	X	X	X	X	X	X	X

* If available ** If applicable

3.0 Introduction

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. (Miller2008). 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.

4.0 Purpose of Investigation

The purpose of the study is to determine the difference between pre- and post-operative levels of patient satisfaction, shoulder function, radiographic alignment, and shoulder pain in patients receiving a PyroTITAN^{TM} HRA Shoulder prosthesis for glenohumeral arthritis. The clinical performance of the PyroTITAN^{TM} HRA Shoulder prosthesis

implanted as a shoulder resurfacing prostheses (i.e. humeral only) evaluated with respect to:

- Short and long term clinical response (ASES, WOOS, Constant Score and EQ-5D, VAS Pain Score)
- Complication rates (including intraoperative)
- Peri-operative clinical parameters (e.g. skin to skin, operative approach)
- Radiographic outcome
- Patient Satisfaction (VAS Questionnaire)

5.0 Study Design

5.1 General

This study is designed as a multi-center, nonrandomized, uncontrolled, unblinded, prospective clinical outcomes investigation to evaluate the short, mid and long term performance of the PyroTITAN™ HRA Shoulder prosthesis humeral replacement. The PyroTITAN™ HRA Shoulder prosthesis device configuration will include humeral resurfacing CAP without cement. Patients will be selected for recruitment into the study based upon the normally accepted criteria for primary shoulder resurfacing arthroplasty.

The investigation will be conducted by up to 10 International surgeons experienced in HRA. 387 subjects with PyroTITAN™ HRA Shoulder prosthesis arthroplasties will be implanted and followed for 10 years. It is anticipated that initial patient accrual will be carried out over a twelve-month period. Amendment 1 of this study increased the number of subjects, expanding the enrollment time to 48 months. Patient selection procedures, data to be collected and patient follow-up schedules are detailed in the following sections of this protocol. In the event that the implanted device is removed, the event will be noted on the Adverse Event case report form. Device-related adverse events include, but are not limited to: breakage, infection, loss of fixation, dislocation and wear.

5.2 Definition of Terms

ASTM = American Society for Testing Materials. Organization established to develop standardized test methods and material specifications.

Clinical Investigation = Human research study administered under a detailed study protocol.

Clinical Investigator = Person responsible for administering the clinical investigational plan and reporting the study data for the respective investigational site. If there are to be multiple clinical investigators, then a primary investigator is designated and those remaining are co-investigators.

CRF = Case Report Form. Form used for recording the Subject data required by the clinical protocol.

CRO = Contract Research Organization. A firm employed by the Sponsor to oversee various aspects of the clinical investigation.

FDA = U.S. Food and Drug Administration

Clinical Investigational Plan (CIP) = Written document describing how the clinical investigation will be conducted.

Investigator's Regulatory Binder = a binder provided to the investigator by the Sponsor and maintained by the investigational site. The binder includes regulatory documents, Ethics Committee documents, correspondences, investigator's responsibilities, study protocol correspondence, all applicable federal regulations, investigator's CV and agreement, and other contents deemed applicable by the Sponsor.

Investigational Site = Institution where the clinical investigation will be administered.

IPC = Informed Patient Consent.

ETHICS BOARD/COMMITTEE = Institutional Review Board. A group of people formally designated by an institution to review and approve all biomedical research involving humans, which is conducted at the hospital/clinic to assure that the rights, welfare and safety of subjects, are protected.

IRR = Independent Radiographic Reviewer

Monitor = Person(s) designated by the Sponsor to review medical records and other source documents pertaining to an investigational study.

Research Subject = Subject who gave his/her consent to participate in the clinical investigation.

Sponsor = Person/Organization responsible for overseeing the conduct of the clinical investigation. In this case, Ascension Orthopaedics, Inc.

Source Documentation = Original documents, data, and records (e.g., hospital records, clinical and office charts, patient completed questionnaires, study worksheets, laboratory notes, X-ray films, other Subject information, etc.) that document Subject care and associated procedures in a clinical investigation.

TSR= Total Shoulder Resurfacing

TSA = Total Shoulder Arthroplasty

TJR = Total Joint Replacement

UADE = Unanticipated Adverse Device Effect is any serious adverse effect on the 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.

VAS = Visual Analog Scale

5.3 Subject Eligibility Criteria

This section details the entry criteria for Subject eligibility for participation in this clinical investigation. Demographic, clinical, and radiographic requirements that must be met (in addition to the diagnostic criteria) are described below. Subjects will be selected for recruitment into this study from the general diagnosis population defined for primary Total Shoulder Resurfacing as an end-stage condition of the Shoulder joint that is refractory to non-surgical treatment (see Inclusion Criteria and Exclusion Criteria).

Subjects who do not meet all of the inclusion criteria or meet any exclusion criteria are automatically excluded from study consideration and participation. Subjects who meet all entry criteria and are properly consented, may be excluded from participation because of:

- surgical preference,
- withdrawal of consent for study participation,
- other reasons.

Inclusion criteria

1. Patients selected for inclusion will present 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 is able to or capable of providing consent to participate in the clinical investigation.

3. Subject agrees to comply with this protocol, including participating in required follow-up visits at the investigations site and completing study questionnaires.

4. Subject is at least 21 years of age and skeletally mature at the time of surgery.

Exclusion Criteria

Patients will be excluded from participation if they:

1. Have destruction of the proximal humerus to preclude rigid fixation of the humeral component
2. Insufficient bone quality as determined by intra-operative evaluation
3. Have arthritis with defective rotator cuff
4. Have had a failed rotator cuff surgery
5. Have loss of musculature, neuromuscular compromise or vascular deficiency in the affected limb rendering the procedure unjustified
6. Have evidence of active infection

7. Present with a condition of neuromuscular compromise of the shoulder (e.g., neuropathic joints or brachioplexis 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 skeletally immature.
10. Have a known allergic reaction to pyrocarbon
11. Have 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. Are currently participating in another clinical study
13. Have known, active metastatic or neoplastic disease
14. Are taking > 10mg/day corticosteroids (e.g. prednisone) excluding inhalers, within 3 months prior to surgery
15. Are under 21 years of age or over 75
16. Require glenoid replacement (Glenoid Classification)

Obesity, heavy labor, metabolic disorders, disabilities of other joints and active sports participation are relative indications for study exclusion since these conditions tend to place the patient at higher risk of failure than other arthroplasty patients. Consideration of such patients for study inclusion is at the discretion of the investigator.

5.4 Screening / Enrollment

The surgeon will recommend whether the patient should be implanted with this device even if the patient decides not to take part in the study.

The patient must be screened against the inclusion and exclusion criteria (Section 5.3). Where a subject fails to fulfill any element of the inclusion and exclusion criteria, this will be documented. The subject will not be advanced any further into this investigation. Screened Subjects who meet all eligibility criteria and consent to participation must be entered into the study.

The subject will only be allocated to the next available investigational subject number when it is confirmed that the subject is eligible and the procedure will ensue. This number will consist of the center study number followed by 001 for the first patient, 002 for the second patient and so on, (e.g. 2001 site 2 subject 1). This number will then become the unique identifier of the subject and will be written on each page of the CRF and all other study documentation relating to that subject. A master subject list which will be kept strictly confidential and will not be removed from the Investigational Site will record the full name, subject number and clinic record number for each enrolled subject.

Any subject who wishes to withdraw from this investigation on his/her own accord and for whatever reason is entitled to do so without obligation and prejudice to further treatment. In addition, the Investigator may decide for reasons of medical prudence, to withdraw a subject. In either event, the Investigator will clearly document the date and reason(s) for the subject's withdrawal from this investigation in the clinic notes and should indicate whether or not he considers it related to the device.

5.5 Success/ Failure Criteria

Clinical requirements for success at 24, 60 and 120 months:

- Device remains implanted
- Absence of device-related complications requiring surgical replacement, removal, or augmentation of components
- Freedom from chronic dislocation

Radiographic and MRI requirements for success:

- No evidence of device radiolucency > 2mm
- Anatomic alignment

6.0 Study Procedures

6.1 Pre-Operative Management

Pre-admission testing may be conducted to satisfy the medical/surgical requirements of each Investigator, hospital or institution participating in the study. Such testing is not intended to determine comparability of the study device and will, therefore, not be documented by the Sponsor. The investigators will obtain the clinical information and record it in the medical chart. Data collected will address the following: demographic information, age, sex, date of birth, patient reported height and weight, hand dominance, side of injury, history of present illness, diagnosis, mechanism of injury, smoking and diabetes status, history of fracture and x-ray availability (all of which are standard data collected during routine history taking). Patients will be asked to verify the information collected from the medical chart and update information as appropriate at designated post-operative visits. Prior to surgery, the following procedures must be completed for each enrolled subject to satisfy study requirements:

1. Executed Informed Patient Consent
2. Verification of all inclusion and exclusion criteria
3. Subject medical history review
4. Radiographic (X-ray and MRI) evaluation
5. Clinical evaluation
6. Subject self-assessments

As part of the pre-operative assessment of each study subject, the investigator will complete the Constant Score CRF based on source documentation. The Subjects will obtain radiographs, complete the WOOS, EQ-5D, the VAS Scales, ASES Shoulder Evaluation, and update Health History Profile. The center will submit x-rays and MRI's for independent evaluation. All data will be compared with the follow-up data obtained at each study interval.

6.2 Operative Management

Each investigator will complete an Operative Details CRF based on source documentation that provides specific information from the Subject's surgery, such as surgical technique, catalog and lot numbers for implanted device. Any complications that occurred during the surgery are reported using the Operative Complications CRF.

The anesthesia procedure will follow the normal clinical practice at the investigation site. All sites are to use general, spinal or epidural anesthesia. Further, it is strongly encouraged that the anesthesia be standardized across all study Subjects within one institution.

In addition, each individual site will designate the surgical approach and any ancillary procedures on the Operative case report form. A surgical technique for the PyroTITAN™ HRA Shoulder prosthesis will be provided to each investigator participating in the study.

The Investigator should record all of the following information after the surgery:

- Subject Historical Profile
- Operative Detail
- Pre-op WOOS Score
- Pre-op ASES Score
- Pre-op Constant Score
- Pre-op Visual Analog Scale (Pain)
- Pre-Op X-rays, MRI and/or CT films

6.3 Post- Operative Management

Immediate post-operative management is at the discretion of the surgeon and support staff. Rehabilitation programs are somewhat individualized and variables such as age, health and physical fitness of the subject must be considered by the surgeon when recommending

a rehabilitation program. The subject should be encouraged to report any unusual changes in the operated extremity to the physician. If any such change is found to be related to the device or procedure, such a report would necessitate submission of an Adverse Event CRF to the Sponsor. General, accepted practices for post-operative care should be followed for each Subject.

Follow up intervals will be calculated from date of surgery as follows:

- Pre-Operative - 180 to -1 day
- 3 months 1 - 120 days
- 6 months 180 days +/- 30days
- 12 months 365 days +/- 60days
- 24 months 730 days +/- 60days
- 36 months 1095 days +/- 90 days
- 48 months 1460 days +/- 90 days
- 60 months 1825 days +/- 90 days
- 96 months 2920 days +/- 90 days
- 120 months 3650 days +/- 90 days

The following case report forms that will be completed and submitted to the sponsor in the noted intervals can be found on the Time and Event Table Section 2.0.

Clinical Outcome Forms

All clinical outcome forms will be performed on each study subject at the intervals specified in Section 2, and will be performed per the standard of care at the institution. The research associates/coordinators, or medically qualified designee (not the Surgeon) per their standard of care for patient management purposes, will perform all of the assessments. The following will be assessed: ASES Shoulder Score, Constant Score, WOOS Score, EQ-5D Health Questionnaire, VAS Pain and Satisfaction Scale, and strength and range of motion.

ASES Shoulder 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 subject 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 subject.

The subject will provide the best possible answer for that day. The form will be completed preoperatively and postoperatively (3 months, 6 months, 12 months, 24 months, 36 months, 48 months, 60 months, 96 months and 120 months).

WOOS Score

The WOOS Score is a quality of life questionnaire that has been validated for various shoulder conditions. This form is used during the clinical process. 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. The form will be completed with each mailing and returned to the Investigator. 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 subject.

The subject will provide the best possible answer for that day. The form will be completed preoperatively and postoperatively (3 months, 6 months, 12 months, 24 months, 36 months, 48 months, 60 months, 96 months and 120 months).

Visual Analog Scale (VAS)

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 subject.

The subject will provide the best possible answer for that day. The subject will provide the best possible answer for that day. The form will be completed preoperatively and postoperatively (3 months, 6 months, 12 months, 24 months, 36 months, 48 months, 60 months, 96 months and 120 months).

EQ-5D Quality of Life Questionnaire

The EQ-5D Questionnaire consists of information pertaining to the current health status of the patient at the time of evaluation. The EQ-5D questionnaire measures physical, emotional, and social status. The subject will take between 10 to 15 minutes to complete the test. The form will be completed at each testing session. The subject will provide the best possible answer for that day. The form will be completed preoperatively and postoperatively (3 months, 6 months, 12 months, 24 months, 36 months, 48 months, 60 months, 96 months and 120 months).The form will be completed with minimum or no assistance from the coordinator. The coordinator can clarify a question but will not influence the subject. The subject will provide the best possible answer for that day.

Constant Score

The Constant Score is a commonly used score of shoulder function.
Collection of this data will allow comparison with both US and European data. The Constant form consists of questions pertaining to shoulder pain, function, and strength. The

form will be completed preoperatively and postoperatively (3 months, 6 months, 12 months, 24 months, 36 months, 48 months, 60 months, 96 months, and 120 months) after the patient has regained function.

Strength

Strength is given a maximum of 25 points in the Constant Score. The significance and technique of strength measurement has been, and continues to be, the subject of much discussion.

The European Society for Shoulder and Elbow Surgery measures strength according to the following method:

- A spring balance is attached distal on the forearm.
- Strength is measured with the arm in 90 degrees of elevation in the plane of the scapula (30 degrees in front of the coronal plane) and elbow straight.
- Palm of the hand facing the floor (pronation).
- The patient is asked to maintain this resisted elevation for 5 seconds.
- It is repeated 5 times immediately after another.
- The average in pounds or kilograms (lb or kg) is noted.
- The measurement should be pain free. If pain is involved the patient gets 0 points.
- If patient is unable to achieve 90 degrees of elevation in the scapula plane the patient gets 0 points.

Range of Motion

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.

Extension

Extension is when the arm is moving straight backwards. Normal range of motion for extension of the shoulder joint is 50 to 60 degrees. The motion starts at 0 degrees. Shoulder extension is the most powerful shoulder movement.

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 hand is pointing forward.

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. The lower arm is parallel to the floor, and the hand is pointing forward.

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.

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 are at the side of the body with palms facing forward. 45 degrees is when the upper arm has moved across the front of the body toward the opposite side.

The patient directed forms will be completed with minimum or no assistance from the coordinator. The coordinator can clarify a question but will not influence the subject. The subjects will provide the best possible answer for that day.

As part of the post-operative assessment of each study Subject, the investigator will complete the Constant Score CRF based on source documentation. The Subjects will obtain radiographs, complete the WOOS, EQ-5D, the VAS Scales, ASES Shoulder Evaluation, and update Health History Profile. The center will submit x-rays and MRI's for independent evaluation. All data will be compared with the follow-up data obtained at each study interval.

6.4 Radiograph Requirements: X-Ray and MRI

The shoulder radiographic views will consist of a true anterior-posterior in the scapular plane, internal and external rotation, axial lateral and an axillary lateral view. The patient will be placed in a shoulder harness to maintain 30 degrees of scapular plane during the examination or subjects may be radiographed supine with wedge support. Patients may come to the office with shoulder radiographs already completed at their first clinical visit.

Additional radiographs may be needed if the radiographs are of poor quality and/or do not provide adequate information on the humeral head.

Radiographs will be completed at the following time periods: pre-operatively within 180 days of surgery and post-operatively: 3 months, 6 months, 12 months, 2 years, 3 years, 4 years, 5 years, 8 years and 10 years. The following will be assessed on the radiographic evaluation: loosening of the humeral component, osseous structures, anatomic alignment, condition of the glenoid and joint congruity.

The patient will not need radiographs if they have had a revision surgery and/or they are lost to follow-up. Radiographs are obtained at the pre- and post-operative intervals, as designated on the Subject Management Schedule.

Radiographic evaluation parameters are provided below. All radiographs are submitted to the Sponsor after the scheduled visit. To avoid potential bias, an independent radiographic reviewer (IRR) will evaluate all radiographs. The reviewer will complete the radiographic evaluation forms and forward them to the Sponsor for entry into the database. Data from the IRR radiographic evaluation will be used for determining the radiographic success criteria.

General Instructions

- All effort should be made to utilize the same X-ray machine with the same settings across time periods for each individual. To ensure consistency in quality of the radiographs, it is recommended the kVp, mAs, FFD, and tube angles must remain the same for a given patient at all time periods.
- Radiographs should be of adequate quality (not over or under exposed).
- All radiographs should be performed using digital DICOM 3 uncompressed format. Digital files should be recorded onto the Study CD labeled with the required patient and visit identifiers.
- All actions must be taken by the site to anonymize the radiographic images.

- Digital images must be submitted at 100% scale or true to size
- For film, the film size should be appropriate to the size of the subject
- Left or right lead markers must be utilized without superimposition of pertinent anatomy.

AP SHOULDER RADIOGRAPH ACQUISITION External Rotation, Neutral Rotation, and Internal Rotation Scapular Plane						
View	kVp	mAs	FFD	Film Size	Centering	Patient Instruction
AP External	70-80	10	Between 40 and 48 inches (100-120 cm)	24 X 30 cm crosswise	The central ray should be perpendicular to film centered to coracoid process	The patient may be examined in the erect or supine position. The erect position is recommended whenever possible so that the patient's body position can be adjusted to require little or no manipulation of the arm.
Neutral Rotation	70-80	10	Between 40 and 48 inches (100-120 cm)	24 X 30 cm crosswise	The central ray should be perpendicular to film centered to coracoid process	The patient may be examined in the erect or supine position. The erect position is recommended whenever possible so that the patient's body position can be adjusted to require little or no manipulation of the arm.
AP Internal	70-80	10	Between 40 and 48 inches (100-120 cm)	24 X 30 cm crosswise	The central ray should be perpendicular to film centered to coracoid process	The patient may be examined in the erect or supine position. The erect position is recommended whenever possible so that the patient's body position can be adjusted to require little or no manipulation of the arm.

AP Shoulder

- Place the patient in the erected position.

- Adjust the patient's body to center the film to the coracoid process. Rotate the patient enough to place the blade of the scapula parallel with the plane of the film.

External Rotation

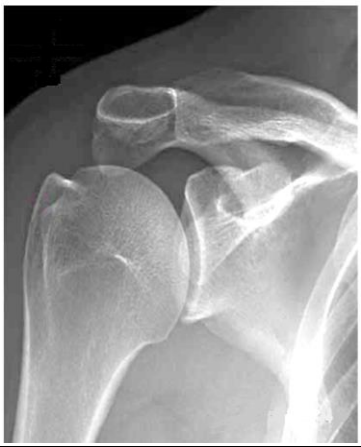
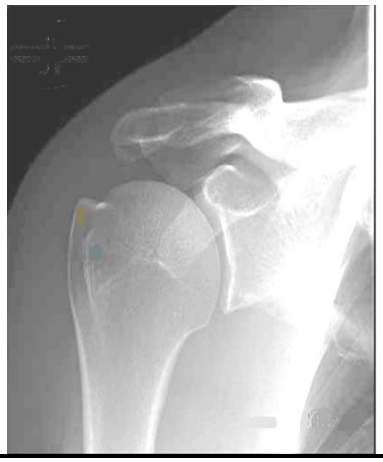
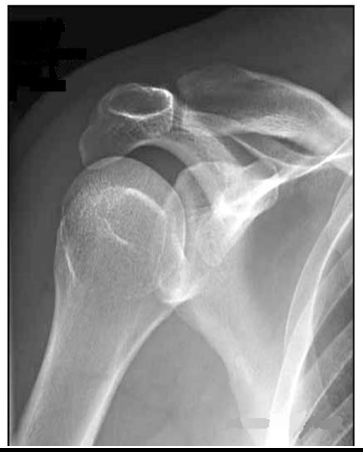
- Ask the patient to turn the palm of their hand forward.
- Abduct the arm slightly and adjust it so that the coronal plane of the epicondyles is parallel with the plane to the film.

Neutral Rotation

- Ask the patient to rest the palm of the hand against his thigh.

Internal Rotation

- Ask the patient to flex their elbow, rotate the arm internally and rest the back of the hand on his hip.
- Adjust the arm to place the coronal plane of the epicondyles perpendicular to the plane of the film.
- If this positioning is too painful for internal rotation, the patient may turn away from the film.

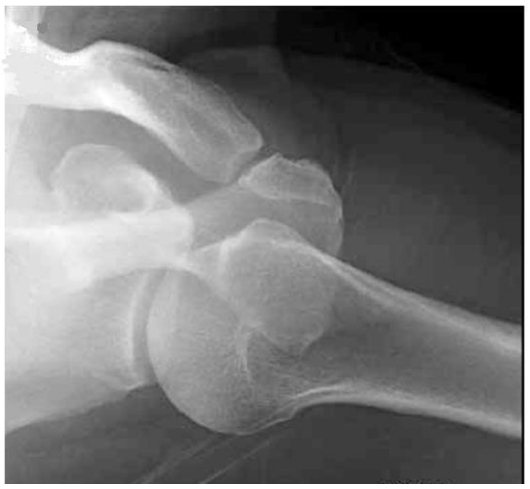
AP External	AP Neutral	AP Internal Rotation
		

LATERAL SHOULDER RADIOGRAPH ACQUISITION Axial Lateral and Axillary Lateral					
kVp	mAs	FFD	Film Size	Centering	Patient Instruction
		Between 40 and 48 inches (100-120 cm)	18 X 24 cm lengthwise	Direct the central ray at angle of 5 to 15 ° toward the elbow.	Seat the patient at the end of the table with the shoulder centered to the midline of the table. The patient should be seated on a stool or chair high enough to enable him to extend the affected should over the cassette.

Axial Projection

- Place the cassette near the end of the table and parallel with its long axis.
- Raise the patient's arm on the affected side to a position as near as possible at right angles to the long axis of the body.
- Have the patient lean laterally over the cassette until the shoulder joint is over the midpoint of the film and bring the elbow to rest on the table.
- Flex the patient's elbow 90° and place the hand in the neutral position.

- Have the patient bend his head toward the unaffected side.

Axial Lateral	Axillary Lateral
	Insert Image

MRI Instructions

1.5 TESLA or 3 TESLA MRI can be utilized for the evaluation. The same MRI unit should be used for all evaluations, e.g, the original MRI is performed using a 1.5 Tesla unit all future evaluation for that patient should be performed on the 1.5 Tesla unit.

Use same series for pre and post operative scans so imaging is comparable

- **AXIAL T1 :** -Resolution 384 x 384 pixels
  -large field of view to include whole scapular body for assessment of glenoid version
  -assess glenoid vault and muscle bulk of spinati

- **AXIAL PD :** -Resolution 512 x 512 pixels
  -small field of view to focus on glenohumeral joint region
  -good for PYC on post-op with less artefact
  -good assessment of interface between Pyrotitan and native glenoid on post op

- **2ND AXIAL PD :** **Fat saturated**
  -Resolution 384 x 384 pixels
  -small field
  -better for oedema, cysts etc

- **CORONAL PD :** - good for anatomic detail of cuff, labrum etc

- **CORONAL T2 :** **STIR** (this is by definition fat sat)
  - less artefact on post op so good for assessing cuff post op

- **SAGITTAL T1 :** **Non fat sat**
  -muscle atrophy
  -comparable to Goutallier type assessment of spinati for fatty atrophy

- **SAGITTAL T2 :** **Fat saturated**
  -good detail and sensitive to fluid around / under prosthesis at bone / prosthesis interface

Radiograph / MRI Submission

The preferred method of radiograph submission is by digital format. The digital images should be saved in JPEG-2000 or dicom format and submitted to the Sponsor on a CD and sent by FEDEX or other over-night carrier. The date of film must either be on the x-ray and designated in the file name. Subjects should be identified by their initials and Subject ID number.

In the event digital images are not available, the site's original radiographs for each x-ray view will be forwarded to the Sponsor. The Sponsor will make digital copies of the original radiographs and return the film copy to the investigational site. All radiographs will be de-identified to the extent possible by the site prior to shipping to the sponsor.

6.5 Subject Withdrawals

Pre-operative Withdrawal

Subjects who withdraw from consideration prior to signing consent or who decline participation or who sign consent, but are pre-operatively excluded are considered "screen failures" and are not entered as subjects into the study. No forms are required to be maintained at the Site or submitted to the Sponsor for screen failures.

Intra-operative Withdrawal

If a subject is withdrawn intra-operatively (e.g. inclusion/exclusion criteria, etc.), then a completed Operative Detail CRF must be submitted to the Sponsor in addition to those listed above.

However, all data obtained up until the time of consent withdrawal will be available for analysis. The Withdrawal CRF must be sent to the Sponsor.

Post-Operative Withdrawal

Subjects withdrawn from the study post-operatively (e.g., withdrawal of consent, etc.) who maintain the investigational components do not require continued follow-up in accordance with the study protocol. However, all data obtained up until the time of consent withdrawal will be available for analysis. The Withdrawal CRF must be sent to the Sponsor.

7.0 Revision/Re-operation

Post-operative surgical procedures associated with the operative shoulder are categorized as Adverse Events. If a Subject undergoes any surgical procedure on the operative shoulder in which all of the original Pyro-Titan Resurfacing Shoulder implant components are retained (debridement etc), the Subject is not withdrawn from the study and all follow-up visits are maintained according to the Subject Management Schedule. If the Pyro-Titan Resurfacing Shoulder prosthesis implant is removed then the Subject is considered revised, is withdrawn from the study, an Adverse Event and Study Completion CRFs must

be submitted to the Sponsor. The remaining study-related follow-up visits are not required in the case of revision. Every attempt should be made to retain the explanted device and return it to the Sponsor for evaluation.

8.0 Lost To Follow-Up

There may be study subjects who will not or cannot return for follow-up examinations as prescribed in the protocol. These individuals will be considered as non-compliant with the study protocol. This group includes:

- Subjects who refuse to return for follow-up,
- Subjects who relocate without notifying the Sponsor or the Investigator, and cannot be located for continued follow-up arrangements.

Subjects that are considered "lost to follow up" are not considered withdrawn from the study. Sites should make every attempt to contact and schedule post-operative visits. In the event a subject does not respond to telephone correspondences regarding a missed visit, a registered letter should be sent to the subject indicating the importance of the follow-up visits and to contact the office immediately. All correspondence to the subject must be documented within the subject's source documentation.

9.0 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 adverse events, device related or procedure related, are transcribed from source documentation onto an Adverse Event CRF and forwarded to the Sponsor (one Adverse Event per CRF).

9.1 Serious Adverse Events (SAEs):

An adverse event that:

- Lead to death;
- Lead to serious deterioration in the health of the subject, that either resulted in:
  - A life threatening illness or injury
  - A permanent impairment of a body structure or a body function
  - In-patient or prolonged hospitalization
  - Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function
- Lead to fetal distress, fetal death or congenital abnormality or birth defect.

Medical and scientific judgment should be exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room for a bronchospasm or convulsions that do not result in hospitalization.

This definition of an SAE is not intended to include hospitalization specifically to treat a condition that existed prior to the patient's enrollment in the study (e.g., pre-existing knee injury that is surgically repaired during the study) or prearranged elective surgery performed during this study period.

9.2 Unanticipated Serious Adverse Device Effect (USADEs):

A serious adverse device effect which, by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

9.3 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

9.4 Adverse Event Severity Determination:

All Adverse Events must be classified by the investigator 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	AE is noticeable to the patient but does not interfere with routine activity and does not require medical treatment.
Moderate	AE interferes with routine activity but responds to symptomatic therapy or rest.

	Usually requires medical treatment.
Severe	AE that results in loss of life or limb.

9.5 Adverse Event Reporting:

Investigators and /or study staff are required to report AEs (and all reportable effects) per their Institutional Review Board/Ethics Committee Standard Operating Procedures.

In the event of a complication, the Investigator and/or other professional personnel in attendance will undertake the appropriate therapy. All adverse signs and symptoms (device or procedure related) that occur during the study are to be recorded on an Adverse Event CRF. The description of adverse events will include cause, date of initial onset, severity, treatment, and date of resolution.

All serious and non-serious device or procedure related adverse events and unanticipated serious adverse device effects that occur during this investigation must be reported in a timely manner by the Investigator using either telephone or fax to:

ATTN: Clinical Research
Ascension Orthopedics, Inc

512-836-6933

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 hospitalisation or significant prolongation of existing hospitalisation)

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:

As the product is CE marked and used in its intended purpose, Medical Device vigilance system applies: The Investigator should report incidents with Medical Device to the manufacturer or to the National Competent Authority, depending on national practice.

10.0 Termination of Subject Participation

Any subject who wishes to withdraw from this clinical investigation on his/her own accord and for whatever reason is entitled to do so without obligation and prejudice to further treatment. In addition, the Clinical Investigator may decide for reasons of medical prudence (e.g. stroke, amputation), to withdraw a subject. In either event, the Clinical Investigator will clearly document the date and reason(s) for the withdrawal on the Withdrawal CRF. The investigator should note if the withdrawal was related to the device.

11.0 Statistical Methods

11.1 Purpose

This is an exploratory study intended to provide data that may be mined for a variety of purposes. The treatment of shoulder pathology with a prosthesis is an area where there is still a great deal to learn. There is no consensus, for example, regarding when a resurfacing is preferred to a total shoulder or hemi arthroplasty in subjects with an intact glenoid.

Accordingly, the study is designed to allow comparisons to these implants either through literature review or other clinical data mined from outcome studies of other implant

configurations. The number of shoulders available must be adequate in number to follow outcomes in the long term, accounting for expected attrition, and in accordance with peer reviewed journal standards.

11.2 Study Design

This clinical investigation is a prospective, non-comparative, multicenter, post market study designed to monitor the clinical safety and performance of the PyroTITAN^{TM} HRA Shoulder prosthesis. Results will be contrasted with results from the literature.

11.3 Sample Size and Power Analysis

The original sample size in this study was 150 enrolled subjects. Additional proof testing and improvements in the device inspection process were employed during the study, at which time it was determined that an additional cohort of subjects was necessary. We are now comparing a cohort of subjects enrolled after these changes to the original cohort of subjects.

With an expected attrition rate of 10% per annum, this will yield an evaluable sample size of 52 shoulders at ten years ($150 * 0.9^{10} = 52.3$, where 0.9 or 90% is the number expected to be retained from one year to the next). Based on past experience, we may obtain clinical follow-up on this number of shoulders, but we may obtain radiographic follow-up on as few as two-thirds of these shoulders (about 35 shoulders). This remaining number of evaluable shoulders with clinical and radiographic follow-up is adequate to establish a reliable ten-year survival estimate of survival for hemi arthroplasty (Dorey and Amstutz, 1986).

For the new cohort, the sample size is calculated based on the non-inferiority of the study device. The success rate for the study device is 96.1% from the original population and is used as reference rate. Therefore, for a conservative success rate of 96.1% of the study device is used in the study. The non-inferiority margin δ of -0.033 is chosen in the study. 212 subjects are required to achieve $100(1 - \beta)$ % =80% power to detect non-inferiority at the Significance level of $\alpha = 0.05$. To account for 10% lost to follow-up, the

total number of additional subjects is 237. Therefore, the estimated enrollment for the study will be 387 subjects.

11.4 Treatment Assignment

All shoulders will be treated with PyroTITAN™ HRA Shoulder prosthesis.

11.5 Interim Analysis

Data will be reviewed for safety in an ongoing manner, according to standard formal procedures at Ascension Orthopedics. No interim analysis per se is planned; but it is anticipated that a number of outcomes will be followed through time; for example, surgical technique, and return to function.

11.6 Data Analysis

Although this study is exploratory in nature, for many investigations the success of the implant will be a primary endpoint.

11.7 Primary Endpoint

Clinical requirements for success will be evaluated at 24, 60 and 120 months:

- Device remains implanted
- Absence of device-related complications requiring surgical replacement, removal, or augmentation of components
- Freedom from chronic dislocation

11.8 Secondary Endpoint

Radiographic and MRI requirements for success at the different time points:

- No evidence of device failure, specifically progressive migration or implant loosening
- Anatomic alignment is a criterion that may be included in the definition of success in some investigations

Clinical outcomes measures at the different time points.

11.9 Other Endpoints

The following will be analyzed at the end of the trial:

Adverse Events including, but not limited to:

- Infection
- Loss of fixation
- Breakage
- Dislocations
- Revisions

Data will be entered, verified and validated using a computer database system. Both the data management and statistical analysis will be performed by Ascension Orthopedics, Inc. Descriptive statistics of patient demographic details will be calculated over all patients. Pre-operative values of outcome variables will be compared to postoperative values at various time points. For interval level data, t-tests will be used; for ordinal level data (ranked data) the Wilcoxon matched-pairs signed-ranks test will be employed, and chi-square or Fisher's exact tests will be used for categorical data. Correlation coefficients may also be employed to determine whether preoperative variables are related to outcome variables.

12.0 Risk Analysis

Radiographs are a normal part of post-operative follow up and the subject will experience no additional radiation exposure beyond what is clinically necessary. The radiation exposure risk is estimated to be 0.004mSv per follow-up interval with 8 intervals in the study. This is comparable to 36 days exposure to natural background radiation. The radiation exposure risk is based on an X-ray to the upper extremity which has a radiation exposure of 0.001mSv per x-ray. Muscle discomfort and/or shoulder joint pain may occur during the musculoskeletal muscle strength and range of motion testing. The patient will be informed that rest and ice should be applied. Additional concerns should be directed towards the treating surgeon for consultation. PyroTITAN^{TM} HRA Shoulder prosthesis risks,

that are no different from other prosthesis, include infection, failure of prosthesis, implant loosening, or shoulder dislocation and/or subluxation. The patient will be told this during the normal pre-surgical information process and sign an Informed Consent related to the surgical procedure acknowledging this information. Any complications can be treated with conversion to total shoulder arthroplasty, reverse shoulder arthroplasty, or shoulder arthrodesis (fusion).

The benefits of shoulder resurfacing surgery depend upon each patient. Benefits usually include a conservation of humeral bone, reduction or relief of pain, restoration or improvement in range of motion and mobility, correction or improvement of disfiguring deformity and an improvement in the patient's quality of life. Participation in this study may benefit society as well as provide valuable information to the orthopaedic community other doctors and help them make informed decisions about the kind of shoulder replacement components most likely to benefit their patients. The patients will benefit by becoming better informed of the status of their shoulder or injury. They will have added contact with their surgeon and his or her staff. The patient will also be informed of the status of the Pyro-Titan Resurfacing Shoulder prosthesis during their follow-up examination assessment visits. Results of this study will provide information about the effect of Pyro-Titan Resurfacing Shoulder prosthesis on the functional outcomes experienced by the subjects post shoulder arthroplasty.

Minimal risks are associated with this study. Subjects may experience infection, failure of prosthesis, glenoid wear, implant loosening, or dislocation post PyroTITAN^{TM} HRA Shoulder prosthesis implant. The risks of harm anticipated in the proposed research are not greater, considering probability and magnitude of those ordinarily encountered in shoulder arthroplasty or during the performance of routine physical and psychological examinations or tests. The patient may or will experience changes in function, pain, and satisfaction levels of activities of daily living. The other alternative is to continue with their current levels of satisfaction, function and pain as related to the shoulder arthritis.

Any surgical procedure poses a potential risk and the procedures undertaken as part of this clinical investigation are no exception. There are known risks associated with the method

of anesthesia (general, epidural, spinal). Separate consent forms will be presented to subjects outlining the risks of shoulder surgery and anesthesia. In addition to these there are risks associated with a surgical procedure that involves a device, including the following: damage to nervous and vascular tissue, infection, long term swelling, fracture of bone surrounding the device, loosening, dislocation or fracture of the device, hemorrhage, decrease in range of motion or mobility deformity, allergic reaction to the device and failure of the device to be incorporated into the body. A complication may require revision surgery. Very rarely a complication may prove fatal. This clinical trial of the CE marked (November 30th, 2009)PyroTITAN™ HRA Shoulder prosthesis, used according to this protocol and labeling indications, poses no additional risks over those normally associated with shoulder resurfacing arthroplasty.

13.0 Device Descriptions

The Ascension® 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. Head sizes are identified using width and height (in millimeters) and are as follows: 38/14, 41/15, 41/18, 44/16, 44/19, 47/17, 47/20, 50/18, 50/21, 53/19, 53/22 and 56/21. The Pyro TITAN™ 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. Device components are provided sterile in packaging containing a single component.

14.0 Investigator Responsibility

Prior to the initiation of this clinical investigation, the Clinical Investigator will approve this CIP by signing a research agreement. This signature confirms that the clinical investigation will be performed in compliance with the CIP.

All Investigators are responsible for maintaining a complete case history for each Subject. This case history must be adequately detailed to cover all data points on the Case Report Forms. Worksheets may be developed and implemented to simplify this process, or it is expected that detailed dictations will be done. The case history is defined as the "source documentation."

Each Investigator and all personnel from the investigational site will maintain records of all correspondence, electronic, written, and verbal, relating to any aspect of the clinical investigation. The records are maintained in the Investigator's Regulatory Binder consisting of, but not limited to correspondence with other participating clinical investigators, the reviewing ETHICS BOARD, and the Sponsor. The study monitor will examine the contents of the correspondence file as part of the monitoring visit.

Prior to the investigational site beginning Subject enrollment, the following documents will be fully executed and returned to Ascension Orthopedics by the clinical investigators:

- Curriculum vitae (c.v.)
- Medical license
- Confirmation of ETHICS BOARD Approval
- Clinical Research Agreement
- Investigator Compensation Agreement
- Financial Disclosure

Copies of the Investigator Agreement will be provided by the Sponsor after contracting.

14.1 Investigator Regulatory Binder

Each investigator must maintain an accurate, complete, and current copy of the Investigator Regulatory Binder. Upon receipt of copies of changes or revision updates to the Investigator Regulatory Binder(s) from the Sponsor, the Investigator or designee will add the updated document to the Regulatory Binder and will mark the outdated portion of the Regulatory Binder as “obsolete” by crossing a diagonal line across the page(s) along with date the page was obsoleted and the initials of the person performing the update. The outdated pages will be removed from their current section and filed in the “Obsoleted” section. The study monitor will examine the contents of the Investigator Regulatory Binder as part of the monitoring visit.

14.2 Case Report Form Completion

Data will be transposed onto the CRF’s or data collection form. Data will be accurately and completely recorded in ink on the CRF’s or electronically on the data collection form. Prior to submission to Ascension, any errors on the forms are to be corrected, either crossed out with a single stroke, initialed and dated on the paper form or by verification and reentry of electronic data. Typing correction fluid must not be used. After submission to Ascension, no changes may be made to the data collection form. Instead, a Data Clarification Form (DCF) must be used to document any modifications to a data collection form. The signed, original DCF is submitted to Ascension and a copy is affixed to the original, corresponding CRF. The personal data recorded on all documents will be regarded as confidential. The Clinical Investigator will be responsible for the timing, completeness, and accuracy of the data collection form and will retain a copy of each completed form.

The Investigator’s copies of the Investigation, including Consent forms and CRF’s should be held for a minimum of fifteen years after the completion of the investigation. In the event the Clinical Investigator retires or moves, the investigator will provide the name and address of the custodian of the study records. Alternatively the custody of the study records may be transferred to the Sponsor with notification to the governing Ethics Board.

The subjects' participation in the investigation must be recorded in the Subject's hospital notes. In addition, the Investigator must keep a separate list of all subjects entered into clinical investigation. This list should include the name, date of birth, and subject number.

15.0 Institutional Review Board (ETHICS BOARD) Action

This study is intended to monitor post-market clinical outcomes of the devices described above. The Notified Body has cleared all devices utilized in this evaluation for general use in accordance with printed indications. It is the responsibility of the investigator to submit a copy of the investigational plan and secure approval of the governing ETHICS BOARD for each institution under consideration for the study. If ETHICS BOARD approval is not required, this must be indicated in a signed letter from the governing ETHICS BOARD.

No subjects should be consented or requested to complete a release of medical records until ETHICS BOARD approval has been obtained. It is the responsibility of the investigator to comply with governing ETHICS BOARD requirements including but not limited to reporting adverse events, reporting consent and protocol deviations, submission of periodic reports in a timely manner and any other institutional, state or federal regulations.

16.0 Informed Consent

Informed consent materials, including a model consent form; will be provided to each investigator. In compliance with Ascension Orthopedics, Inc. policy, no subject is to be enrolled in this study without adequate informed consent being provided or a waiver of consent granted by the ETHICS BOARD. The informed consent process should be documented in the subject's medical record. Failure to obtain, or improper documentation of, informed consent is in violation of Ascension policy and the study protocol unless

exempted by an ETHICS BOARD waiver. In the event of such an exemption, a release of Medical Records shall be obtained.

Some ETHICS BOARD's require modifications to the Informed Patient Consent form (IPC) to satisfy specific institutional requirements. Use of modified consent forms is permitted provided they meet the local requirements.

The investigator will solicit the informed consent of any patient meeting the selection criteria prior to surgery. The investigator will answer all questions the subject may have and will explain the following features of the study thoroughly including:

- The purpose of the study
- Possibility of failure and subsequent treatment(s)
- Alternative procedures
- Requirements of the study (follow-up visits),
- All of the Subject's rights as a subject in the clinical investigation.

If the patient agrees to participate in the study, either an IPC form as approved/required by each ETHICS BOARD or a release of medical records as appropriate must document this. One completed copy of the consent and/or release form is to be given to the patient, another placed in the hospital files if required. The original IPC form remains with the clinical investigator (i.e., within the CRF booklet or clinic chart). The IPC **is not forwarded to the Sponsor**. Once a Subject has executed the IPC documentation, they are considered a study subject.

Subject should sign and date the IPC form prior to any study required assessments or exams as described in Section 6.0 above, and prior to the day of surgery. However, if the IPC is signed on the day of surgery, then the source document must state that the subject

was given adequate time prior to the time of surgery to review and give consent. In such a case, the time the Subject signed the IPC form must be documented.

For the purposes of this study, the success or failure of the Product will be based upon the patient's clinical results as measured using the clinical and radiographic parameters detailed herein. Investigators should document each death using the Adverse Event/Withdrawal CRF.

17.0 Review of Source Documents

Source data is all information, original records of clinical 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 Examples of these original documents, and data records include: hospital records, clinical and office charts, laboratory notes, patient completed evaluation forms, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, magnetic media, x-rays, subject files, and records kept, at the laboratories, and at technical departments involved in the clinical trial.

The Investigator is responsible for ensuring that the data on the case report forms is consistent with the data in the source documentation. The Investigator may designate a medically trained designee to sign all forms **except** the Withdrawal form and the Adverse Event form. The Investigator must make source documentation available for monitoring by the Sponsor or delegate, the ETHICS BOARD, and other authorized government agencies. Failure or unwillingness to provide this access will disqualify the site and Investigator from participation in this clinical evaluation.

18.0 Record of Device Inventory

This is a post market study and all devices are CE marked. Therefore inventory control is not a regulatory requirement.

19.0 Sponsor Obligations

19.1 Investigator Training

All participating investigators will undergo training on the PyroTITAN™ HRA Shoulder prosthesis either through a hands-on training session or by a Sponsor approved training module.

19.2 Monitoring

The Sponsor will designate qualified individuals to monitor the progress of the clinical investigation. The monitor(s) responsibilities include:

- Visiting the Investigator periodically to ensure the fulfillment of all obligations associated with the clinical investigation.
- Reviewing individual Subject records and other supporting source documentation, comparing those records with CRFs prepared by the Investigator and submitted to the Sponsor, and ensuring that data submitted to the Sponsor is accurate and complete.
- Maintaining a record of each on-site visit to an Investigator noting findings, conclusions, and actions taken to correct deficiencies.

19.3 Sponsor Study Termination

Both the sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Ascension Orthopedics and the Investigator will assure that adequate consideration is given to the protection of the patient's interests.

20.0 Changes to Investigational Plan

No changes to this protocol with the exception of those of an emergent nature will be made without written consent from the sponsor and mutual agreement between the investigators and sponsor. The investigators, sponsor, and investigators' governing ETHICS BOARD will record all changes.

Applicable ETHICS BOARD approval will be obtained prior to implementation of changes in the Investigational Plan that may affect the scientific soundness of the investigation, or the rights, safety, or welfare of study subjects.

21.0 Confidentiality

Information about study subjects will be kept confidential and managed according to the requirements of the country of the participating clinical investigator.

Data protection and data transfer

In order to observe the confidentiality of personal data, each patient will be allocated a confidential identification code consisting of the investigator centre number and a 3 figures patient number.

CRF or other documents submitted to the sponsor will identify a patient by this identification code. Each investigator will keep in his file a screening Log and a patient identification list (including complete name and date of birth of each patient). To allow compliance with GCP principles, each patient will be asked for consent regarding the access to source documents for monitoring, audits, and inspections.

The Information Letter and Data Transfer Authorization form explain that the study data will be kept in an electronic form, confidentially, in accordance with the French law N°78-17. All the computerised data will be identified by "centre n°/ patient n°".

The information Letter and Data Transfer Authorization Form will specify that the sponsor representative and the competent authorities will have direct access upon request to the source documents related to the study, including medical antecedents, to check the accuracy of the data.

Study documents and records will be kept for at least 15 years after the end of the study by the investigator: this includes codes allowing the identification of patients, medical files and all the source data, the CRF, the queries, the patient's information letter and DTA, the copies of IEC and competent authorities approval (if necessary) and any other document pertinent to the study.

Integra LifeSciences Corp. will store all of the documents relating to the study throughout the lifespan of the product and for a minimum of 15 years:

- The text of the clinical protocol and its annexes;
- The EC opinion;
- The case report forms;
- The anonymised data in a database;
- The monitoring documents (correspondence, memos, etc.)

22.0 Withdrawal or Termination of the Clinical Investigation

Any subject who wishes to withdraw from this investigation on his/her own accord and for whatever reason is entitled to do so without obligation and prejudice to further treatment. In addition, the Investigator may decide for reasons of medical prudence, to withdraw a subject. In either event, the Investigator will clearly document the date and reason(s) for the subject's withdrawal from this investigation in the clinic notes and should indicate whether or not he considers it related to the device.

Both the sponsor and the Investigator reserve the right to terminate the study at any time. Should this be necessary, both parties will arrange the procedures on an individual study basis after review and consultation. In terminating the study, Ascension Orthopedics and the Investigator will assure that adequate consideration is given to the protection of the patient's interests.

APPENDIX A
CASE REPORT FORMS