Pyrocarbon IDE Study
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IDE#: G140202

Clinical Investigational Plan

Version: 6
Date: Final – January 6, 2017

Sponsor
Tornier, Inc.
10801 Nesbitt Ave South
Bloomington, MN 55437 USA
Phone: 952-921-7600
Fax: 952-291-7601

Signature page

Signature page

SPONSOR

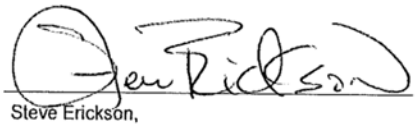
Tornier

10801 Nesbitt Ave South

Bloomington, MN 55437

1 952-426-7600

APPROVER'S SIGNATURE

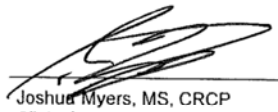


Steve Erickson,
Director of Clinical Affairs, Wright Medical

06 JAN 2017

Date

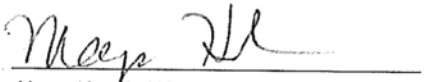
CLINICAL TRIAL MANAGER'S SIGNATURE



Joshua Myers, MS, CRCP
Clinical Operations Manager
Wright Medical

06 Jan 2017

STATISTICIAN'S SIGNATURE



Manya Harsch, MS
Principal Statistician
Technomics Research, LLC

06 JAN 2017

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Final

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Synopsis

Sponsor	Tornier, Inc.
Study Title	Pyrocarbon IDE Study
Device Name	Aequalis™ Pyrocarbon Humeral Head
Associated Devices	The Aequalis Pyrocarbon Humeral Head is used in combination with the Aequalis™ Ascend™ Flex Shoulder System.
Intended and Indications for Use	This system is intended to be used to partially replace the shoulder joint in primary treatment. The Aequalis Pyrocarbon Humeral Head associated with the Aequalis Ascend Flex stem is indicated for use as a replacement of deficient humeral head joints disabled by: • Non-inflammatory degenerative joint diseases (osteoarthritis, avascular necrosis) • Traumatic arthritis, The Aequalis Pyrocarbon Humeral Head shoulder prosthesis combined with the Aequalis Ascend Flex stem, are to be used only in patients with an intact or reconstructable rotator cuff and if the native glenoid surface is intact or sufficient, where they are intended to increase mobility, stability, and relieve pain.
Study Purpose	The purpose of this study is to demonstrate safety and effectiveness of the Aequalis Pyrocarbon Humeral Head in hemiarthroplasty at 24 months. Subject outcomes will be compared against a performance goal.
Type of Study	Prospective, single arm, multi-center
Primary Composite Endpoint	The primary endpoint is the rate of patient success at 24 months. A subject is a success at 24 months if: • Their change in Constant score is ≥17 and • They did not have revision surgery; and • There is no radiographic evidence of system disassembly or fracture, and • They did not have a system-related serious adverse event. Subjects that undergo revision surgery will be considered a primary endpoint failure at the time any component of the system is revised.
Secondary Endpoints	The following data will be tested to detect a significant change at 24 months compared to baseline: • Constant score and Adjusted Constant score • American Shoulder and Elbow Surgeons (ASES) Score • Single Assessment Numeric Evaluation (SANE) • EQ-5D • Pain measured by a visual analog scale (VAS) • Range of Motion (ROM) • Strength The following data will be summarized: • Adverse events • Revision rate • Level of satisfaction with the shoulder • X-ray data: glenohumeral joint space width, glenoid osteophytes, glenoid morphology, glenoid erosion, humeral component radiolucency, osteolysis, migration, subsidence, subluxation, acromiohumeral distance, anatomic fracture, and additional observations

Statistical Considerations	Statistical considerations for the primary endpoint: The study is designed to test non-inferiority of the composite success endpoint to a performance goal derived from the Tornier Aequalis Post-Market Outcomes Study. • 80% power with a one-sided 0.025 level of significance • Non-inferiority test of one proportion • 10% non-inferiority margin and performance goal of 85% • Assumed success rate of 85% • Attrition rate of 15% The resultant sample size under these assumptions is 133 subjects with an implant attempt and evaluable endpoint data. With 15% attrition, 157 total implant attempts are needed. Up to 190 subjects may be enrolled to account for pre and intra-operative screen failures. Enrollment will stop once 157 subjects have had an implant attempt. Statistical considerations for secondary objectives: The overall type I error for the powered secondary endpoints will be controlled using the Hochberg method for adjusting for multiple comparisons, and will be tested only if the primary endpoints are met.
Enrollment Method	Subjects are recruited from the patient population within the medical practice of the clinical investigators.
Inclusion Criteria	A subject must meet all of the following inclusion criteria in order to enter the study: • Adult subject 22 years or older. • Scapula and proximal humerus must have reached skeletal maturity. • Clinical indication for hemiarthroplasty due to primary diagnosis of arthritis or avascular necrosis. Primary arthritis for this study includes osteoarthritis with pain and/or post-traumatic arthritis. • Willing and able to comply with the protocol. • Willing and able to sign the informed consent form (or the Legally Authorized Representative will sign for the subject).
Exclusion Criteria	A subject will not be eligible to participate in the study if any of the following conditions are present: • Active local or systemic infection, sepsis, or osteomyelitis. • In the opinion of the clinician, there is insufficient bone stock to support implants in the humeral metaphysis or poor bone quality. • In the opinion of the clinician, there is insufficient bone stock or excessive deformation of the native glenoid to allow normal functioning of the glenohumeral joint. • In the clinician's opinion, the subject is unwilling or unable to be compliant with the recommendations of the healthcare professional. • Metabolism disorders that could compromise bone formation, or Osteomalacia. • Infection at or near the implant site, distant foci of infections that could spread to the site of the implant, or systemic infection. • Rapid destruction of the joint, marked bone loss, or bone resorption apparent on X-ray.

	• Known allergy or suspected allergy to implant materials. • Female subjects who are pregnant or planning to become pregnant within the study period. • Medical conditions or balance impairments that could lead to falls. • Prior arthroplasty or prior failed rotator cuff repair on the affected shoulder; (successful rotator cuff surgery may be included). • A rotator cuff that is not intact and cannot be reconstructed. Subjects with a massive rotator cuff tear (>5cm) will be excluded. • Nonfunctional deltoid muscle. • Neuromuscular compromise condition of the shoulder (e.g., neuropathic joints or brachial plexus injury with a flail shoulder joint). • Known active metastatic or neoplastic diseases, Paget's disease, or Charcot's disease. • Currently, within the last 6 months, or planning to be on chemotherapy or radiation. • Known alcohol or drug abuse as defined by DSM-5. • Taking > 5mg/day corticosteroids (e.g. prednisone) excluding inhalers, within 3 months prior to surgery. • Currently enrolled in any clinical research study that might interfere with the current study endpoints. • Known history of renal or hepatic disease/insufficiency. • Anatomy cannot be replicated using current available system sizes.
Visit Schedule	Subjects will be assessed at: • Baseline • Surgery • Post-op (1-3 weeks) • 3 months • 6 months • 12 months • 24 months • Annual visits after 24 months, if needed
Duration of Investigation	The study duration is expected to be approximately 4 years, including 18 months of enrollment and 24 months of follow-up.
Number of Patients and Sites	Up to 190 subjects enrolled at up to 20 sites to ensure 157 implant attempts.

Sponsor Contact Information

Josh Myers, MS, CRCP
Clinical Operations Manager
10801 Nesbitt Ave South
Bloomington, MN 55437 USAA
Phone: 952-921-7119
Fax: 952-487-3677
Email: josh.myers@wright.com

Contents

1 Definitions and Acronyms

Term or Acronym	Definition
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs in subjects, users or other persons, whether or not related to the investigational medical device.
ASAP	As soon as possible
ASES	American Shoulder and Elbow Surgeons Standardized Shoulder Assessment. The original ASES consists of 2 portions, a medical professional assessment section and a patient self-report section. The patient self-report section utilized in this study is a condition specific scale intended to measure functional limitations and pain of the shoulder. The assessment takes approximately 5 minutes to complete and consists of 2 dimensions: pain and activities of daily living. The pain score is calculated from the single pain question and the function score from the sum of the 10 questions addressing function. The pain score and function composite score are weighted equally (50 points each) and combined for a total score out of a possible 100 points [1].
CIP	Clinical Investigational Plan
CoCr	Cobalt Chromium
(Adjusted) Constant score	In this score, 35 points are allocated for subjective assessments of pain and activities of daily living and 65 points are available for objective measures of range of movement and shoulder strength. A young healthy patient can therefore have a maximum score of 100 points [2]. Adjusted Constant Score: The strength of each subject's normal shoulder may differ because gender and age differences. The Constant score calculation will be adjusted using normative values for the Constant score based on age and gender [3].
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
Device Related Adverse Event	An adverse event that results from the presence or performance of the device.
DOS	Day of Surgery
Fixed Force Gauge	A fixed force gauge is a device for measuring force, moment of force (torque), or power. They are used in shoulder orthopedics for measuring the arm strength of patients in order to evaluate physical status, performance and task demands.
eCRFs	Electronic Case Report Forms
EDC	Electronic Data Capture
EQ5D	EQ-5D™ is a standardized instrument for use as a measure of health outcome. [1]
FCI	Functional Comorbidity Index if a self-administered, general population index of comorbid diseases with physical function as the outcome of interest [4]
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HA	Hemiarthroplasty

[1] *© EuroQol Research Foundation. EQ-5D™ is a trade mark of the EuroQol Research Foundation*

HH	Humeral Head
IA	Investigator Agreement is a signed agreement documenting his or her commitment to conduct the investigation in accordance with this Clinical Investigational Plan, all applicable regulations, and any conditions imposed by the IRB.
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ICMJE	The International Committee of Medical Journal Editors
IFU	Instructions For Use
Institution Review Board (IRB)	An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.
ITT	Intent-to-treat
"Must", "Required", "Shall"	These words mean that the definition is an absolute requirement of the protocol.
"Must Not", "Shall Not"	These phrases mean that the definition is an absolute prohibition of the protocol.
PI	Principal Investigator
PP	Per protocol
Procedure Related Adverse Event	An adverse event that occurs as a result of the implant procedure.
PyC	Pyrocarbon
ROM	Range of Motion

Serious Adverse Event (SAE)	An adverse event is serious when it:
	• Led to death,
	• Led to serious deterioration in the health of the subject, that either resulted in
	  o A life threatening illness or injury, or
	  o A permanent impairment of a body structure or a body function, or
	  o In-patient or prolonged hospitalization, or
	  o Medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
	• Led to fetal distress, fetal death or a congenital abnormality or birth defect.

"Should", "Recommended"	These words mean that there may exist valid reasons in particular circumstances to ignore a particular item, but the full implications must be understood and carefully weighted before choosing a different course.
"Should Not", "Not Recommended"	These phrases mean that there may exist valid reasons in particular circumstances when the particular behavior is acceptable or even useful, but the full implications should be understood and the case carefully weighed before implementing any behavior described with this label.
Single Assessment Numeric Evaluation (SANE) Score	The SANE rating is determined by the subject's written response to the following question "How would you rate your shoulder today as a percentage of normal (0% to 100% scale with 100% being normal)?"

Sponsor	An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.
Sub-I	Sub-Investigator
Subject	An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.
Subject Satisfaction	Subject satisfaction will be measured by asking each subject a single subjective question at baseline and each subsequent follow-up visit. Subjects will be asked "How satisfied are you with your shoulder?" Response options include: "Very Satisfied, Satisfied, Dissatisfied, and Very Dissatisfied".
TSA	Total Shoulder Arthroplasty
Unanticipated Adverse Device Effect (UADE)	Any serious adverse effect on health or safety, 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 study protocol or informed consent; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.
Unavoidable Adverse Event	Those that are expected to occur and inherent with the surgical procedure. These only need to be reported if they are deemed by the investigator to be more serious in duration or intensity than expected. Unavoidable AEs include: • Anesthesia related nausea/vomiting • Low-grade fever for ~48 hours post-op • Incisional pain for ~72 hours post-op • Mild to moderate bruising or hematoma for ~ one week post-op • Sleep problems (insomnia) for ~ 72 hours post-op • Back pain related to lying on table • Normal incision redness
US	United States of America
VAS	Visual Analog Scale
Walch Glenoid Morphology Classification	A classification of glenoid morphology in OA: Type A: Humeral head centered • A.1 – minor erosion • A.2 – major erosion Type B: Humeral head subluxed posteriorly • B.1- posterior joint space narrow, subchondral sclerosis, and osteophytes • B.2- Retroverted glenoid with posterior rim erosion Type C: Glenoid retroversion > 25 degrees regardless of erosion
Modified Favard Glenoid Erosion Classification	Classification of glenoid erosion. The modified classification includes a fifth classification when glenoid erosion is predominantly located at the inferior part of the glenoid.

2 Introduction

2.1 Study Purpose

Tornier, Inc., (Sponsor) is sponsoring the Pyrocarbon IDE Study, a multi-center, prospective, single arm, and investigational clinical study. The purpose of this clinical study is to evaluate the safety and efficacy of the Aequalis™ Pyrocarbon Humeral Head (Pyrocarbon HH). The data generated by this study are intended to provide adequate safety and effectiveness information necessary to support a Food and Drug Administration (FDA) submission for device clearance. Data from this clinical study may be used to support future regulatory submissions, including those outside of the United States (US).

2.2 Study Scope

The study will be conducted at up to 20 sites in the US. Each participating site will be encouraged to enroll approximately 5 subjects in a 12 month time period, or until the implant attempt limit is met (N=157).

Up to 190 subjects will be enrolled to ensure 157 implant attempts with a Pyrocarbon HH to further ensure at least 133 evaluable subjects are available for the primary endpoint analysis. It is anticipated that this study will require approximately 24 months for subject enrollment. To ensure data are adequately distributed among sites and geographies, no more than 20% (n=31) of implant attempts may occur at a single site. Each site should attempt to implant approximately 5 subjects within 12 months of activation. There is no minimum requirement for enrollments per site.

Subjects who have a successful implant attempt will be followed for at least 24 months. Unsuccessful implant attempt and screen failure follow-up is outlined in section 7.1. Study duration (first site activation to final subject follow-up) is expected to be approximately 4 years. Subjects will be followed annually after their 24 month visit until the last subject with an implant attempt completes their 24 month visit or is determined lost to follow-up; all subject follow-up will be complete at that time. If deemed necessary, subjects may be asked to return for additional visits beyond their final protocol visit to collect long-term data.

2.3 Governing Regulations

The Pyrocarbon HH is classified as a significant risk investigational device in the US. This Clinical Investigational Plan (CIP) will be submitted to the FDA for approval under an Investigational Device Exemption (IDE) and is subject to 21CFR812. This study will be conducted according to this Clinical Investigational Plan (CIP) and in accordance with 21 CFR Parts 50 and 56 concerning medical research. The following guidance documents and regulations were consulted in preparing the study's protocol and procedures.

- Title 21 of the Code of Federal Regulations (21 CFR) Parts 11 (Electronic Records; Electronic Signatures), 50 (Protection of Human Subjects), 56 (Institutional Review Boards), and 812 (Investigational Device Exemption).
- International Conference on Harmonization (ICH) E6 Good Clinical Practice (GCP) guidelines

3 Background and Justification

Dr. Charles Neer introduced shoulder arthroplasty for the treatment of displaced fractures of the proximal humerus in 1955 [5]. Dr. Neer later modified his prosthesis to treat the degenerative humeral head [6]. Shoulder arthroplasty has evolved into a viable option for patients with non-inflammatory degenerative joint diseases, rheumatoid arthritis, trauma, and correction of functional deformities. Shoulder replacement is effective at restoring range of motion and strength, as well as decreasing pain. It can also help patients return to normal daily activities that were previously limited by the shoulder disease [7] [8] [9]. Anatomic shoulder arthroplasty can be done in two different configurations: Total shoulder arthroplasty (TSA) and hemiarthroplasty (HA). TSA includes artificial components on both the humeral and glenoid sides of the glenohumeral joint, while hemiarthroplasty only involves the humeral side.

The Tornier Aequalis Ascend Flex System is a shoulder arthroplasty system that is currently available on the market. Typical anatomic implantation of this system includes the Ascend Flex Stem, and a cobalt chrome (CoCr) or Titanium (Ti) humeral heads. The Investigational component of this study is a Pyrocarbon HH which is intended to be used with the stems from the Ascend Flex system, and, while the Ascend Flex/ HH system is indicated for both TSA and hemiarthroplasty, the Ascend Flex/ Pyrocarbon HH System is only indicated for primary hemiarthroplasty.

The technological characteristics of the traditional CoCr HH and the Investigational Pyrocarbon HH are similar. The two systems have similar articulating geometry and have identical head to stem tapers. The significant difference between the devices is the material composition of the bearing surface being either Pyrocarbon composite or traditional CoCr. In both systems, the head is assembled onto the stem by the surgeon during implantation. The Ascend Flex stems used in both systems are identical.

Pyrocarbon has a unique biomechanical profile of wear resistance and biocompatibility when compared to metals such as titanium and CoCr that are typically utilized for manufacture of replacement humeral heads. In comparison to these materials, pyrocarbon has a lower coefficient of friction and modulus of elasticity making it more similar to bone. Pyrocarbon's elastic modulus is similar to cortical bone and is intended to reduce subsidence and bone loss (Table 1, [10]), and allow a more even distribution of forces in the implant and the surrounding bones.

While pyrocarbon has not been previously cleared in the US for articulation against cartilage in the shoulder, this articulating couple has been cleared in other orthopedic indications, including the hand and foot. Literature supports the advantages of using pyrocarbon to articulate against native cartilage and bone. It has been shown to have high strength and good resistance to fatigue [11]. Pyrocarbon is highly wear resistant when in contact with bone and cartilage, and is intended to reduce wear and inflammation. [12] [13] [14]. Wear testing shows that pyrocarbon demonstrates up to 300 times less wear on bone than zirconia and medical grade metals [15] [16].

Table 1: Average Elasticity by Material Type

	Silicon	**Polyethylene**	**Bone**	**Pyrocarbon**	**Ta6V**	**CoCr**	Al2o3
Young Modulus GPa	0.004	1	15-20	20-25	110	200-240	407

4 System Description, Indications, and Intended Use

4.1 Investigational Device: Pyrocarbon Humeral Head

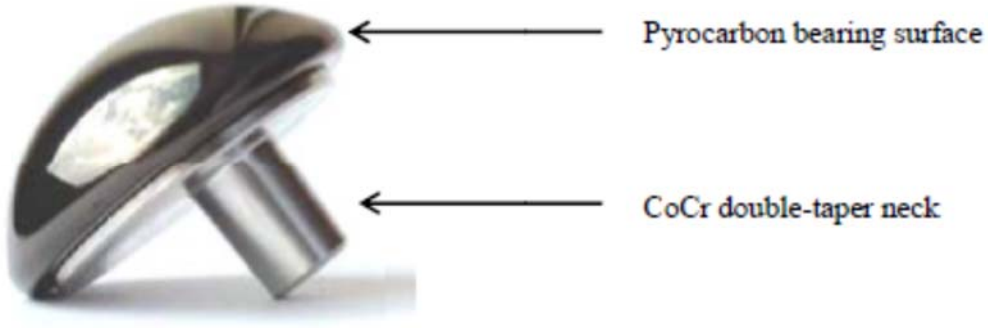
The Pyrocarbon HH is composed of two parts:

- A pyrocarbon bearing surface
- A double-taper neck made of CoCr

Both parts are permanently assembled together in Tornier's cleanroom before packaging and sterilization. They are provided to the user as a single assembly, not as modular components. Testing has been performed to evaluate the strength of the assembly during manufacturing, demonstrating that the components cannot be disassembled by the user.

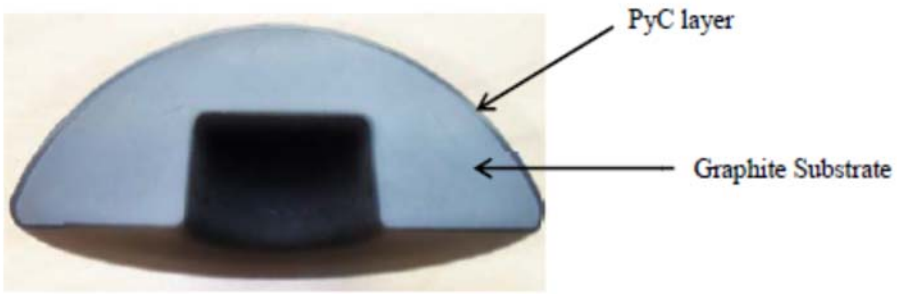
Figure 1: Pyrocarbon HH Components Pre-Assembly

Figure 2: Pyrocarbon HH After Assembly



The pyrocarbon bearing surface is made of a graphite core (also called substrate) covered with a layer of pyrocarbon which completely covers the surface so that the body is not in contact with the graphite. The graphite core is made from grade AXF-5Q10W graphite that is impregnated with 10% in weight of Tungsten for radio-opacity.

Figure 3: Cross Section of the Pyrocarbon bearing surface



The Pyrocarbon HH features a male taper compatible with Aequalis Ascend Flex stems. The head's dimensions (size, eccentricity) are similar to the dimensions of the metallic humeral heads used with the traditional Ascend Flex System. The types and sizes of Pyrocarbon HH devices are listed in Table 2.

Table 2: Sizes of Pyrocarbon Humeral Heads

Diameter (mm)	Height (mm)	Eccentricity (mm)	Catalog Numbers
39	14	1.5	DWH039U
41	15		DWH041U
43	16		DWH043U
46	17		DWH046U
48	18		DWH048U
50	16		DWH050U
52	19		DWH052U
54	23		DWH054U
39	14	3.5	DWH139U
41	15		DWH141U
43	16		DWH143U
46	17	4	DWH146U
48	18		DWH148U
50	16		DWH150U
52	19		DWH152U
54	23		DWH154U

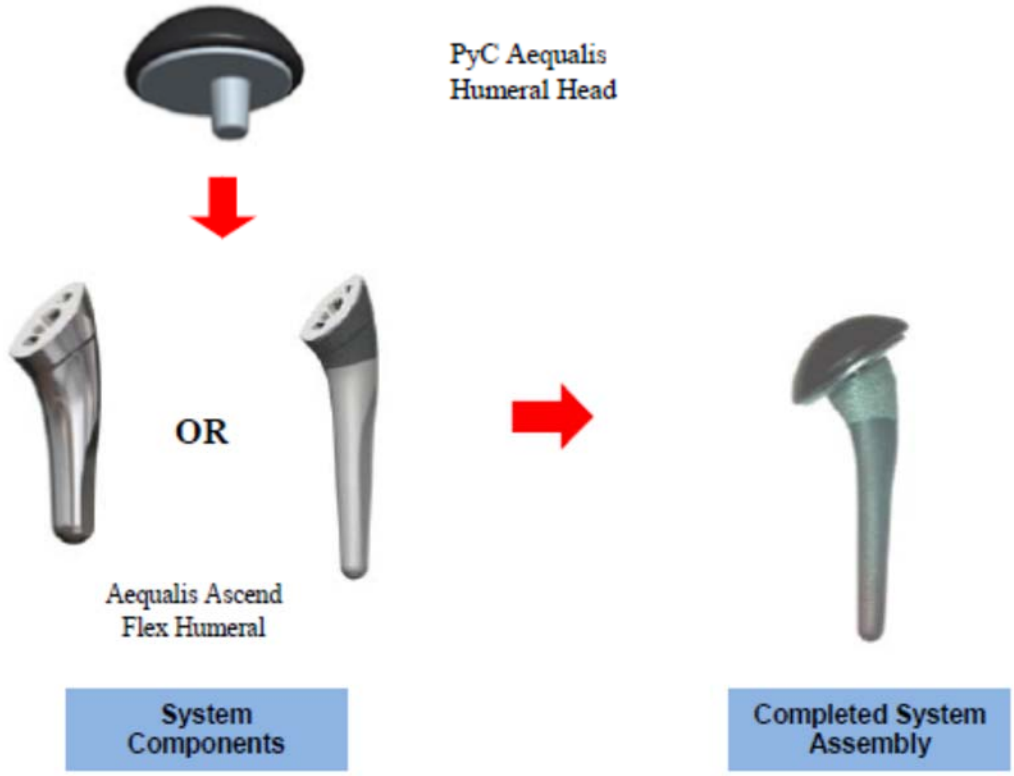
The Pyrocarbon HH is an investigational device. The investigator will have access to two devices of each size during the surgical procedure and will ultimately implant one per subject. Investigational devices will only be used by investigators approved to participate in the clinical study. Pyrocarbon HH devices will be labeled as investigational and device disposition will be tracked.

4.1.1 Aequalis Ascend Flex Stem

The Aequalis Ascend Flex System is cleared for use in the US and is not investigational. When the Ascend Flex stem is used with a Pyrocarbon HH in a subject, it becomes an investigational system. Ascend Flex stems will be purchased through normal distribution channels. Shipping and disposition will not be tracked prior to implant in a study subject, but will be tracked after implant and if explanted. Ascend Flex stems are available press fit or cemented in standard or long lengths, each in a variety of

sizes. All commercially available Ascend Flex stems may be used in the study. The appropriate stem will be used based on physician preference and standard of care.

Figure 4: Pyrocarbon HH with Ascend Flex stems



4.1.2 Instruments

Instruments are provided for use during the procedure. The instruments are described in detail in the Surgical Manual (NOTE: The large impactor tip and silicone tips marked for use with head sizes 46, 48, and 50 must be used with the large head sizes: 52 and 54). The standard instrumentation provided for a traditional Ascend Flex System implant is also used for a Pyrocarbon HH implant. The only difference between the procedures is that the impaction step *must* be completed using the Spring Impactor for the Pyrocarbon HH, whereas the use of this tool is *optional* with a traditional Ascend Flex System implant. This tool is used during the final implantation step to deliver the exact amount of energy necessary to impact the humeral head onto the stem without damaging the pyrocarbon coating.

4.2 Indications and Intended Use

This system is intended to be used to partially replace the shoulder joint in primary treatment.

The Aequalis Pyrocarbon Humeral Head associated with the Aequalis Ascend Flex stem is indicated for use as a replacement of deficient humeral head joints disabled by:

- Non-inflammatory degenerative joint diseases (osteoarthritis, avascular necrosis)
- Traumatic arthritis,

The Aequalis Pyrocarbon Humeral Head shoulder prosthesis combined with the Aequalis Ascend Flex stem, are to be used only in patients with an intact or reconstructable rotator cuff and if the native glenoid surface is intact or sufficient, where they are intended to increase mobility, stability, and relieve pain.

4.3 Surgical Procedure

It is required that implanting physicians have experience with at least 15 cases using the Ascend Flex System prior to implanting a Pyrocarbon HH device into a study subject. This is required so the investigator is familiar with the system, which will reduce the risk to study subjects when the system is combined with the investigational device.

The surgical procedure is detailed in the Surgical Manual and summarized below. The surgical procedure is the same as it would be for a traditional Ascend Flex System implant. Use of the Spring Impactor is required for the impaction step. Some steps in the surgical procedure will be standardized for the study to reduce confounding factors.

1. **Positioning:** If the implanting physician elects to use the beach chair position, recent literature states patients undergoing shoulder surgery in the beach chair position may be at increased risk for serious neurocognitive complications due to cerebral ischemia [17].
2. **Humeral Exposure**: To gain access to the glenohumeral joint and dislocate the humeral head, surgeons typically utilize a delto-pectoral approach. For the purpose of the study, all investigators will use the delto-pectoral approach.
3. **Soft-Tissue Dissection:** Long head biceps tenodesis must be performed. Subscapularis resection, transosseous suture, tendon to tendon suture, tendon to bone suture, lesser tuberosity fleck osteotomy are all acceptable
4. **Humeral Head Preparation and Resection:** The humeral head is dislocated after the soft-tissue dissection is complete. After dislocation, osteophytes are removed (if necessary) and the humeral head is resected (cut) from the humerus. This may be done either free hand or with the assistance of a cutting guide.
5. **Distal Preparation**: The medullary canal is prepared using "Sounders". Sounder sizes are progressively increased until contact is made with the cortical wall of the canal.
6. **Proximal Preparation**: The opening to the medullary canal is further widened using guided punches to score the proximal metaphyseal cancellous bone. Once the cancellous bone has been scored, the Sounder, Punch, and scored bone are removed.
7. **Metaphyseal Compaction**: The compaction tool is advanced into the canal until a satisfactory fit is achieved. The inclination angle is locked so it can be read at a subsequent step. The compactor is temporarily left inside the humerus as the trial implant.
8. **Surface Planning**: With the final compactor in place, a surface planer is utilized to ensure a flat resection true to the implant.

9. **Glenoid Treatments, if any**: Glenoids may be prepared by reaming and/or reshaping to remove calcified cartilage and irregular surfaces to ensure smooth rotation of the humeral head on the glenoid face. If there is eccentric wear of the glenoid, smoothing, reaming, and/or reshaping of the glenoid face is allowed to ensure proper version and balance to the joint. The procedure guidelines are as follows:

    The glenoid is exposed. Any remaining cartilage and marginal osteophytes are then removed from the glenoid. Reaming may be performed with a motorized bur or reamer. If reshaping with a motorized reamer, a starting hole is made at the center of the glenoid face to receive the nub of the reamer. Reaming is conservative, preserving as much bone stock as possible. It is continued only until a concentric surface is achieved across the entire face of the glenoid. If the glenoid is biconcave with substantial posterior erosion, the crest between the two concavities is removed and the glenoid is then reamed until a single concavity is achieved.

    Excessive reaming or reshaping that severely compromises the structure of the glenoid surface will not be permitted and if excessive reaming or reshaping is performed this will cause the subject to be considered an unsuccessful implant attempt. Excessive reaming is defined as an amount of reaming that removes excessive bone so that the remaining glenoid will not adequately support articulation with the humeral head. This limit will be defined by the operating surgeon. The patient would then receive an alternate treatment, e.g., glenoid bone grafting in conjunction with use of a conventional hemiarthroplasty or reverse total shoulder prosthesis.

10. **Humeral Head Sizing**: The correct Pyrocarbon HH device size will be determined using the trial heads. The humeral head trials are positioned onto the compactor to achieve optimal coverage of the resecting and the humeral head trial is reduced into the glenoid. Mobility testing is performed with the trial construct in place. Once the humeral head size, offset, and rotation have been confirmed, the shoulder is dislocated and the trial construct is removed.
11. **Final Stem Implantation:** To avoid repeated impactions onto the Aequalis Pyrocarbon Humeral Head, the definitive uncemented stem is first impacted into the humerus. The Aequalis Pyrocarbon Humeral Head will then be impacted onto the stem. If the chosen definitive stem is cemented the Pyrocarbon head shall be impacted onto the stem on the back table.
12. **Final head Implantation**: During this step, the Spring Impactor is used to impact the Pyrocarbon HH onto the Ascend Flex stem. The elasticity of the Spring Impactor should be tested prior to impaction. Ensure the appropriate silicone tip is well connected to the Spring Impactor prior to use. Hold the Spring Impactor with the handle facing down, the handle should not fall under its own weight and should stay in touch at the bottom of the sleeve. Make sure to visualize the contact between the hammer and the bottom of the sleeve via the fluid evacuation holes near the tip of the Spring Impactor. It is necessary to activate and release the Spring Impactor 3 times to achieve adequate fixation. The final implant is done in vivo for press-fit stems. Back table assembly is allowed for the cemented stem.
13. **Testing and Closure**: After the joint has been washed and the prosthesis reduced, the stability and mobility of the shoulder are tested. The subscapularis must be repaired, if detached. The joint and wound are closed. Post-operatively the arm is immobilized in a simple sling.

14. **Post-Operative Rehabilitation**: Rehabilitation will be standardized for study subjects, and will align with Ascend Flex System recommendations from the Surgical Manual Study specific rehabilitation instructions are found in section 7.6.3.

5 Methodology

This is a multicenter, prospective, single arm, investigational study designed to evaluate the safety and efficacy of the Pyrocarbon HH when used with the Ascend Flex System in the primary replacement of the humeral side of the shoulder joint.

5.1 Primary Endpoint

The primary endpoint is the rate of patient success at 24 months. A subject is a success at 24 months if:

- Their change in Constant score is ≥17 and
- They did not have revision surgery; and
- There is no radiographic evidence of system disassembly or fracture, and
- They did not have a system-related serious adverse event.

Subjects that undergo revision surgery will be considered a primary endpoint failure at the time any component of the system is revised.

5.2 Secondary Endpoints

The following data will be tested to detect a significant change at 24 months compared to baseline:

- Constant Score and Adjusted Constant Score
- American Shoulder and Elbow Surgeons (ASES) Score
- Single Assessment Numeric Evaluation (SANE)
- EQ-5D
- Pain measured by a visual analog scale (VAS) from the ASES questionnaire
- Range of Motion (ROM)
- Strength

The following data will be summarized:

- Adverse events
- Revision rate
- Level of satisfaction with the shoulder
- X-ray data: glenohumeral joint space width, glenoid osteophytes, glenoid morphology, glenoid erosion, humeral component radiolucency, osteolysis, migration, subsidence, subluxation, humeral head integrity, acromiohumeral distance, anatomic fracture, and additional observations.

5.3 Subject Selection

The study population will be patients seen by the investigators for treatment of shoulder pain. Tornier will provide investigators with training on subject recruitment and provide recruitment materials, such as brochures, peer to peer letters, and advertisement options, if requested. All recruitment materials must be approved by the institution's Institutional Review Board (IRB) before use.

Subjects must consent to participate in the study prior to any study specific procedures being performed to determine if the subject is eligible for the study. Each subject who signs the study Informed Consent Form (ICF) will be considered an enrolled subject. All enrolled subjects will be documented in the electronic data capture (eDC) system via electronic Case Report Forms (eCRFs). Subjects will count towards the implant attempt limit of 157 subjects once the inclusion/exclusion criteria are met (including both successful and unsuccessful implantation of a PYC HH).

Investigators may only implant one Pyrocarbon HH in one shoulder per subject. Subjects are not allowed to have Pyrocarbon Humeral Heads implanted into both shoulders as a part of this study.

5.3.1 Inclusion Criteria

A subject must meet all of the following inclusion criteria in order to enter the study:

- Adult subject 22 years or older.
- Scapula and proximal humerus must have reached skeletal maturity.
- Clinical indication for hemiarthroplasty due to primary diagnosis of arthritis or avascular necrosis. Primary arthritis for this study includes osteoarthritis with pain and/or post-traumatic arthritis.
- Willing and able to comply with the protocol.
- Willing and able to sign the informed consent form (or the Legally Authorized Representative will sign for the subject).

5.3.2 Exclusion Criteria

A subject will not be eligible to participate in the study if any of the following conditions are present:

- Active local or systemic infection, sepsis, or osteomyelitis.
- In the opinion of the clinician, there is insufficient bone stock to support implants in the humeral metaphysis or poor bone quality.
- In the opinion of the clinician, there is insufficient bone stock or excessive deformation of the native glenoid to allow normal functioning of the glenohumeral joint.
- In the clinician's opinion, the subject is unwilling or unable to be compliant with the recommendations of the healthcare professional.
- Metabolism disorders that could compromise bone formation, or Osteomalacia.
- Infection at or near the implant site, distant foci of infections that could spread to the site of the implant, or systemic infection.
- Rapid destruction of the joint, marked bone loss, or bone resorption apparent on X-ray.
- Known allergy or suspected allergy to implant materials.
- Female subjects who are pregnant or planning to become pregnant within the study period.
- Medical conditions or balance impairments that could lead to falls.
- Prior arthroplasty or prior failed rotator cuff repair on the affected shoulder; (successful rotator cuff surgery may be included).
- A rotator cuff that is not intact and cannot be reconstructed. Subjects with a massive rotator cuff tear (>5cm) will be excluded.
- Nonfunctional deltoid muscle.

- Neuromuscular compromise condition of the shoulder (e.g., neuropathic joints or brachial plexus injury with a flail shoulder joint).
- Known active metastatic or neoplastic diseases, Paget's disease, or Charcot's disease.
- Currently, within the last 6 months, or planning to be on chemotherapy or radiation.
- Known alcohol or drug abuse as defined by DSM-5.
- Taking > 5mg/day corticosteroids (e.g. prednisone) excluding inhalers, within 3 months prior to surgery.
- Currently enrolled in any clinical research study that might interfere with the current study endpoints.
- Known history of renal or hepatic disease/insufficiency.
- Anatomy cannot be replicated using current available system sizes.

5.4 Minimization of Bias

Potential sources of bias in this study may result from selection of subjects, treatment of subjects, and evaluation of study data. The following methods have been incorporated into the study protocol to minimize potential bias:

- Patients will be screened to confirm eligibility for enrollment with defined inclusion/exclusion criteria prior to implant attempt.
- To ensure data are distributed among sites and geographies, the number of successful implants per site cannot exceed 20% (n=31) of the total implant attempts.
- All sites will use the same version of the CIP and data collection materials.
- An independent core lab will perform data analysis for x-rays.
- All study and Sponsor personnel will be trained on their respective aspects of the study using standardized training materials.
- All study personnel will be trained on and required to follow the CIP.
- An independent physician consultant, not associated with the study, will regularly review and adjudicate reported adverse events.
- All study investigators will be required to comply with 21 CFR Part 54, Financial Disclosure by Clinical Investigators.
- Tornier will monitor the investigation for adherence to GCP the CIP and accurate data reporting.

6 Study Site Information

6.1 Agreements

Tornier will obtain two signed agreements from each participating principal investigator (PI).

1) Investigator Agreement (IA): A signed agreement documenting his or her commitment to conduct the investigation in accordance with this Clinical Investigational Plan, all applicable regulations, and any conditions imposed by the IRB.
2) Clinical Trial Agreement (CTA): This is an agreement between Tornier and the PI and/or investigative site. This agreement will outline the financial and contractual arrangements between the parties.

Sub-investigators will sign a Sub-Investigator Acceptance Form, which is an exhibit included in the CTA.

6.2 Institutional Review Board (IRB)

IRB approval of the current CIP, ICF, and any other study materials provided to prospective subjects is required prior to enrolling any subjects into this study. Recruitment materials must be approved by the IRB prior to their presentation to prospective subjects. Continuing review is required throughout the duration of the study until the time of study closure.

6.3 Investigator Responsibilities

The investigator is responsible for understanding and complying with all investigator responsibilities described in:

- 21 CRF 812 Subpart E, Responsibilities of Investigators
- Guidance for Industry: Investigator Responsibilities- Protecting the Rights, Safety, and Welfare for Study Subjects
- Good Clinical Practices (GCP) Section 4, Investigators.

The responsibilities described in these documents are summarized below.

- The investigator is responsible for ensuring that this study is conducted according to the signed agreements, this CIP, all applicable regulations, and any conditions imposed by the IRB. The investigator must document and explain any deviation from this CIP.
- The investigator is responsible for ensuring all IRB policies and procedures are followed.
- The investigator is responsible for protecting the rights, safety, and welfare of subjects under the investigator's control.
- The investigator is responsible for ensuring that informed consent is obtained in accordance with 21 CFR 50, Protection of Human Subjects.
- The investigator is responsible for control of investigational devices in his or her facility and must ensure they are only used by authorized persons for subjects in this study, and must ensure they are returned to Tornier when requested.
- An investigator may determine whether potential subjects would be interested in participating in an investigation, but shall not request the written informed consent of any subject to participate, and shall not allow any subject to participate before obtaining IRB approval.
- An investigator must disclose sufficient accurate financial information to satisfy requirements under 21 CFR part 54, Financial Disclosure. The investigator must promptly update the information if any relevant changes occur throughout the study and for one year following study closure.
- The investigator must maintain a list of appropriately qualified persons to whom the investigator has delegated study activities. This document is referred to as the Delegation of Authority Log for this study. Even though tasks may be delegated, the investigator is ultimately responsible for the conduct of the study at his or her institution. The investigator must not allow persons on the delegation log to perform study activities until they are trained by the Tornier study team.
- The investigator must have sufficient time and resources to properly conduct and complete the study.

- The investigator, or a sub-investigator, must be responsible for all study related medical decisions and ensure that adequate medical care is provided to a subject for adverse events.
- The investigator should ensure the accuracy, completeness, and timeliness of all data and reports submitted to Tornier and the IRB.

6.4 Study Training

Persons who conduct study activities under this CIP must be trained prior to performing study activities.

Principal investigators (PI) and sub-investigators (Sub-I) must be trained on the use of the Ascend Flex System. Implanting investigators must have used the Ascend Flex System in at least 15 cases prior to using it with the Pyrocarbon HH in a study subject. This requirement does not apply to investigators who will not perform study surgeries.

The site PI must be trained before the site may be activated. PIs will be trained on the following:

- The Pyrocarbon HH surgical manual and aspects of the surgery that are required for the study.
- CIP, including but not limited to: visit procedures, informed consent, subject recruitment, investigator's responsibilities, investigational device usage and handling, data collection, electronic data capture system, adverse events, reporting requirements, subject withdrawal, and study deviations.
- ICH Guideline on Good Clinical Practices (GCP) E6, Section 4, Investigator
- Investigator responsibilities described in 21 CRF 812 Subpart E
- Investigators will be trained on the requirement to inform women of child bearing age of the unknown risk of harm to the fetus during the informed consent process.

All other site and sponsor personnel who perform study activities must be trained on study activities relevant to their roles and responsibilities.

6.5 Site Activation

Site activation is defined as the point in time where the sponsor notifies the PI in writing that the study may begin and subjects may be enrolled at his or her site. All local regulatory requirements must be fulfilled before the site can be activated. Tornier will provide each PI written notification upon site activation. The following must be complete and received by Tornier prior to a site's activation:

- FDA approval of the IDE application
- Financial Disclosure Form: The PI must disclose any financial arrangements he or she has with Tornier that meet the following requirements per 21CFR54:
    - Payment to the PI that could be influenced by the outcome of the study.
    - Any significant payments (≥ $25,000) of other sorts, such as research grants, consulting, etc.
    - Any proprietary interest in the investigational product
    - Any significant equity interest in Tornier (≥ $25,000)
- Study Training for any investigator who is performing implants
- IRB approval of the CIP
- IRB approved ICF
- Current Curriculum Vitae (CV) of the PI

- Fully executed CTA between Tornier and the PI and/or Institution
- IA form signed and dated by the PI
- Confirmation the implanting physician has completed at least 15 Ascend Flex implants

Other study site personnel, including sub-investigators, may not participate in study activities until they meet all individual requirements. This may occur at the same time as PI/site activation, or at a later date.

The following must be completed before individual site personnel may perform study activities:

- Site activation must be complete (the PI must have all items above completed)
- Training pertinent to the individual's role
- Individuals must be named on the list of appropriately qualified persons to whom the investigator has delegated significant study-related duties.
- Current Curriculum Vitae (for sub-investigators only)
- Sub-investigators must sign the Sub-Investigator Acceptance Form
- Financial Disclosure Form (for sub-investigators only)

6.6 Access to Study Records

The PI and site personnel must permit study-related monitoring, audits, IRB review and regulatory inspections by providing direct access to source documents. The PI should be available to the clinical study team to discuss the results of monitoring visits. Access to subject records (including hospital and clinic records) and regulatory documents must be granted to the Sponsor's monitors.

7 Study Procedures

7.1 Overview of Study Design

Figure 5 outlines the study overview and subject flow. Subjects who are screened and provided informed consent are considered enrolled and will complete a pre-operative baseline study assessment.

Subjects who are enrolled and have a successful implant attempt (implant stable through wound closure) will have study assessments at 2 weeks, 3 months, 6 months, 12 months, 24 months, and annually thereafter (until the last subject with an implant attempt completes their 24 month visit or is determined lost to follow-up) following surgery. Subjects will exit the study after the last subject with an implant attempt completes their 24 month assessment unless it is determined, at the end of the study, to follow subjects long-term.

Subjects who are enrolled and have an unsuccessful implant attempt (attempt to implant the Pyrocarbon Humeral Head was not successful during the index procedure) will have annual post-op visits at 12 and 24 months in order to collect any available safety information. This also includes subjects who are excluded due to excessive glenoid reaming performed with the intent of implanting the Pyrocarbon Humeral Head. Subjects will exit the study after the 24 month assessments are complete.

Subjects who are enrolled but become screen failures intra-operatively (prior to the implant attempt) will have the reason for screen failure documented and then will be followed annually to collect any available safety information. Subjects will exit the study after the 24 month assessments are complete.

Subjects who are enrolled but become screen failures pre-operatively (prior to surgical procedure) will have the reason for screen failure documented then will be exited from the study.

If any component of the investigational system is revised, the subject will follow the planned follow-up visits. If any component of the investigational system is permanently explanted during the course of the study, the subject will only have annual post-op visits at 12 and 24 month to gather available safety information. Revisions and explants are defined in section 7.7

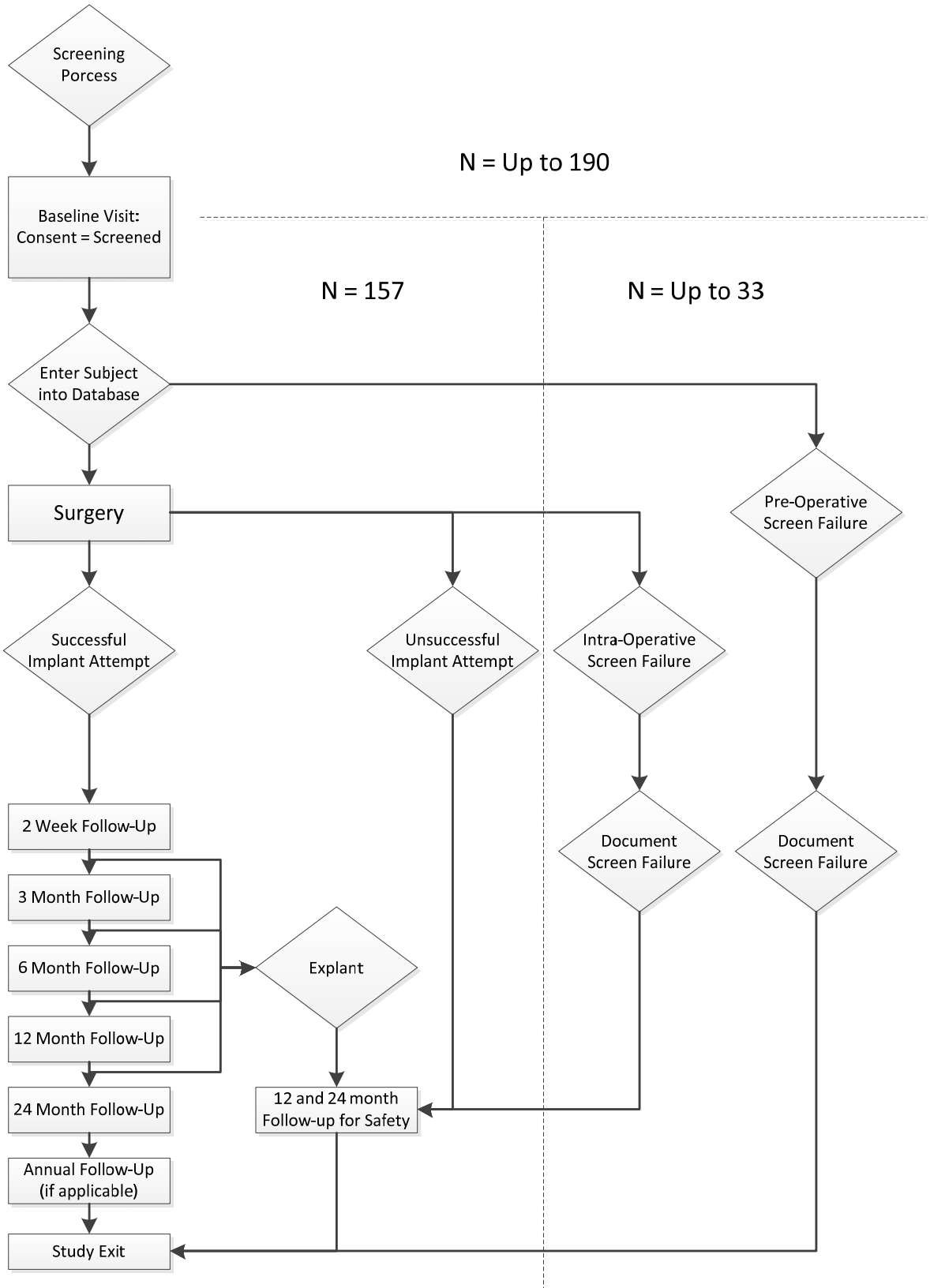


Figure 5: Study Overview

7.2 Informed Consent Process

Informed Consent is a legally effective, documented confirmation of a subject's voluntary agreement to participate in a clinical investigation after information has been given to the subject on all aspects of the clinical investigation that are relevant to the subject's decision to participate. The CIP and ICF will be approved by an IRB prior to the commencement of the clinical investigation at an investigative site. Any changes to the ICF must be approved by the IRB reviewing the application before being used to consent a prospective study subject. It is recommended, but not required, that changes made to the ICF be submitted to Tornier for review prior to being used to consent a prospective study subject. The current IRB approved version of the ICF must be used. Subjects must provide informed consent prior to any study-related procedures.

The process of obtaining a patient's informed consent will:

- Ensure that the PI or his/her authorized designee conducts the informed consent process
- Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
- Provide opportunity for subject to ask questions
- Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
- Not waive or appear to waive subject's legal rights
- Use native language that is non-technical and understandable to the subject
- Provide ample time for the subject to consider participation
- Provide the subject with a copy of the ICF
- Ensure important new information is provided to new and existing subjects throughout the clinical study
- Ensure female subjects of child bearing age understand that the risk of harm to the fetus is unknown.

The original signed and dated ICF must be retained at the investigative site and available for monitoring and auditing. A copy of the signed and dated ICF (and data privacy language where required by law) must be provided to the subject (or person who signed the form in the case of a legally authorized representative). Data protection authorization/or other privacy language needs to be collected where required by law or local regulation. If using an electronic ICF, there needs to be a documented electronic signature process which is in compliance with applicable regulations (see 21 CRF part 11). It is recommended that the informed consent process is documented in the subject's medical records. Any new information should be provided to the subject if it could affect the subject's willingness to participate.

7.3 Description of Study Procedures

Subject Questionnaire

The subject will complete a questionnaire that has questions about quality of life, daily activities, pain and satisfaction with the shoulder. The answers to the questions are used to calculate the Constant score, Age Adjusted Constant Score, ASES, SANE, EQ5D, and subject satisfaction scores. The questionnaire is in a paper format and will include brief instructions. Site personnel who will administer the questionnaire will explain the instructions to the subject. If a subject does not speak English, the questionnaire will either be translated, or read to the patient in a language he or she can understand. Subjects must complete the questionnaire on their own unless they are unable to read or write. In the case where the subject is unable to complete the questionnaire on their own, the site personnel may read the questions and answers to the subject and document their verbal response. If this occurs, it must be documented in the subject's medical records.

The Constant score, Adjusted Constant Score, ASES, SANE, Subject Satisfaction, EQ5D, and FCI assessments are described below:

- Constant score: In this score, 35 points are allocated for subjective assessments of pain and activities of daily living and 65 points are available for objective measures of range of movement and shoulder strength. A young healthy patient can therefore have a maximum score of 100 points [2].
- Adjusted Constant Score: The strength of each subject's normal shoulder may differ because of gender and age differences. The aforementioned Constant score calculation will be adjusted using normative values for the Constant score based on age and gender.
- ASES: The original American Shoulder and Elbow Surgeons Score consists of 2 portions; a medical professional assessment section and a patient self-report section. The patient self-report section, utilized in this study, is a condition specific scale intended to measure functional limitations and pain of the shoulder. The assessment takes approximately 5 minutes to complete and consists of 2 dimensions: pain and activities of daily living. The pain score is calculated from the single pain question and the function score from the sum of the 10 questions addressing function. The pain score and function composite score are weighted equally (50 points each) and combined for a total score out of a possible 100 points [1].
- SANE: The Single Assessment Numeric Evaluation rating is determined by the subject's written response to the following question "How would you rate your shoulder today as a percentage of normal (0% to 100% scale) with 100% being normal [18].
- EQ-5D: a standardized instrument for use as a measure of health outcome. It is cognitively simple, takes only a few minutes to complete, and provides a simple descriptive profile as well as a single index value for health status.
- Subject Satisfaction: Subject satisfaction will be measured by asking each subject a single subjective question. Subjects will be asked "How satisfied are you with your shoulder?" Response options include: "very satisfied, satisfied, dissatisfied, and very dissatisfied".
- FCI (Baseline ONLY): Physical function, health status, and perceived quality of life are important indicators, from the patient's perspective, of the success of medical and surgical

interventions. As a result, condition-specific and generic measures of health are used ubiquitously to evaluate medical and surgical interventions. However, in many types of research it is essential to adjust for other diseases, called comorbid diseases, in addition to the disease of concern, which may be related to the outcome(s) of interest. This is of particular importance in research conducted in older populations where many chronic illnesses may be present in the same patient. The Functional Comorbidity Index is a self-administered, general population index of comorbid diseases with physical function as the outcome of interest. The underlying premise is that diagnoses associated with physical function would be, at least in part, different from those associated with mortality, and therefore, an index designed with physical function as the outcome would perform better than indices designed with mortality as the outcome of interest. The FCI contains 18 diagnoses scored by adding the number of "yes" answers, with a score of 0, indicating no comorbid illness, and a score of 18, indicating the highest number of comorbid illnesses. [4]

Instability Tests [19]

- Sulcus sign: With the arm straight and relaxed to the side of the subject, the elbow is grasped and traction is applied in an inferior direction. With excessive inferior translation, a depression occurs just below the acromion. The appearance of this sulcus is a positive sign.
- Anterior Drawer Test: With the subject supine and the shoulder just over the edge of the table, the examiner abducts the subject's arm 60-70˚ with a slight internal rotation. A slight axial load is applied to the arm, the humeral head is translated anteriorly over the glenoid rim, and then the degree of anterior translation determined.
- Posterior Drawer Test: With the subject supine and the shoulder just over the edge of the table, the examiner abducts the arm 50˚-60˚ and in neutral rotation. The examiners hand is placed with the thumb on the anterior humeral head and the remaining fingers behind the humeral head. As the thumb pushes the humeral head posteriorly, the arm is flexed forward toward the examiner. The fingers placed posteriorly can be used to feel the humeral head subluxate over the posterior glenoid rim and then the degree of posterior translation determined.

Range of Motion

Range of Motion (ROM) is a movement test conducted on a joint to diagnose level of pain and function. The shoulder joint has a greater Range of Motion than all other joints in the body, and therefore it is important that accurate measurements be obtained to diagnose shoulder health and dysfunction.

There are various methods to measuring active and passive Range of Motion in the shoulder; visual estimation, goniometry, and still photography (among other less common methods). Each of these methods has been shown to offer fair-good levels of accuracy of measurement by an experienced clinician or trained measurer. In this study, ROM will be measured using a goniometer for forward flexion in relation to the thorax, abduction, and external rotation (arm at side and arm abducted to 90°) [20]. In addition, internal rotation will be measured using anatomical landmarks [2]**.**

Strength

The subject's strength will be assessed using a fixed force gauge. The fixed force gauge is held in place by the examiner and the subject pulls upward with maximum effort for approximately five seconds. The test can be completed up to three times and the maximum score is used, however all three pulls will be recorded. The test is done only on the affected arm. The result of this test contributes to the adjusted Constant score calculation [2] [3]. The strength test is further described in Appendix 2.

X-Ray

At least two x-ray views of the shoulder must be taken. Required views include the external rotation Grashey and axillary. Exceptions will be allowed at the immediate post-op follow-up visit if reasonable and necessary.

X-rays will be submitted to centralized independent reviewers for analysis. Two independent reviewers will analyze each x-ray and a third reviewer will adjudicate discrepancies. The reviews will be recorded electronically in the study database.

Baseline x-rays will be assessed for acromiohumeral distance, glenohumeral joint space width, glenoid osteophytes, glenoid morphology, and glenoid erosion. Follow-up x-rays will be assessed for the same things as well as humeral component radiolucency, osteolysis, migration, subsidence, subluxation, integrity, anatomic fracture, and any additional observations.

Refer to the Imaging Charter for additional information.

7.4 Data Collection

The study data that will be collected at each visit is listed in Table 3. Data will be submitted to Tornier via an Electronic Data Capture (EDC) system using electronic Case Report Forms (eCRFs). Worksheets will be provided to investigative sites to aid in data collection during subject visits. Data should be entered into the database in a timely manner. Queries will be issued via the EDC system as a part of data quality assurance and monitoring.

Table 3: Data Collection Overview

	Baseline (Pre-op)	**Day of Surgery** (DOS)	**Post-op Follow-up** (5-21 days)	**Follow-up 3M** (69-111 days)	**Follow-up 6M** (159-201 days)	**Follow-up 12M** (323-407 days)	**Follow-up 24M** (688-772 days)	**Follow-up Annual** (if applicable)
Demographics, Medical History and Indication	X							
Intraoperative Data		X						
Subject Questionnaire	X			X	X	X	X	X
Range of Motion	X			X*	X*	X	X	X
Strength Test	X			X*	X*	X	X	X
Pain Medications	X	X	X	X	X	X	X	X
Adverse Event Assessment		X	X	X	X	X	X	X
X-ray	X		X		X	X	X	X

*Optional

7.5 Subject Follow-up Schedule

Visit windows are provided to allow scheduling flexibility. Subject follow-up visits or procedures that do not occur in the windows listed in Table 4 will be considered a study deviation and require completion of a study deviation form. The day of surgery (DOS) is considered day zero. The baseline visit is preferred to occur as close as possible to the surgery and must be within 60 days prior to surgery.

Table 4: Visit Windows

Study Visit	Visit Window
Baseline	60 days pre-op through DOS
Post-op Follow-up	5-21 days post-op
3 Month Follow-up	90 Days post-op ± 21 days
6 Month Follow-up	180 Days post-op ± 21 days
12 Month Follow-up	365 Days post-op ± 42 days
24 Month Follow-up	730 Days post-op ± 42 days
36 Month Follow-up (if applicable)	1095 Days post-op ± 84 days
48 Month Follow-up (if applicable)	1460 Days post-op ± 84 days
60 Month Follow-up (if applicable)	1825 Days post-op ± 84 days
72 Month Follow-up (if applicable)	2190 Days post-op ± 84 days

7.6 Required Study Visits

Study specific procedures and assessments for all subject visits must be completed by persons authorized by the principal investigator and trained by the Tornier study team.

7.6.1 Baseline Visit

Subjects need to provide informed consent prior to any study specific procedures being performed and prior to providing subject information to the study sponsor. Inclusion and exclusion criteria will be verified at the baseline visit. Some of the inclusion/exclusion criteria need additional verification at the time of surgery. The subject is enrolled once they provide consent.

The following baseline data will be collected for all subjects prior to surgery. The baseline visit must occur within 60 days prior to surgery, except for shoulder X-rays which must be performed within 90 days prior to surgery. If the timeline is exceeded, the baseline visit assessments or X-ray must be repeated.

- Informed consent
- Data privacy language where required by law
- Subject demographics, medical history, indication for arthroplasty, tobacco use
- Pain medications usage
- Instability
    - Sulcus sign
    - Anterior and Posterior drawer test
- X-ray – physician will utilize the X-rays to assess the glenoid using the following criteria:
    - Morphology (Walch Classification) [21]
    - Erosion (modified Favard Classification) [22]
    - Joint Space (subjective measurement)

- X-ray – independent radiologist will utilize imaging to assess X-ray data (defined in Section 7.3)
- ROM test
- Strength test
- Subject Questionnaire (FCI will only be completed at baseline)

CT Scan is recommended for the most accurate assessment of glenoid type if there is concern regarding the glenoid bone stock. CT data is not required but may be reported if collected per investigators standard of care.

MRI is recommended to confirm the integrity of the rotator cuff (cuff tear and fatty infiltration) if there is a clinical question about the cuff integrity. MRI data is not required but may be reported if collected per investigators standard of care.

7.6.2 Day of Surgery

The general surgical procedure is described in Section 4.3. It is required that an investigator or sub-investigator perform the surgical procedure. During the surgery, the investigator will be required to assess the following exclusion criteria prior to implanting the Pyrocarbon HH. A subject will not have a Pyrocarbon HH implant attempt and will be considered an intra-operative screen failure if any of the following conditions are present.

- In the opinion of the clinician, there is insufficient bone stock to support implants in the humeral metaphysis or poor bone quality.
- In the opinion of the clinician and prior to any glenoid treatments, there is insufficient bone stock or excessive deformation of the native glenoid to allow normal functioning of the glenohumeral joint.
- A rotator cuff that is not intact and cannot be reconstructed. Subjects with a massive rotator cuff tear (>5cm) must be excluded.
- Anatomy cannot be adequately replicated using current available system sizes.

If any of the aforementioned conditions are present, the implanting physician should utilize his or her standard bailout procedure. Bailout procedures may include, but are not limited to: traditional total shoulder arthroplasty, reverse shoulder arthroplasty, another hemi shoulder arthroplasty device, or no implant.

The following data associated with the surgery will be collected and reported into the study database:

- Pregnancy Test
- Intraoperative data and observations
- Adverse events
- Pain medication usage

7.6.3 Rehabilitation Guidelines

This section describes the recommended guidelines for the subject's rehabilitation program. These guidelines may be modified by the surgeon using his/her judgment taking into consideration the subject's pathology and physical condition.

1. Subjects should wear the sling every night for at least the first 6 weeks.

2. Subjects should push themselves up in bed or from a chair using their non-surgical arm.
3. Subjects should follow their program of home exercises and don't do more than prescribed, as overuse of the shoulder can be harmful.
4. No sports or heavy lifting for at least 4-6 months.
5. Investigators will let the subject know when it is safe to drive.
6. Investigators should provide subjects with a specific rehabilitation protocol.
    - Passive motion only for up to 4 weeks after surgery.
    - Begin passive assisted forward elevation and external rotation on the first day after surgery.
    - Place no limit to forward elevation, but limit external rotation to the side to 30 degrees.
    - At two weeks, begin internal rotation stretching. Encourage active use of the arm for activities of daily living.
    - Active assistive motion may be initiated at 3-4 weeks.
    - Active phase initiated at 6-8 weeks, limit external rotation to 45 degrees and internal rotation to L5.
    - Isometric phase may be initiated at 3 months.
    - No vigorous strengthening until 20 weeks post-op

The study specific guidelines (Appendix 3) should be provided to subjects upon hospital discharge.

7.6.4 Post-op Follow-up

Subjects will be seen between 5-21 days after the surgery for a post-op follow-up visit. The main purpose of this visit is to assess the subject for adverse events and obtain an x-ray. The following data will be collected and reported in the database:

- Adverse event assessment
- Pain medication usage
- X-ray – independent radiologist will utilize imaging to assess X-ray data (defined in Section 7.3)

7.6.5 Follow-up: 3 Months and 6 Months

Subjects will be seen three months post op (± 21 days), and six months post-op (± 21 days). The main purpose of these visits is to assess the subject for adverse events and collect the data required to calculate all outcome measures (ASES, Constant score, Age Adjusted Constant Score, SANE, EQ-5D, subject satisfaction, pain). ROM and Strength tests are optional at both three and six month visits. X-rays are not completed at 3 months. The following data will be collected and reported in the database:

- Adverse event assessment
- Pain medication usage
- X-ray (6 month only) – independent radiologist will utilize imaging to assess X-ray data (defined in Section 7.3)
- Subject Questionnaire
- ROM test (optional)
- Strength Test (optional)

7.6.6 Follow-up: Annual

Subjects will be seen 12 months post-op (± 42 days), 24 months post-op (± 42 days), and annually thereafter until the last implant attempt subject completes their 24 month post-op visit or determined lost to follow-up. Annual visits, after 24 months, will have a window of ± 84 days. The main purpose of the these visits is to assess subjects for adverse events and collect the data required to calculate all outcome measures (ASES, Constant score, Age Adjusted Constant Score, SANE, EQ-5D, subject satisfaction, pain). The following data will be collected and reported in the database:

- Adverse event assessment
- Pain medications
- X-ray – independent radiologist will utilize imaging to assess X-ray data (defined in Section 7.3)
- Subject Questionnaire
- ROM test
- Strength test

Subjects may be asked to return for additional visits after the study is completed, if deemed necessary.

7.6.7 Follow-up: Pre-Operative Screen Failures

Reason for the pre-operative screen failure will be documented on the eligibility form and then the subject will be exited.

7.6.8 Follow-up: Intra-Operative Screen Failures

Reason for the intra-operative screen failure will be documented on the eligibility form. Subjects will be seen at 12 and 24 months to gather available safety information. These visits may occur over the phone if the subject is unable to attend in person. Subjects will be exited after the 24 month visit.

7.6.9 Follow-up: Unsuccessful Implant Attempt

Reason for the unsuccessful implant attempt will be documented on the surgical form. Subjects will be seen at 12 and 24 months to gather available safety information. These visits may occur over the phone if the subject is unable to attend in person. Subjects will be exited after the 24 month visit.

7.6.10 Follow-up: Revisions

If a subject has revision surgery, the subject shall remain in the study and complete all required follow-up visits.

7.6.11 Follow-up: Explants

Subjects who have the Pyrocarbon HH explanted shall remain in the study and complete annual follow-up visits to gather available safety data

7.7 Additional Data Collection

Subjects may call or visit the investigative site at times other than for required study visits. It is only required to notify Tornier if the visit or phone call is associated with an adverse event, revision, device explant, reoperation, device malfunction, subject death, or study exit. Data associated with these events must be documented and reported in the database on the associated eCRFs.

Revision and Device Explants

A revision is a procedure that adjusts or in any way modifies or removes any component of the original implant configuration, with or without replacement of a component, after the initial surgery. A revision may also include adjusting the position of the original configuration.

An explant is a revision that includes permanent removal of any system component. If a subject has a revision that includes an addition of a glenoid component (revision to TSA) the Pyrocarbon humeral head must be permanently explanted.

All explanted system components, including the Pyrocarbon HH devices and stems, must be returned to Tornier for analysis per the system retrieval and analysis protocol in Appendix 4.

Reoperation

A reoperation is any invasive procedure to the affected shoulder that does not include removal, modification or addition of any components to the original implant configuration (e.g., drainage of a hematoma at the surgical site). Subjects will not be considered a failure solely due to a reoperation and will follow their original follow-up schedule.

Device Malfunction

All failures and malfunctions of the implant system must be reported to Tornier as soon as possible. In the event of a system malfunction, every effort must be made to return the suspected system to Tornier for analysis.

Death

During the study, all deaths must be reported to the Sponsor within 10 working days of the study personnel's knowledge of the death. A copy of death records, medical records for the events that led to the subject's death, death certificate (if available) and an autopsy report (if performed) must be sent to the Sponsor as soon as they become available.

7.8 Study Exit

Subjects will exit the study after the last subject with an implant attempt completes their 24 month follow-up visitor is determined lost to follow-up. Reasons for exiting a subject early may include:

- Subject voluntary withdraw of participation
- Investigators may withdraw subjects from the study if the investigator feels it is in the subject's best interest to withdraw or if the subject demonstrates non-compliance to the CIP.
- Death
- Subject lost to follow-up.
- It was determined that subject did not meeting inclusion/exclusion criteria prior to surgery (pre-operative screen failure)

In the case that the subject is determined to be lost to follow-up, at least three documented attempts must be made to contact the subject and at least one of the attempts must be in writing via certified letter. Subjects who exit the study prior to study completion will not be replaced.

8 Investigational Device Handling and Traceability

The Ascend Flex System stems and associated instruments are not investigational and will not require tracking while at the investigative site. When the Pyrocarbon HH is paired with the Ascend Flex stem, and implanted in the body, the system (Pyrocarbon HH and Ascend Flex Stem) are both considered investigational and require tracking.

The Pyrocarbon HH is investigational and will be tracked from the time it is shipped from Tornier until it is either implanted into a study subject, or returned to Tornier after completion of the enrollment. A Device Accountability Log will be maintained at each study site and will be provided by Tornier in the Regulatory Binder. Devices allocated for investigational site use will be recorded in the Device Accountability Log upon delivery to the study site and will be stored in a secured area until use. No devices will be shipped to an investigative site until the site receives IRB approval to conduct the study. Each site will be responsible for tracking the receipt and disposition of all study devices. All unused study devices must be returned to Tornier.

The Device Accountability Log will be updated as devices are received, opened, used or returned. It will contain: receipt dates of devices and their lot or serial numbers; subject study identification number and their implant dates; and dates devices were returned to Tornier, along with the reason for the return.

9 Study Deviations

A study deviation is defined as an event within a study that did not occur according to the CIP or the CTA. Prior approval by the Tornier Clinical Study Manager is expected in situations where the investigator anticipates, contemplates, or makes a conscious decision to deviate. Prior approval is not required when a deviation is necessary to protect the life or physical well-being of a subject in an emergency or in unforeseen situations beyond the investigator's control (e.g., subject failure to attend scheduled follow-up visits, inadvertent loss of data due to computer malfunction, etc.). All study deviations must be reported regardless of whether medically justifiable, pre-approved by Tornier, an inadvertent occurrence, or done to protect the subject in an emergency. The deviation must be recorded with an explanation for the deviation. Reporting of deviations must comply with IRB policies, local laws, and/or regulatory agency requirements. An investigator shall notify Tornier and the reviewing IRB of any deviation from this CIP taken to protect the life or physical well-being of a subject in an emergency. This must be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Tornier is responsible for analyzing deviations, assessing their significance, and identifying any additional corrective and/or preventive actions (e.g. amend the CIP, conduct additional training, etc.). Repetitive or serious investigator compliance issues may require initiation of a corrective action plan with the investigator, and in some cases, necessitate suspending site enrollment until the problem is resolved or ultimately terminating the investigator's participation in the study.

10 Adverse Events

10.1 Adverse Event Assessment Process

An adverse event (AE) assessment must be completed for each subject at every study visit. Ongoing AEs will be assessed at each study visit and the update reported to Tornier. If the AE is still unresolved at study exit, it must be updated to state "unresolved at study exit".

If the subject is treated by a health-care professional other than the investigator for treatment-related AEs, the investigator must request copies of the medical records and complete all required AE data collection. If the investigator is unable to obtain these medical records, efforts to obtain them should be documented in the subject's medical record.

10.2 Adverse Event Definitions

Adverse Event (AE): An Adverse Event is any unfavorable or unintended sign, symptom, condition or disease in a study subject, where the experience occurs during the course of the study; regardless of its relationship to the test product or surgical procedure.

An Adverse Event may be volunteered spontaneously by the subject or discovered as a result of questioning or by physical examination by the Investigator or clinical study, or recorded anywhere in the patient's medical record. An Adverse Event must be documented in the progress notes and on an AE eCRF.

For the purpose of this study, investigators are required *to report all adverse events*.

The relationship of the AE to the study system or the implant procedure will be determined by the investigator and reported on the eCRF. An independent physician consultant will review each reported AE for appropriate classification.

Device Related: An AE that results from the presence or performance of the device.

Procedure Related: An AE that occurs as a result of the implant procedure.

Definitions of Relatedness:

- **Definite**: A definite or certain association exists between the AE and the study device/system or implant procedure.
- **Possible**: The AE cannot be explained by other causes (underlying disease, concomitant medical or concurrent treatment) and is possible that the AE occurred as a result of the study device/system or implant procedure.
- **Not related**: The AE has no relationship with receipt of the study device or implant procedure, or it can be explained by other factors; including underlying disease, concomitant medication or concurrent treatment.

Unavoidable Adverse Events: those that are expected to occur and inherent with the surgical procedure. These only need to be reported if they are deemed by the investigator to be more serious in duration or intensity than expected. Unavoidable AEs include:

- Anesthesia related nausea/vomiting
- Low-grade fever for ~48 hours post-op
- Incisional pain for ~72 hours post-op
- Mild to moderate bruising or hematoma for ~ one week post-op
- Sleep problems (insomnia) for ~ 72 hours post-op
- Back pain related to lying on table

- Normal incision redness

Serious Adverse Event (SAE)

An adverse event is serious when it:

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

Unanticipated Adverse Device Effect (UADE)

Any serious adverse effect on health or safety, 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 study protocol or informed consent; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Anticipated Adverse Events

The risks associated with the Pyrocarbon HH used with the Ascend Flex stems are listed below. The complications could cause inflammation, resulting in increased pain and the need for revision surgery.

- Dislocation
- Component loosening
- Component breakage
- Component wear
- Component migration
- Delayed wound healing
- Bone resorption
- Glenoid erosion
- Poor bone growth
- Over tension of the soft tissues
- Impingement of tendons or bursa in the shoulder from bones of the shoulder
- Rotator cuff tear
- Instability
- Stiffness
- Weakness
- Chronic postoperative pain/disability
- Nerve damage causing paralysis
- Tissue lesion
- Vascular Injury

- Infection or any other event that could follow surgery (pulmonary embolism, heart attack, etc.)
- Fracture below the humeral implant.
- Possible metal sensitivity
- Oversized or undersized humeral head (the "ball portion") could cause loss of mobility and pain.

10.3 Adverse Event Reporting

Adverse events shall be submitted to Tornier via the electronic data capture (EDC) system.

Unanticipated Adverse Device Effects must be reported by the investigator to the Sponsor and IRB as soon as possible, but no later than 10 working days after the investigator first learns of the effect. The sponsor shall report the results of the evaluation of a UADE to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. If a UADE is determined to pose an unreasonable risk to study subjects, the study must be suspended within 5 business days of that determination but no later than 15 days from awareness of the event.

All adverse events and device deficiencies will be forwarded to the appropriate Tornier Complaint Handling group per Tornier Standard Operating Procedures.

Table 5: Adverse Event Reporting Requirements

AE Type	Reporting Requirements
AE	Complete eCRF and report to the IRB per the IRB guidelines.
Serious AE	Complete eCRF and inform Sponsor as soon as possible (preferably within 10 days) and report to IRB per their guidelines.
Unanticipated Adverse Device Effect	Report to Sponsor and IRB as soon as possible but no later than 10 working days of knowledge of the event.

10.4 Adverse Event Review

All reported AEs will be reviewed by a physician independent of the study (not participating as a PI). They will be reviewed individually to determine if they were classified appropriately according to the definitions in the CIP. AEs will be reviewed in aggregate with the Clinical Study Manager periodically throughout the study. During the aggregate data reviews, AEs and device deficiencies will be analyzed for important safety information.

11 Risk Analysis

11.1 Potential Risks

There are risks to the subject associated with study participation. The risks include standard surgical and anesthesia risk, risks associated with the Ascend Flex System, additional risks associated with the Pyrocarbon HH (investigational piece of the system), risks associated with the clinical study procedures, and standard risks of participating in a clinical study.

Surgical implantation involves the same risks and discomforts associated with any other kind of surgical procedure and use of anesthesia. In general, a subject could experience allergic reaction to medicines, breathing problems, bleeding, blood clot and infection.

The risks associated with the Pyrocarbon HH used with the Ascend Flex System are listed in the Anticipated Adverse Event section.

The risks of participating in this clinical study include:

- Study participation requires that the subject undergo at least five x-rays over the course of two years. Exposure to radiation is a risk associated with X-ray imaging.
- There are standard risks of participating in a research study which include the loss of confidentiality. Every attempt will be made to ensure subject confidentiality.

The risks of harm to the fetus is unknown, should a subject become pregnant.

11.2 Risk Minimization

The potential risks associated with the Pyrocarbon HH were identified and have been mitigated. Risks are mitigated through design, bench testing, design verification testing, quality checks in manufacturing, labeling (warnings and contraindications), and physician training. Any potential risks associated with this study are further minimized by selecting qualified investigators and training study personnel on the CIP. In addition, investigators will be actively involved in the surgery and follow-up of the subjects implanted with the Pyrocarbon HH. Risks will be minimized by careful assessment of each subject prior to, during, and after implant of the device. Tornier has further minimized risks by: providing guidelines for subject selection and evaluation, and providing adequate instructions and labeling for the investigational device. Subjects will be followed at regular intervals to monitor the condition of the shoulder system after implantation. At each protocol required follow-up, the investigator or designee must assess the subject for adverse events. Investigators and sub-investigators are required to have sufficient experience with the Ascend Flex System before they can use it with the Pyrocarbon HH.

11.3 Potential Benefits

The Pyrocarbon HH may offer no additional benefit over currently available arthroplasty systems. The potential benefits of having a Pyrocarbon HH includes less wear on the native glenoid than traditional CoCr humeral heads. This could result in less pain and fewer or less frequent revision surgery. The information gained from this study could result in the product being approved by the FDA and available to persons outside of the clinical study. Additionally, the information collected from this study may assist in the design of new products, therapies, and instructions for use. There is no guarantee that subjects will have any benefit from participating in the study.

12 Planned Study Closure, Early Termination of Study or Study Suspension

12.1 Planned Study Closure

Study closure is a process initiated once all subjects have completed their final study visit. The process is complete when all Tornier and/or regulatory requirements have been fulfilled and upon distribution of the final report and closure letter. IRB renewals/approvals are required until the overall study closure process is complete.

12.2 Early Termination or Suspension

Early termination is the closure of this clinical study at a site that occurs prior to the planned study closure. This is possible for the whole study (all sites) or a single site. Study suspension is a temporary

postponement of study activities related to enrollment. This is possible for the whole study (all sites) or a single site.

Possible reasons for considering study suspension or premature termination of the whole study may include:

- Observed/suspected performance different from the product's design intent
- Decision by Tornier or regulatory body

Possible reasons for clinical investigator or site termination or suspension include, but are not limited to:

- IRB approval expiration while the study is in progress.
- Consistent non-compliance to the clinical investigation (e.g. failure to adhere to inclusion/exclusion criteria, failure to follow subjects per scheduled follow-up visits, etc.).
- No subject enrollments within six months of study activation.
- Noncompliance to regulations and the terms of the CTA (e.g., failure to submit data in a timely manner, failure to accommodate a monitor, etc.).
- IRB suspension of the site.

If Tornier terminates or prematurely suspends the study, the investigators will be promptly informed of the rationale. Regulatory authority(ies) will be informed where required per regulatory requirements. In the case of study termination or suspension for reasons other than a temporary IRB approval lapse, the investigator will promptly inform the IRB. In the case of study termination, the investigator must inform the subjects. In the case of study suspension, subjects already enrolled may continue to be followed in the study unless prohibited by the IRB.

If the investigator terminates or suspends the study without prior agreement of Tornier, the investigator will promptly inform Tornier and provide a detailed written explanation of the termination or suspension. The investigator will promptly inform the institution (where required per regulatory or local requirements), the IRB, and the subjects.

If the IRB terminates or suspends its approval of the study, the investigator will promptly inform Tornier and provide a detailed written explanation of the termination or suspension. Subject enrollment must stop until the IRB suspension is lifted. Subjects already enrolled should continue to be followed in accordance with IRB policy or its determination that an overriding safety concern or ethical issue is resolved. The investigator will inform his/her institution (where required per regulatory or local requirements). The investigator will promptly inform the subjects of the rationale for the study termination or suspension.

13 Statistical Methods and Data Analysis

More detailed analyses will be provided in a separate Statistical Analysis Plan. The SAP will be submitted to the FDA with the IDE. The final SAP will include the additional details of the methods for group comparability and outcome comparison.

13.1 General Methods

The Intent-to-Treat (ITT) population will consist of all subjects who have undergone attempted or successful implantation of the test system. The Per-Protocol (PP) population will include all subjects who have undergone successful implantation of the test system, completed 24 months of follow-up, and have

had no major protocol violations (defined as not meeting inclusion/exclusion criteria or not being consented properly). The primary composite endpoint analyses will be performed on the ITT population. Analysis of the PP population will used in support the ITT analyses. The safety analysis will be performed on the ITT population.

Data will be summarized using descriptive statistics. Continuous data will be summarized using mean, standard deviation, minimum, and maximum. Where appropriate, non-parametric measures of location (e.g. median, interquartile range) may be provided. For categorical data frequencies and percentages will be provided.

All statistical analyses will be completed using SAS software (SAS Institute, Inc., SAS Campus Drive, Cary, NC 27513, USA.). In the event an analysis is required that is better suited for a statistical package other than SAS, another package may be used.

13.2 Primary Endpoint

The primary study endpoint will be compared for non-inferiority to a performance goal success rate of 85%. The Tornier Aequalis Post-Market Outcomes Study is the source of the data for the control group that was used to create the performance goal. Subjects with the appropriate indications with at least two years of follow up data (or revision prior to two years) were included in the cohort used to calculate the performance goal.

13.2.1 Hypothesis Test

The primary endpoint will evaluate the non-inferiority of the composite success endpoint to the Aequalis dataset rate.

Formally, the hypothesis to be tested is:
H_0: $p \leq PG - \delta$
H_A: $p > PG - \delta$

Where p is the proportion of subjects with a success for the composite success endpoint, PG is the performance goal (Aequalis dataset rate), and δ is the non-inferiority margin.

13.2.2 Sample Size

Statistical considerations for powering the primary endpoint include the following:

- 80% power with a one-sided 0.025 level of significance
- Non-inferiority test of one proportion
- 10% non-inferiority margin, and performance goal of 85%
- Assumed success rate of 85%
- Attrition rate of 15%

The sample size for this endpoint was calculated using SAS (Version 9.3) under a one-sided z-test of a binomial proportion. The minimum required sample size is estimated using the above list of statistical considerations. The resultant sample size under these assumptions is 133 subjects with an implant attempt and evaluable endpoint data. With 15% attrition, 157 total implant attempts are needed. Up to 190 subjects may be enrolled to account for pre and intra-operative screen failures. Enrollment will stop once 157 subject have had an implant attempt.

13.2.3 Analysis

The number and proportion of subjects reaching the composite success outcome will be summarized. Additionally, a 95% confidence interval (CI) will be calculated for the proportion. The non-inferiority of the test system to the performance goal will be evaluated using the 95% CI for the observed test system success rate. The study will be considered a success if the lower bound of the confidence interval is greater than 75% (85% - 10%).

The primary analysis will be based on the ITT population with available 24 month data. A supportive analysis based on the PP population will also be presented. The impact of missing 24 month data will be evaluated through sensitivity analyses, described in the next section.

13.2.4 Missing Data

The impact of missing data due to loss to follow-up prior to 24 months will be assessed by sensitivity analyses. The primary endpoint analysis will be repeated once under the assumption that all missing subjects were successful, a second time under the assumption that all missing subjects were failures, as the most conservative assessment, and a third time using multiple imputation for missing values. The results of these analyses will be presented.

13.3 Secondary Endpoints

13.3.1 Inferential Secondary Endpoints

The following secondary data will be evaluated for significant change from baseline to 24 months. The overall type I error will be controlled using the Hochberg method for adjusting for multiple comparisons, and will be tested only if the primary endpoint is met. Endpoints will be evaluated at a one-sided alpha level of 0.025.

- Constant Score and Adjusted Constant score
- American Shoulder and Elbow Surgeons (ASES) Score

- Single Assessment Numeric Evaluation (SANE)
- EQ-5D
- Pain (VAS)
- Range of Motion
- Strength

13.3.1.1 Hypothesis Tests

The hypothesis test for each of the above endpoints, with the exception of Pain (VAS), will be of the form:

H_0: $\mu \leq 0$

H_A: $\mu > 0$

Where μ is the mean change from baseline to 24 months (follow-up minus baseline) for that endpoint.

The hypothesis test for the Pain (VAS) endpoint will be of the form:

H_0: $\mu \geq 0$

H_A: $\mu < 0$

Where μ is the mean change from baseline to 24 months (follow-up minus baseline) in the VAS Pain score.

13.3.1.2 Analysis

For each endpoint, descriptive statistics will be provided for subjects at baseline and 24 month follow-up. The difference from baseline to 24 months will be summarized using descriptive statistics, and a paired t-test will be performed. Additionally, the 95% confidence interval will be calculated for the change from baseline.

13.3.2 Additional Secondary Endpoints

The following secondary endpoints will be presented using descriptive statistics only.

- Adverse events
- Revision rate
- Level of satisfaction with the shoulder
- X-ray data: glenohumeral joint space width, glenoid osteophytes, glenoid morphology, glenoid erosion, humeral component radiolucency, osteolysis, migration, subsidence, subluxation, humeral head integrity, acromiohumeral distance, anatomic fracture, and additional observations

Note that safety is included in the primary composite endpoint and also as a descriptive secondary endpoint. The objective of the safety analysis is to demonstrate that the test system has an acceptable safety profile. Adverse events will be summarized by the proportion of subjects with serious adverse events, system-related adverse events and unanticipated adverse device effects. Subjects with system related SAEs will be counted as a failure towards the composite endpoint.

13.4 Baseline Assessment

Demographics and baseline characteristics will be assessed by descriptive statistics. These factors will include (but not be limited to):

- Age

- Sex
- Body Mass Index (BMI)
- Medical history (included diagnosis)
- Constant Score
- Adjusted Constant score
- EQ-5D
- Pain

13.5 Comparability to Aequalis Dataset

Demographics and baseline characteristics for subjects in the Aequalis dataset and subjects with the test system will be compared by t-tests for continuous factors and chi square tests for categorical factors, non-parametric or exact tests may be used when appropriate. These characteristics will include age, gender, diagnosis, and baseline adjusted Constant score. Additional baseline measures may be considered if sufficient non-missing values are available. A propensity score analysis may also be performed on the subjects with complete 24 month status/data available. The propensity score analysis will incorporate data from Aequalis dataset used to derive the performance goal and subjects enrolled in the current investigation. If significant differences are found between groups, the impact of relevant factor(s) on success rates will be assessed by logistic regression.

13.6 Poolability

A pooling analysis will be performed to assess the poolability of sites with respect to the primary endpoint measure in the ITT subjects. A Fisher's Exact Test will be used to test for a difference in composite success rate across sites. A significance level of 0.1 will be used to determine whether the sites are poolable. If a significant difference is found between sites, additional analyses will be done to identify factors that may be associated with this difference. Additionally, if a significant difference is observed, a random site adjusted estimate of the composite success rate, along with 95% CI, will be provided.

Although enrollment will be monitored in an effort to strive for even allocation between sites, for purposes of the poolability analysis those sites with less than five (5) evaluable patients enrolled will be combined into a pseudo-site for purposes of analysis. To protect against having an overly large pseudo-site, when one pseudo-site exceeds five (5) evaluable, a second pseudo-site will be formed. This process will continue as needed each time a pseudo-site exceeds five (5) evaluable.

14 Data and Quality Management

All information and data sent to Tornier concerning subjects or their participation in this study will be considered confidential. All data used in the analysis and reporting of this clinical study will be used in a manner without identifiable reference to the subject. The investigator consents to visits by Tornier staff and authorized governmental bodies to review the study subjects' medical records, including any test or laboratory data that might have been recorded on diagnostic test media (e.g., X-rays).

Data will be stored in a secure, password-protected database. Data will be reviewed using programmed and manual data checks. Data queries will be made available to sites for resolution. Study management reports may be generated to monitor data quality and study progress. At the end of the study, data will be frozen and retained by Tornier per document retention policies at the time of study termination. Procedures for data review, database cleaning, issuing and resolving data queries, verification, validation and securing of electronic clinical data systems, and data retention will be documented separately.

15 Monitoring, Auditing, and Inspecting

15.1 Monitoring Plan

It is the responsibility of Tornier to ensure proper monitoring of the study per regulations. Trained Tornier personnel or delegates appointed by Tornier will perform study monitoring at the study site in order to ensure the study is conducted in accordance with the CIP, the CTA, and applicable regulatory requirements. Tornier must therefore be allowed access to the subject's clinic and hospital records when so requested as per the subject informed consent document, Privacy Authorization, and CTA.

The primary focus of the monitoring visits will be on the processes critical to protecting human subjects, maintaining the integrity of study data, and compliance with applicable regulations. The findings will be used to correct investigator and site practices that could result in inadequate human subject protection and/or poor data quality. Both on-site and centralized monitoring will be conducted as detailed in the study Monitoring Plan. The Monitoring Plan will include a risk assessment that considers the types of data to be collected, the specific activities required to collect the data, and the range of potential safety and other human subject protection concerns associated with specific data points. The risk assessment will determine the type, frequency, and intensity of monitoring activities that will be performed and will be documented separately in the monitoring plan.

15.2 Audits

In the event of any inspection by any Regulatory Authority, the investigators agree to cooperate with representatives of the Regulatory Authority, and to provide the Regulatory Authority representative access to records as required by applicable Laws. Site personnel shall immediately notify Tornier upon learning that an inspection by a Regulatory Authority is scheduled to take place, or, if there is no prior notice by the Regulatory Authority, that an inspection has commenced relating to the Study. If any Regulatory Authority issues any notice of observations or warning letter relating to the Study, the investigator shall send a copy of the document to Tornier and provide Tornier with a copy of a draft response.

16 Medicare Study Criteria

It is not anticipated the device under investigation will affect the Medicare population any differently than patients found the investigators' general population for patients requiring treatment for shoulder pain including populations eligible for Medicare due to age (e.g., 65 years or older), disability, or other eligibility status. The study's subject selection will include adults 22 years or older. Because the study's inclusion criteria includes an adult patient population with no upper age limit, it is anticipated the study's enrolled population will be represented by a proportion of patients eligible for Medicare primarily due to age (E.g., 65 years or older). Moreover, the strength of each subject's normal shoulder may differ because gender and age differences as measured by the study's Constant score test. This test will be administered according to a modification of the standard procedure established in the updated paper by Constant, et al. in the Journal of Shoulder and Elbow Surgery, 2008 [2]. The Constant score calculation will be adjusted using normative values for the Constant score based on age and gender. Because the Adjusted Constant score will be adjusted using normative values for the Constant score based on age and gender, this outcome measure is expected to be generalizable to the Medicare beneficiary population due to age (e.g., 65 years or older) but not necessarily due to disability or other eligibility status.

Access to clinical study data provides opportunities to conduct further research that can help advance medical science or improve patient care. This helps ensure the data provided by research participants are used to maximum effect in the creation of knowledge and understanding. To this end, the study's results information on all pre-specified outcomes, including negative outcomes, will be submitted to ClinicalTrials.gov not later than one year after the study completion date of the study, where the completion date is defined as the date that the final subject was examined or received an intervention for purposes of data collection for the primary outcome measure. Results submission could be delayed if an extension is granted to the results submission deadline; however, the release of all results on pre-specified outcomes will be hastened if the study is terminated early.

17 Required Records and Reports

Investigators and Tornier shall maintain records for this study for a period of at least 2 years after the date on which the investigation is terminated or completed. An investigator may withdraw from the responsibility to maintain records for this period and transfer custody of the records to any other person who will accept responsibility for them. Notice of a transfer shall be given to FDA not later than 10 working days after transfer occurs.

17.1 Investigator Records

The investigator is responsible for the preparation and retention of the records cited below. All of the below records, with the exception of case history records and electronic case report forms, should be kept in the Investigator Site File (i.e., the study binder provided to the investigator), or Subject Study File. Electronic case report forms (eCRFs) may be maintained and signed electronically within the electronic data capture system during the study.

- All correspondence between the IRB, Sponsor, another investigator, monitor, FDA and/or the investigator that pertains to the investigation, including required reports.
- Subject's case history records, including, but not limited to:
    - Signed and dated informed consent form
    - Signed and dated privacy authorization form (may be combined with the informed consent form)
    - Observations of adverse events/adverse device effects.
    - Medical history
    - Implant and follow-up data
    - Documentation of the dates and rationale for any deviation from the protocol.
- Signed and dated eCRFs
- Investigational device traceability records
- All approved versions of the CIP and Report of Prior Investigations
- Signed and dated CTA
- Investigator's current CV
- Delegation of Authority Log
- IRB study approval documentation, including written confirmation that the investigator or other study staff, if a member of the IRB, did not participate in the approval process.

17.2 Investigator Reports

The investigator shall prepare and submit in a complete, accurate, and timely manner, the reports listed in this section.

Table 6: Investigator Reporting Requirements

Report	Submit to:	Description/Constraints
UADE	Sponsor and IRB	ASAP, but no later than 10 working days after the investigator first learns of the effect.
Withdrawal of IRB approval	Sponsor	An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB.
SAE	Sponsor	ASAP, preferably within 10 working days
	IRB	Report per the IRB's policies and procedures
Deviations from the CIP	Sponsor and IRB	An investigator must notify the sponsor and IRB of any deviation from the CIP to protect the life or physical well-being of a subject in an emergency. Such notice shall be given ASAP, but no later than 5 working days after the emergency occurred.
Failure to obtain informed consent prior to investigational device use.	Sponsor and IRB	If an investigator uses a device without obtaining informed consent, the investigator shall report such use within 5 working days after device use.
Final report	Sponsor	This report must be submitted within three months of study completion or termination of the investigation or the investigator's part of the investigation.
Progress	Sponsor and IRB	An investigator shall submit progress reports to the sponsor and IRB/MEC at regular intervals, but in no event less often than yearly.
Other	IRB and FDA	An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation
Device Malfunction	Sponsor	ASAP, preferably within 24 hours of notice

17.3 Sponsor Records

Tornier will maintain the following accurate, complete, and current records relating to this investigation:

- All correspondence with an investigator, an IRB, or FDA, including required reports.
- Records of shipment and disposition. Records of shipment shall include the name and address of the consignee, type and quantity of device, date of shipment, and batch number or code mark. Records of disposition shall describe the batch number or code marks of any devices returned to Tornier, repaired, or disposed of in other ways by the investigator or another person, and the reasons for and method of disposal.
- Signed investigator agreements including the financial disclosure information required to be collected under 812.43(c) (5).
- Records concerning adverse events.

17.4 Sponsor Reports

Table 7: Sponsor Reporting Requirements

Report	Submit to:	Description/Constraints
UADE Evaluations	FDA, all participating IRBs	10 working days after the sponsor first receives notice of the effect. Thereafter, Tornier shall submit such additional reports concerning the effect as FDA requests.
Withdrawal of IRB approval	FDA, all reviewing IRBs and participating investigators	Within 5 working days after receipt of notice of the withdrawal of approval.
Withdrawal of FDA approval	All reviewing IRBs and participating investigators	Within 5 working days after receipt of notice of the withdrawal of approval.
Current investigator list	FDA	Tornier shall submit, in 6 month intervals, a current list of the names and addresses of all investigators participating in the investigation.
Progress Reports	FDA and all reviewing IRBs	At regular intervals, at least yearly
Recall and device disposition	FDA and all reviewing IRBs and participating investigators	Any request that an investigator return, repair, or otherwise dispose of any unit of a device shall be reported within 30 working days after the request is made and shall state why the request was made.
Completion or termination of the investigation	FDA	Within 30 working days
Final Report	FDA and all reviewing IRBs and participating investigators	Within 6 months of study termination.
Informed Consent	FDA	Within 5 working days of receipt of notice of device use without obtaining informed consent.
Other	FDA, reviewing IRB/MEC	Provide accurate, complete and current information about any aspect of the investigation as requested at any time.

18 Publications

Tornier will form a Publication Committee to manage publications that utilize data from this study. The committee will develop a publication plan outlining the details related to primary, secondary, and ancillary publications and authorship rules. The responsibilities of the committee will include reviewing publication ideas and proposals, providing input on their scientific merit and clinical relevance, and prioritizing them accordingly. Membership in the publication committee or participation as an investigator in this study does not guarantee authorship. Publication Committee membership criteria will be established and documented by Tornier.

Primary study results will be published following the final study analyses.

The International Committee of Medical Journal Editors (ICMJE) authorship guidelines will be used. The ICMJE guidelines require the conditions below are met to be included as an author:

- Substantial contribution to conception and design, or acquisition of data, or analysis and interpretation of data
- Drafting the article or revising it critically for important intellectual content
- Final approval of the version to be published

This study will be registered in www.clinicaltrials.gov, and results will be posted.

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Appendix 2 Strength Testing Protocol

The Constant Score

This test will be administered according to a modification of the standard procedure established in the updated paper by Constant, et al. in the *Journal of Shoulder and Elbow Surgery,* 2008 [2].

Further modifications to the described procedure for this test are related only to the use of equipment:

1) For the strength component of the score, a fixed force gauge as depicted in Figure 6 will be used.
2) For Visual Analog Scales (VAS), either a paper form with a graduated line or the study electronic database, will be used.

Figure 6: Fixed Force Gauge

Strength (Power) Measurement

A fixed force gauge is a device for measuring force, moment of force (torque), or power. It is used in shoulder orthopedics for measuring the arm strength of patients to evaluate physical status, performance and task demands.

Method

The evaluation method for this study will be performed using the fixed force gauge device supplied or approved by Tornier and a modification of the standard methods as described below [2]

- The assessment will use a fixed force gauge as depicted in the photograph above.
- The test position is the subject standing with the arm in 90° elevation in the scapular plane, elbow extended and forearm pronated. An adjustable strap is placed around the forearm just proximal to the radio carpal joint and attached to the fixed force gauge.
- The fixed force gauge is firmly secured by the examiner. The subjects are instructed to pull upward with maximum effort until requested to stop.
- The reading of the fixed force gauge is taken after five seconds of maximum effort.
- At least one pull is required, but three are suggested. All measurements will be collected.
- Patients unable to reach the test position will receive the value of zero.

Appendix 3 Subject Rehabilitation Guidelines

You are being asked to follow specific guidelines during your post-study implant rehabilitation. Your doctor may provide you with more detailed instructions in addition to the study guidelines. The following instructions inform you when to start using passive and active motion. Passive motion is the use of an external force (e.g., other arm) to move your treated arm. DO NOT use your treated arm muscles during passive motion. Active motion is when you start using your muscles of the treated arm without assistance.

Below are general guidelines to keep in mind during your recovery.

- Wear the sling every night for at least the first 6 weeks.
- Push yourself up in bed or from a chair using your non-surgical arm.
- Follow your program of home exercises and don't do more than prescribed, as overuse of the shoulder can be harmful.
- No sports or heavy lifting for at least 4-6 months.
- Do not drive. Your doctor will let you know when it is safe to drive

After your surgery, you should limit your shoulder motion as follows

- Passive motion ONLY for up to 3 weeks.
- Limit forward elevation to 120 degree for the first 6-8 weeks. (Figure 1)
- Passive external rotation to the side should be limited to 30 degrees (Figure 2).
- At 3-4 weeks you may begin active assistive motion. During this phase you should begin using your treated shoulder muscles along with assistance (similar to the passive phase).
- At 6-8 weeks you may begin active motions without assistance. Limit external rotation to 45 degrees and internal rotation to L5. (Figure 3)
- Isometric strengthening phase may be initiated at 3 months.
- Do not begin any vigorous strengthening until 20 weeks after surgery.

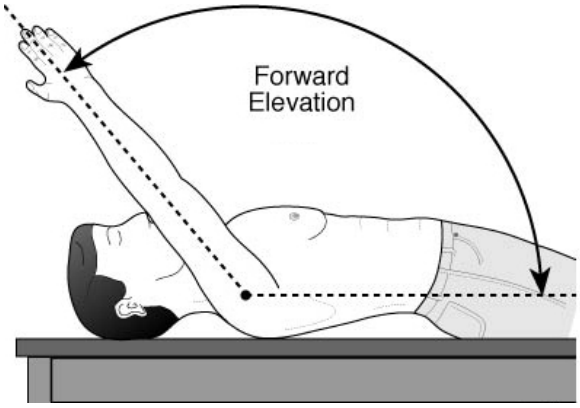

Figure 1: Active assisted Forward Elevation

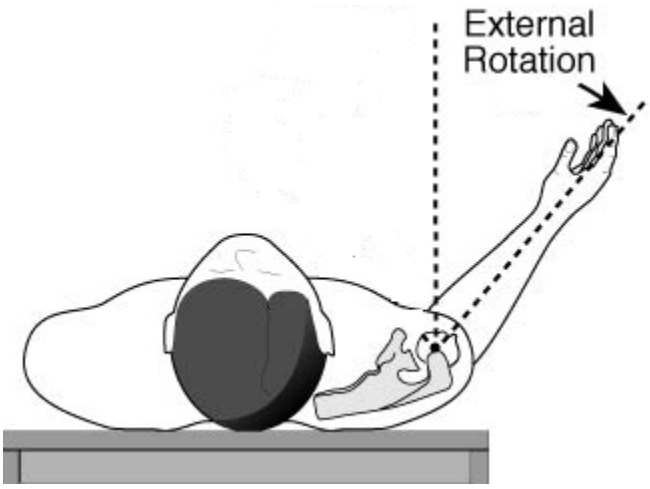

Figure 2: External Rotation

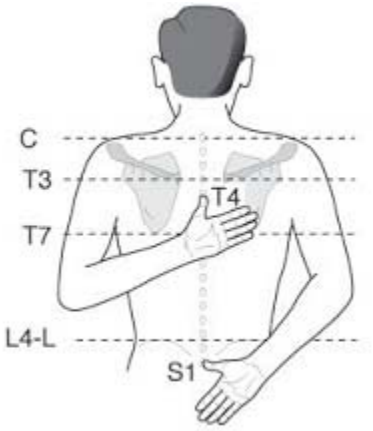

Figure 3: Internal Rotation

Images adapted from http://shoulderarthritis.blogspot.com/2011_03_01_archive.html

Appendix 4 System Retrieval and Analysis Protocol

TORNIER

Pyrocarbon IDE Study
Protocol #: 15A-T-PYC-R
IDE#: G140202

Device Retrieval and Analysis Protocol

Version: 1
Date: Final – 17 July 2015

Sponsor
Tornier, Inc.
10801 Nesbitt Ave South
Bloomington, MN 55437 USA
Phone: 952-921-7600
Fax: 952-291-7601

Contents

1. Scope

This process covers the retrieval, handling, and analysis of implanted Flex Shoulder System with Pyrocarbon humeral heads and associated specimens that are removed from subjects during revision surgery. The aim is to provide guidance in preventing damage to the associated specimens which could obscure the investigational results, and in gathering data at the proper time and circumstance to validate the study.

2. References

- ASTM F561-13: Standard Practice for Retrieval and Analysis of Medical Devices, and Associated Tissues and Fluids

3. Terms and Definitions

- Antiseptic: A germicide that is used on skin or living tissue for the purposes of inhibiting or destroying microorganisms.
- Decontamination: A process or treatment that renders a medical device, instrument, or environmental surface safe to handle. Ranges from sterilization to cleaning with soap and water.
- Disinfectant: A germicide that is used solely for destroying microorganisms on inanimate objects.
- Disinfection: Generally less lethal than sterilization. It eliminates virtually all recognized pathogenic microorganisms but not necessarily all microbial forms on inanimate objects. It does not ensure overkill.
- Sterilization: Use of a physical or chemical procedure to destroy all microbial life; including large numbers of highly resistant bacterial endospores.

4. Procedures for Retrieval, Handling, and Packaging

Any part of the Tornier Flex Shoulder System with a Pyrocarbon humeral head that is removed from a study subject must be returned to Tornier for analysis.

Please contact Tornier Clinical Department to request a Return Material Authorization number (RMA) which details return instructions.

The following steps are important and necessary to aid in the analysis of an explanted device:

4.1. Pre-explant functional check:

- Whenever possible, a pre-explant functional check of the implant is recommended to assist in post-explant analysis. Objective measurements of shoulder function should be obtained when possible. These measurements include: American Shoulder and Elbow Surgeons Standardized Shoulder assessment (ASES),

Constant score, Single Assessment Numeric Evaluation (SANE), and shoulder satisfaction (since they were used as measures of the system's performance in this study) as well as other clinical indicators such as EQ5D, pain, tenderness, swelling, etc.

- A non-invasive examination of the implanted system via X-ray should be performed in accordance with the Pyrocarbon IDE Study protocol X-ray procedures.

4.2. Explant record

- If any components are misaligned in any way due to migration or surgical mal-positioning at the time of revision surgery, then every effort should be made to mark the components prior to removal in order to preserve their in situ orientation. Ideally, the operating surgeon should be asked to make a small mark(s) with a fine osteotome at the 12 o'clock (mid-line) position on the CrCo double taper neck component before dismounting from stem. The metallic osteotome should not touch the Pyrocarbon bearing surface component, otherwise it could damage it. If the bearing surface is damaged, the position of the contact/damage on the Pyrocarbon bearing surface would be recorded. If the implants are not marked before extraction or immediately after, then the true location of the wear scars/features can only be guessed. If possible, photos of the marks made should be taken immediately after they are made. If the 12 o'clock position is not accessible and another marking position is used, photographic records as well as a written note of the position should be documented.
- Shortly after removal, a detailed record of any damage caused to the components during extraction should be documented, especially in the presence of the operating surgeon. Adequate macro photography can also be helpful. This information should be adequately labeled and should accompany the explanted components. This should facilitate the ability to differentiate between damaged regions caused in vivo and those caused during extraction.

5. Collection of clinical history of the implant and patient

Subject Information (data previously collected in Baseline CRF)

- Subject Identification Number
- Subject's height and weight
- Female/male
- Date of birth
- Number of previous surgeries prior to implantation of current device
- Known metal sensitivities

Initial Surgery Details (data previously captured in the initial Operative CRF)

- Original diagnosis
- Date of Implantation
- Hospital where implantation occurred
- Surgeon name
- Surgical site, left or right
- Implanted components (serial numbers, size, and reference numbers)

Revision/Explant Information (will be collected on revision/explant CRF)

- Date of removal
- Hospital where explant occurred
- Surgeon name
- Surgical site description
- Subject's height and weight at retrieval
- Reasons for device removal (primary clinical diagnosis)
- Tissue samples, descriptions or tissues, if applicable
- Description of how the device was removed
- Surgeon commentary/observations at revision, including assessment of bone quality if applicable
- Other mitigating factors, if applicable

Other Data Collected

- Length of follow-up (automatically calculated in database)
- Age at retrieval (automatically calculated in database)
- Any complications occurring during the removal procedure (Complete AE CRF)
- Any radiographs and/or other imaging available for analysis (Complete Imaging CRF)
- Patient activity, experience with implant, and clinical performance (complete QOL forms)

6. Collection of tissue and fluid samples near the implant,

Collection of tissue and fluids will depend on how invasive is the revision, and particularly whether the stem will be removed, and also whether a glenoid component will be implanted. Surgeons shall not remove more fluid or tissue than those necessary for the revision. Data will be collected as follows:

- Whenever it's possible and before opening articular capsule:
  (a) Extraction of synovial fluid by puncturing the joint (ideally 1ml, 1 ml of physiological saline can be injected and recovered),
  (b) extraction of 1ml blood (ideally decision made at the time of operation) each sample rapidly frozen and stored at - 20 °C to measure blood ion levels.

NOTE: Fluid samples should not be sent to Tornier. Analysis should be completed at the hospital, as appropriate.

- Extraction of a piece of articular capsule (minimum 1cm of length)
- Extraction of a portion of cartilage (in the glenoid side) with a form of "carrot" whenever it's possible (or another form), to analyze the bone cartilage interface and the cartilage status, by histological methods.
- If important black color is detected (presence of wear particles), additional portions of tissues should be extracted and placed into a separate solution (see part 8.4)
- If the stem is removed, a portion of bone at the interface with stem should be extracted to identify the bone status at this region.
- A photographic record of the position of the removed bone and/or cartilage removed will be performed before retrieval.

7. Photographic record of the explanted device and tissues,

- A photographic record of both the retrieved components (humeral head or stemmed component) and any tissues/bone dissections should be performed immediately after revision surgery. This can be done after the scrub nurse has wiped the components free of excess blood and passed them from the sterile field-ideally onto a tray covered with a clean surgical towel. A surgery label as used with tissue specimens (i.e., showing the patient ID/number, date, etc.) should be photographed at the beginning of the series and included in the photos where possible. One photo should be taken at a magnification that allows all of the removed components to be viewed together, and subsequent photos should be taken of individual components at a magnification that allows their features to be clearly seen, including the laser markings and any obvious wear or damage to the parts. The retrieved components should be photographed on both sides.

8. Containing, labeling, cleaning, decontaminating, packaging and shipping of retrieved implant, tissue, or fluid samples,

8.1. Labeling the explanted materials for future identification

- Stem and head are laser etched, so there is no need to affix a label to it. Nevertheless, each component or tissue removed from the patient will be sealed in a container that is subsequently labeled with the following information:
    - Patient ID number
    - Date explanted
    - Surgeon name
    - Hospital name

8.2. Documentation

- Documentation must accompany the explanted materials to assist Tornier with identification of the retrieved materials. Please see Section 5 for additional information on what must be recorded and documented.
- Documentation shall begin when the implant is recovered and continue until examination and analysis is complete.
- Treat the documented information as Confidential.
- The following procedure should be used for recording retrieval information:
    - Record the cleaning and sterilizing method used to decontaminate the material. Please see section 8.3 for details on how to perform these activities.
    - Record the name of the shipping service (i.e. postal service, courier, etc.), shipping number, date of shipment, and time of release.
    - If the surgical implant is to be stored prior to shipment, record the storage location.
    - The documentation shall reflect the names of all responsible individuals handling the implant during retrieval and preparation for shipping, as well as any activities performed in conjunction with its handling.

8.3. Cleaning and Decontamination/Sterilization

Clean and decontaminate/sterilize the explanted system component(s) recovered in accordance with your facility's best and safe practices for analysis prior to shipment and examination by Tornier.

The following cleaning and decontaminate/sterilize methods are recommended by Tornier for the individual system components:

- Cleaning method:
    - Intense water rinse
    - 70 % to 80 % aqueous ethanol or isopropanol rinse with subsequent ultrasonic treatment or proteolytic enzyme or 1:100 solution sodium hypochlorite
- Decontaminating and sterilizing method of components and tissues:
    - When decontaminating/sterilizing the explanted components, they should be done so in a manner that does not alter features or surfaces which may be essential in determining failure modes. In consequence, cold sterilization techniques are recommended. The explanted components should be placed into separate plastic containers filled with 10% neutral buffered formalin to at least twice the volume of the implant. The containers

must each have a standard surgical specimen label showing the medical record number, date of procedure, surgeon, and the patient number. The member of the surgical staff who provides this container and receives the specimen should write the description of the individual specimens on the individual container (for example: 'Removed Humeral Head', or 'capsule fragment 1 out of 2').

- Extracted tissues (bone, cartilage and capsule) should be placed into separate plastic containers filled with 10% neutral buffered formalin to at least twice the volume of the tissue. If important black color is detected (presence of wear particles), additional portions of tissues should be extracted and placed into glutaraldehyde, usually as a 2.5% solution in phosphate buffered saline). The containers must each have a standard surgical specimen label showing the medical record number, date of procedure, surgeon, and the patient number. The member of the surgical staff who provides this container and receives the specimen should write the description of the individual specimens on the individual container.
- A period of 24 hours is sufficient for explants with no or minimal tissue adherence, but specimens with substantial amounts of adherent bone (for example end-plate components), or tissue of a larger volume will require more time in formalin. Formalin does not adversely affect the subsequent analysis of the surface, so for all explants (tissue, implant), a permanent storage in formalin will be used to store and transport the samples.
- Note: Other methods of sterilization such as autoclaving are forbidden as they might result in irreversible damage in the form of permanent adherence of residual blood or fluids, and will render adherent tissues unsuitable for subsequent histological analysis.

- Care should be taken during any subsequent handing of the specimens to avoid damage to the parts such as rubbing the articulating surfaces together, dropping or knocking the parts or allowing tissue attached to the implants to dry out.

8.4. Packaging and Shipping the explant for shipment

Each retrieved component should be individually wrapped and stored in its own container, then placed in a larger container with all the other retrieved components. (i.e., do not place humeral head and flex stemmed component in the same bag or container.) This will prevent damage to the explants, which can be difficult to distinguish from in situ damage.

Packaging

- Place the cleaned and decontaminated/sterilized explanted component(s) or tissues (see method above) in a durable, primary container.
- Securely seal the primary container.
- Package the primary container in an outer shipping container using shock-resistant packing material.
- Securely seal the outer shipping container.

Labeling of the package

- The inner and outer shipping containers shall bear a label with the name, address and telephone number of the sender.
- The outer shipping container shall also contain a label, which instructs anyone handling the package to isolate the package upon discovery of damage and to notify the sender.
- The outer package shall include all of the information required by Tornier (i.e. RMA number).
- The package shall be shipped to Tornier at the following address: 10801 Nesbitt Ave South, Bloomington, MN 55437 (ATTN: RMA Number XXXXX)
- Call Tornier Clinical and advise them of the return shipping information.

Documentation

- Affix all packing slips, documents and correspondence with Tornier to the outer shipping container so that the receiving facility will not be required to open the package in order to identify its contents or intended receiver.

9. Analysis of tissue and fluids

9.1. Fluid analysis:

Fluid (blood and synovial) analysis needs to be completed per the hospital standard procedures to assess for: debris, metal, abnormalities. The following guidelines should be followed, if appropriate.

<u>For blood samples:</u>

Blood samples drawn from patients should be done using polypropylene syringes. The blood can be allowed to clot at room temperature and centrifuged for 30 minutes to separate serum and clot fractions. Blood may also be drawn in heparinized vacutainer tubes. The blood may be allowed to settle so as to isolate red and white cells, or be centrifuged at 400 g and plasma supernatant drawn off. Plasma is diluted at least 2× in 1 % nitric acid. (ASTM standard F516-part 9.4.3.1)

Then to assess inflammation (depending of hospital), Erythrocyte sedimentation rate (ESR) could be performed. A blood sample is taken and put in a tube that contains a chemical to stop the blood from clotting. The tube is left to stand upright. The red blood cells (erythrocytes) gradually fall to the bottom of the tube (as a sediment). The clear liquid plasma is left at the top. The ESR measures the rate at which the red blood cells separate from the plasma and fall to the bottom of a test tube. The rate is measured in millimeters per hour (mm/hr). This is easy to measure as there will be a number of millimeters of clear liquid at the top of the red blood after one hour. If certain proteins cover red cells, these will stick to each other and cause the red cells to fall more quickly. So, a high ESR indicates inflammation.

A quantification of the percentage of ionic metal may also be extracted from the blood test analysis with high resolution inductively coupled plasma mass spectrometry (HRICPMS), if available

For synovial liquid:

Digestion Protocol (ASTM Standard F561-13, part 11.4):

- Mix 150 µL of 1M HEPES (pH=7.5), 6 µL of 1 M MgCl2, 75 µL of 0.5 M CaCl2, and 2.8mL of synovial fluid for a total of 3 mL in a 50 mL siliconized blue capped tube. (In less than 2.8 mL of synovial fluid are available, add deionized water to a total volume of 2.8 mL.) Add 300 µL of dilute Hyaluronidase (0.05 % (g ⁄100 mL) Hyaluronidase, 0.1 MNaH2PO4 (pH 5.3), 0.15M NaCl) to the synovial fluid mix.
- Incubate at 37ºC with a gyration of 250 rpm for 6 hours. Add 5µl of diluted Benzonase (that is, 5 µL of Benzonase in 50 µL of: 50 % glycerol, 0.02 M Tris HCl (pH=8.0), 0.002 M MgCl2, 0.02 M NaCl) to each sample.
- Incubate at 37ºC with a gyration of 250 rpm overnight (total fluid 3.305 mL).
- Follow the protocol established for the digestion and separation of the metal/ceramic particles (11.2.6, standard F561-13). Since synovial fluid does not contain EDTA as in simulator lubricant, the amount of calcium to be added should lead to 18 mmol/l rather than 40mmol/l as per the simulator extraction.

Several stages of filtration may be necessary to effectively isolate the different particles of interest.

The characterization and the quantification of wear particles can be performed over two different supports: silicon wafers used for scanning electron microscopy (SEM) analysis and TEM grids for transmission electron microscopy analysis. Chemical analysis methods such as EDXA and FTIR could also be employed to determine the chemical nature of the particles.

9.2. Macroscopic Examination of Tissues:

Record a gross pathologic description of extracted tissues, as to consistency and color, as seen by the naked eye. Record any differences between the implant-tissue interface and the tissues not in direct contact with the implant. Describe the specimen size either by dimensions or weight.

Where appropriate and feasible, obtain photographic documentation of the explant and adjacent tissue, as well as a photographic record of subsequent dissections describing the edges tissues and indicating in which side the tissue rubbed against the implant.

9.3. Histological procedure

The standard steps are: Fixation that preserves the tissue, Processing that dehydrates, clear and infiltrate the tissue with paraffin wax, Embedding that allows orientation of the specimen in a “block” that can be sectioned and is easy to store and handle, and Sectioning using a microtome to produce very thin sections that are placed on a microscope slide ready for staining and staining and diagnosis.

These following procedures may be applicable for paraffin embedding, methacrylate embedding or other special procedures.

9.3.1. Fixation:

Tissues are fixed in 10% neutral buffered formalin (4% formaldehyde in phosphate buffered saline for light microscopy. For electron microscopy, the most commonly used fixative is glutaraldehyde. These fixatives preserve tissues or cells mainly by irreversibly cross-linking proteins. The main action of these aldehyde fixatives is to cross-link amino groups in proteins through the formation of methylene bridges (-CH2-), in the case of formaldehyde, or by a C5H10 cross-links in the case of glutaraldehyde. This process, while preserving the structural integrity of the cells and tissue can damage the biological functionality of proteins, particularly enzymes, and can also denature them to a certain extent. This can be detrimental to certain histological techniques.

9.3.2. Processing:

For light microscopy, paraffin wax is most frequently used. Since it is immiscible with water, the main constituent of biological tissue, water must first be removed in the process of dehydration. Samples are transferred through baths of progressively more concentrated ethanol to remove the water. This is followed by a hydrophobic clearing agent (such as xylene) to remove the alcohol, and finally molten paraffin wax, the infiltration agent, which replaces the xylene. Paraffin wax

does not provide a sufficiently hard matrix for cutting very thin sections for electron microscopy. Instead, resins are used. Epoxy resins are the most commonly employed embedding media, but acrylic resins are also used, particularly where immunohistochemistry is required. Thicker sections (0.35µm to 5µm) of resin-embedded tissue can also be cut for light microscopy. Again, the immiscibility of most epoxy and acrylic resins with water necessitates the use of dehydration, usually with ethanol.

9.3.3. Embedding

After the tissues have been dehydrated, cleared, and infiltrated with the embedding material, they are ready for external embedding. During this process the tissue samples are placed into molds along with liquid embedding material (such as agar, gelatin, or wax) which is then hardened. This is achieved by cooling in the case of paraffin wax and heating (curing) in the case of the epoxy resins. The acrylic resins are polymerized by heat, ultraviolet light, or chemical catalysts. The hardened blocks containing the tissue samples are then ready to be sectioned. Because Formalin-fixed, paraffin-embedded (FFPE) tissues may be stored indefinitely at room temperature, and nucleic acids (both DNA and RNA) may be recovered from them decades after fixation, FFPE tissues are an important resource for historical studies in medicine.

After the sufficient period of fixation and processing (determined by the histological laboratory) tissues sections are deparaffinated in xylene for 5 min twice, and then rehydrated with absolute ethanol for 3 min, 95 % ethanol for 3 min, and then in 70 % ethanol for 3 min. The sections are then placed in a methanol-hydrogen peroxide solution for 30 min to diminish the background level of peroxidase in the tissue. The sections are rinsed in water, next placed in buffered saline, and then the slide around the section is dried.

9.4. Histological analysis

9.4.1. Histopathological analysis

Routine staining with hematoxylin and eosin (H & E) or toluidine blue are recommended for light microscopy of soft tissues and bone. Hematoxylin, a basic dye, stains nuclei blue due to an affinity to nucleic acids in the cell nucleus; eosin, an acidic dye, stains the cytoplasm pink. Uranyl acetate and lead citrate are commonly used to impart contrast to tissue in the electron microscope. This analysis allows to identify soft tissue damage/destruction via metallosis, i.e., the build-up of corrosion products in tissues, bony destruction (osteolysis), giant cell activity,

9.4.2. Immunohistological analysis

These procedures can be used for identifying specific cell types and extracellular matrix tissue responses to implantable materials and prosthetic devices, in particular macrophage activity, white blood cell infiltration, blood cell death, and presence/absence of germinal centers. This field is constantly changing, and therefore only one such approach is provided as an example. We are looking for Lymphoid populations (B and T lymphocytes) and histiocytic macrophage population.

9.4.2.1. Lymphoid populations

Typical markers chosen are for the presence of immunoglobulins on lymphocytes to indicate B cells or on monocytes/macrophages to indicate activation, the presence of CD2 markers to indicate immature T cells, the presence of CD3 markers to indicate mature T cells, and markers to indicate activated macrophages. Then we can go further by distinguishing the populations of B and T lymphocytes (CD3 or CD20 markers). After sectioning, the slide is then placed in a humidity chamber, covered with buffer, and the first antibody is added. This will be the antibody specific for the marker (for example, CD2) and will be either of mouse or rabbit origin. This is incubated overnight, then rinsed with buffer, drained, and the slide around the tissue dried.

9.4.2.2. Histiocytic macrophage populations:

We apply the same protocol using CD68

10. Analysis of retrieved components – Stage 1: visual analysis,
General scheme of the retrieved components analysis:

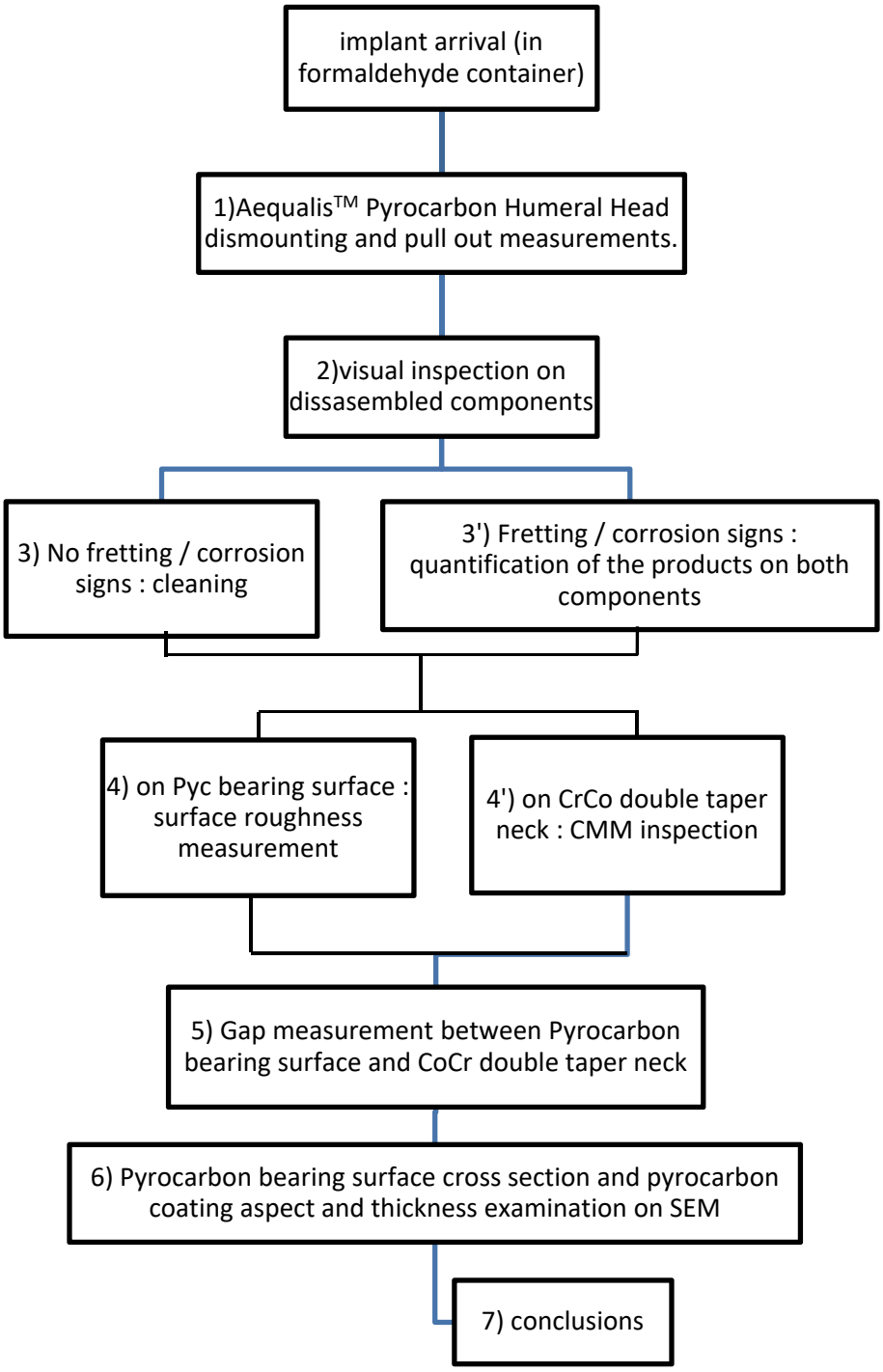

Figure 8: Retrieved Component Analysis

Note: Step 2 is a visual analysis, steps 1, 3, 3', 4, 4', and 5 are physical analysis, and step 6 is destructive analysis

Step 1: Aequalis™ Pyrocarbon Humeral Head dismounting and pull out measurements.

If the stem has been removed in the same surgical procedure than the head (case of loosening) i.e. the head is still fixed on the stem, then the pull out resistance between the Aequalis™ Pyrocarbon Humeral Head and the Aequalis™ Ascend ™ stem will be measured as follows:

A disassembly rate of **0,05 mm/sec** is applied to construct and the maximum load at p
'F1' is recorded.

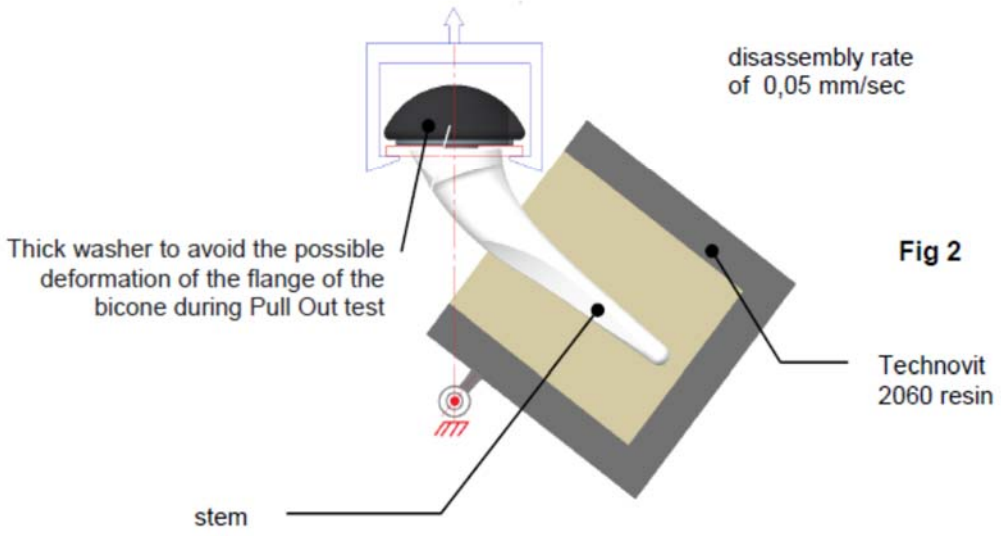

Figure 9: Head and Stem Pull Out Test

If the Aequalis™ Pyrocarbon Humeral Head has been retrieved separately from the Aequalis™ Ascend ™ stem, or when the Aequalis™ Pyrocarbon Humeral Head will have been dismounted from the Aequalis™ Ascend ™ stem following the previous protocol, the pull out resistance between the Pyrocarbon bearing surface and the CrCo double taper neck will be measured as follows :

Disassembly test is completed following ASTMF 2009-0 (§7) with a speed rate equal to **0,05 mm/sec** .

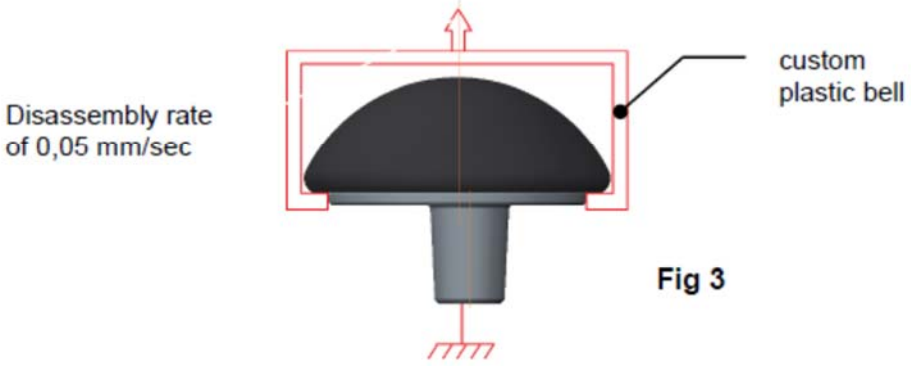

Figure 10: Pyrocarbon Bearing Surface and CrCo Double Taper Neck Pull Out Test

The curve load/displacement will be recorded. Particular attention will be paid not to damage the components during dismounting, particularly in the area of contact between Pyrocarbon bearing surface and CoCr double taper neck.

After pull out, the components are gently dried, with particular care to not touch area of possible fretting corrosion (area of contact between Pyrocarbon bearing surface and CoCr double taper neck)

Step 2: General visual inspection of the components.

The goal of this first step of visual inspection is to determine, before any further manipulation of the device, if there is the presence of wear, scratching, cracking or fretting/corrosion between Pyrocarbon bearing surface and CoCr double taper neck. The 2 retrieved components (Pyrocarbon bearing surface and CoCr double taper neck) will be examined on all surfaces. For detailed exam mapping, the schematic images should include a number of views of the components, including top and bottom views, with clear identification of areas of interest, such articular wear, transitional wear zones, light scratching, heavy scratching, cracking, substrate (graphite) exposure or wear-through, embedded particles, impingement, corrosion of either articular or modular surface, contamination/discoloration/staining areas, backside wear, front face/rim wear, surface pitting, taper wear/corrosion, tribochemical layers, etc. The above schematic images should be accompanied by a series of SEM images of areas of interest, importantly,

showing the location of where the images were taken. When pictures show some deposit on the surface, EDX exam will be executed to determine what is the physical nature of this deposit.

A particular attention will be paid to fretting-corrosion phenomenon, and the use of the scoring method described in Goldberg et al [1]. The grading will allow to graduate between 1 (none) to 4 (severe) the corrosion and fretting of the different parts as follows:

- None (score 1): No visible corrosion observed. No visible signs of fretting observed
- Mild (score 2) : <30% of taper surface discolored or dull. Single band or bands of fretting scars involving three or fewer machine lines on taper surface.
- Moderate (score 3) : >30% of taper surface discolored or dull, or <10% of taper surface containing black debris, pits, or etch marks. Several bands of fretting scars or single band involving more than three machine lines.
- Severe (score 4) : >10% of taper surface containing black debris, pits, or etch marks. Several band of fretting scars involving several adjacent machine lines, or flattened areas with nearby fretting scars.

Five scores will be established:

- One score for the morse taper of the CoCr double taper neck which was in connection with the stem (metal/metal connection);
- One score for the other morse taper of the CoCr double taper neck (which was in connection with the Pyrocarbon bearing surface);
- One score for the surface of the CoCr double taper neck which was in contact with the Pyrocarbon bearing surface (disk shaped surface);
- One score for the surface of the Pyrocarbon bearing surface which was in contact with the CoCr double taper neck surface (disk shaped surface);
- And one score for the female morse taper the Pyrocarbon bearing surface.

For the contact between Pyrocarbon and metal, the philosophy of the score will be used, but slightly adapted because of the difference of material and thus the difference of phenomenon that can appear (wording slightly different as colored surface instead of discolored surface).
Pyrocarbon bearing surface will thus benefit of 2 scores. CoCr double taper neck will benefit of 3 scores. All scores will be documented and reported with appropriate pictures.

Parts being scored at 1 (no corrosion) will proceed to step 3, and parts scored from 2 to 4 at even only one of their score will proceed to step 3' for quantification and qualification of metallic deposits on the parts.

11. Analysis of retrieved components and records – stage 2: physical analysis,

Step 3: Cleaning of parts having no fretting corrosion phenomenon.

Parts not featuring signs of fretting will be cleaned by ultrasonic bath in alcohol for 15mn, for future physical exams (step 4).

Step 3': Quantification of the fretting corrosion deposits on the components.

Parts being scored 2 to 4 at the fretting-corrosion scoring of step 2 will be treated as follows.

The aim of this study is to quantify the metals residue that can be found on the two components of the Aequalis™ Pyrocarbon Humeral Head after implantation.
The metals to be quantified are those produced by the possible damage of the CoCr double taper neck material, and visualized by EDX probe at step 2, i.e. Cobalt, Chromium, Manganese, Nickel and Molybdenum.

Each item is soaked in 50 ml of water and sonicated for 210 minutes, the solution is then diluted 1:2 and 1:10 to obtain values that fall into the range of the available standards for all the investigated metals. Solutions are evaluated by ICP-MS, and quantity of metal expressed in µg/component.

Step 4: surface roughness measurement on Pyrocarbon bearing surface
For implants that did not exhibited early loosening (<3 months), surface roughness measurements of the surface features of the Pyrocarbon bearing surface should include at least: average roughness (Ra), surface texture (Rz), maximum scratch height (Rp) and skewness (Rsk), plus be accompanied by close-up photographs for each measurement site to provide a visual indication of the amount of wear that took place and what wear processes were involved. At a minimum, surface roughness should be measured at sites of high polishing and obvious damage areas, i.e. (if applicable), 1) main wear zones, 2) areas of heavy scratching, 3) sites of impingement, 4) sites of corrosion, 5) sites of surface cracking, 6) sites of stripe wear, 7) backside wear and 8) coloration or staining.
Note: pyrocarbon bearing surface not being of a simple geometry, the wear assessment will be performed by measurement of the gap value (see step 5) for the assessment of the wear in the morse taper and by cross section of the part (see step 6) in all possible wear area.

Step 4': CMM inspection on CrCo double taper neck

For implants that did not exhibited early loosening (<3 months), then every effort should be made to estimate the total volumetric wear from the explanted CoCr double taper neck. A suggested technique includes a three-dimensional coordinate measuring machine

(CMM) to measure changes in component dimensions of both worn and unworn surfaces. Estimations of volumetric wear can then be determined using 3D modeling software.

Step 5: Gap measurement between Pyrocarbon bearing surface and CoCr double taper neck

Measurement of the Gap between Pyrocarbon bearing surface and CoCr double taper neck will be measured with the same or better accuracy than it had been measured before assembly of the parts in the clean room. Value obtained will be compared to the initial value recorded in the clean room. Any sign of limping or mismatch of the morse taper assembly will be recorded. Note: the gap will be measured with the parts positioned in the same dial orientation than they were before disassembly

12. Analysis of retrieved components – stage 3: destructive analysis,

Step 6: Pyrocarbon coating aspect and thickness examination on

After completion of all non-destructive tests and exams on both parts (Aequalis™ Pyrocarbon Humeral Head and CoCr double taper neck), a cross section of the Aequalis™ Pyrocarbon Humeral Head will be performed, perpendicular to the area of possible maximum wear. In case of doubt to situate this area, several cross sections will be performed. SEM pictures of this cross section will measure the PyC layer thickness, and compare it to the thickness of the layer right next to this contact area, in an area proven not be in contact. Thickness values will be compared, to calculate the possible worn thickness.

13. Determination of the mode and cause of failure.

Best efforts will be made to integrate all data given by the different exams to build a structured explanation of the mode and cause of fail.

14. Bibliography

[1] J. Goldber, J. Gilbert, J. Jacobs, T. Bauer, W. Paprosky and S. Leurgans, "A multicenter retrieval study of the taper interfaces of modular hip prostheses," *Clin Orthop Relat Res,* no. 401, pp. 149-164, 2002.