DePuy Synthes CLINICAL RESEARCH	
CLINICAL INVESTIGATION PLAN (CIP)	
Actis® Total Hip System 2-Year Follow-up	
Clinical Investigation Plan (CIP) Number:	14014
Country:	U.S.
CIP Prepared By:	PPD DePuy Synthes
CIP Version:	Version Date: May 7, 2018 Version B
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1 PROTOCOL SIGNATURE PAGE (PRINCIPAL INVESTIGATOR)

Actis® Total Hip System 2-Year Follow-up 14014

I have read this protocol and agree to conduct this clinical investigation plan in accordance with the design and specific provisions outlined herein.

I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practices, Declaration of Helsinki, applicable FDA regulations and ISO 14155 standards, local regulations, and the signed agreement with DePuy Synthes and with the protocol outlined herein.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who will assist in the conduct of this study. I will discuss this material with them to ensure they are fully informed regarding the device and the conduct of the study.

I will fulfill the requirements of my Institutional Review Board (IRB/REB/EC), or other oversight committee, to ensure complete and continual oversight of this clinical investigation.

I will use an Informed Patient Consent Document approved by DePuy Synthes and my reviewing oversight committee.

I agree to report all information or data in accordance with the protocol and I agree to report any serious adverse events as defined in this protocol to DePuy Synthes and my reviewing oversight committee.

I agree to permit DePuy Synthes, the IRB/REB/EC or other applicable regulatory authorities, direct access to all records, including source data/documents, relating to the clinical investigation, whether paper-based or electronic data capture (EDC).

The below signature confirms I have read and understood this clinical investigational protocol and its associated amendments or attachments, and will accept respective revisions or amendments provided by DePuy Synthes.

PRINTED OR TYPED NAME	**SIGNATURE**	**DATE**
Principal Investigator		

2 CONTENTS

3 TABLE 1 LIST OF APPENDICES

Table 1 List of Appendices	
Appendix	**Details**
A	Electronic Case Report Forms (eCRFs)
B	Informed Patient Consent Template
C	Surgical Technique
D	Radiographic Protocol
E	Device Product Codes for Actis® Total Hip System
F	References
G	Patient Activity Tracking Device and ActiTrack™ Application (app)

4 TABLE 2 STUDY SUMMARY

Table 2 Study Summary	
Title:	Actis® Total Hip System 2-Year Follow-up
Treatment Device:	Actis® Total Hip System (Featuring DUOFIX® Technology)
Control Device:	None: this is a non-comparative study

Table 2 Study Summary	
Title:	Actis® Total Hip System 2-Year Follow-up
Intended Use for Actis® Total Hip System:	Cementless Total Hip replacement is indicated in the following conditions: A severely painful and/or disabled joint from osteoarthritis, traumatic arthritis, rheumatoid arthritis, or congenital hip dysplasia. Avascular necrosis of the femoral head. Acute traumatic fracture of the femoral head or neck. Cementless Hemi-hip arthroplasty, or replacement, is indicated in the following conditions: Acute fracture of the femoral head or neck that cannot be appropriately reduced and treated with internal fixation. Fracture dislocation of the hip that cannot be appropriately reduced and treated with internal fixation. Avascular necrosis of the femoral head. Non-union of femoral neck fractures. Certain high sub-capital and femoral neck fractures in the elderly. Degenerative arthritis involving only the femoral head in which the acetabulum does not require replacement. Pathology involving only the femoral head/neck and/or proximal femur that can be adequately treated by hemi-hip arthroplasty. The Actis® Total Hip System has been optimized for use with the ***anterior approach*** (AA with broach only technique).
Primary Objective:	Two-year (2-year) information regarding the performance of the commercially available Actis® Total Hip System in order to obtain and evaluate the clinical outcomes on a series of cementless primary total hip arthroplasty (THA) and hemi-hip arthroplasty procedures using clinical, radiographic and device and procedure related adverse event assessments.
Study Design:	A prospective, uncontrolled, non-randomized, multicenter study. A total of 255 Subjects to include a minimum of 225 Primary THA Subjects and a cohort with a minimum of 30 hemi-hip arthroplasty Subjects will be prospectively enrolled into the study. All Subjects will be seen for a preoperative clinic visit at the time of consent, and evaluated at the time of surgery, 6 weeks, 3 months, minimum 1 year, and minimum 2-years postoperatively.

Table 2 Study Summary	
Title:	Actis® Total Hip System 2-Year Follow-up
Number of Sites:	A minimum of 10 study sites will participate. Any one site may not enroll more than 40 Subjects (inclusive combination of both THA and hemi-hip arthroplasty Subjects) after reallocation from low enrollment sites, which will ensure that in a worst-case scenario, a minimum of 4 sites must contribute enrollment to the final sample size to represent variability across surgeons.
Subject Population:	Subjects at participating sites who meet the inclusion/exclusion criteria for this study.
Sample Size:	Sites will prospectively enroll a total of 255 Subjects to include a minimum of 225 Primary THA Subjects, and a cohort of a minimum of 30 hemi-hip arthroplasty Subjects.
Study Duration:	The anticipated duration of this investigation is approximately 3- to 4-years from the time of study initiation given that: • It may take up to 1-year from the time of study initiation to enroll total hip arthroplasty Subjects. It is expected that the hemi-hip arthroplasty cohort may take longer than 1-year to enroll. • Each Subject will be followed until they have completed their minimum 2-year follow-up. • The study will be closed when all Subjects have completed minimum 2-year follow-up.

Table 2 Study Summary	
Title:	Actis® Total Hip System 2-Year Follow-up
Primary, Secondary and Tertiary Endpoints:	**Primary endpoint:** Harris Hip Score at minimum 2-years postoperatively. **Secondary endpoints:** • Harris Hip score at 3-months and 1-year • Radiographic evaluation at 2-years postoperatively, inclusive of leg length discrepancy • Type and frequency of device and procedure related AEs through 2-years postoperatively • Device survivorship at 2-years postoperatively **Tertiary endpoints:** • Change in Subject Outcomes (*i.e.,* FJS-12, HOOS and Subject Hip Evaluation) will be measured and compared from preoperative to 6-weeks, 3-months, minimum 1-year and minimum 2-years. • Study Sites will be given the opportunity to participate in a non-required parallel activity (to collect tertiary outcomes) of this study, specifically, "Patient Activity Tracking". • At the participating study sites, Subjects choosing to participate in Patient Activity Tracking will wear a device that looks somewhat like a wrist watch. The Patient Activity Tracking device will link via a downloaded mobile application (app) (*i.e.,* ActiTrak™) to the Subject's smartphone (*i.e.,* iPhone or Android phone) or to a Sponsor provided Android tablet. Any Sponsor provided Android tablet will be for study use only in order to provide pre-populated passive and actively reported Subject activities such as Pain, Location of Pain, Mood/Emotion, Activities of Daily Living, and Range of Motion from the time of consent preoperatively through 3 months postoperatively. After surgery, there will be question about Subject Satisfaction periodically. Any Sponsor provided Android tablet will be returned to the Sponsor at the 3-month follow-up interval or at any premature study termination after consent and enrollment.

Table 2 Study Summary	
Title:	Actis® Total Hip System 2-Year Follow-up
Procedure Schedule:	Subjects will be seen at the following intervals: preoperative, operative, 6-weeks, 3-months, minimum 1-year, and minimum 2-years postoperatively.
Safety:	Only device or procedure related adverse events (AEs) for enrolled Subjects are to be reported.

5 TABLE 3 DEFINITION OF TERMS

Table 3 Definition of Terms	
Term	**Definition**
ActiTrak™ Application (app)	A mobile application (app) is a computer program designed to run a mobile device, such as a smartphone (*e.g.,* iPhone or Android phone) or tablet. For the purposes of this study the ActiTrak™ app will link the mobile Patient Activity Tracking device (the watch-like device that some Subjects may choose to wear in the study) to the study database.
Android Tablet	An Android tablet is a tablet-sized (small) personal computer (PC) that runs on Google's Android operating system (OS). Android tablets include almost all the key features found in a regular PC, including office applications, games, Web browsers and many other programs. For the purposes of this study, an Android tablet will be used to download the ActiTrak™ application to capture passive and active patient activities. (Reference: http://www.techopedia.com/definition/25194/android-tablets).
Activity of Daily Living (ADLs)	Activities of Daily Living: a term used in healthcare to refer to daily self-care activities within an individual's place of residence, in outdoor environments, or both.
Clinical Investigation Plan (CIP)	The CIP is a written document describing how the clinical investigation will be conducted. It includes the rationale, objectives, design and proposed analyses, methodology, monitoring, conduct and record-keeping of the clinical investigation. Clinical investigation is interchangeable with the term 'study'.
Code of Federal Regulations (CFR)	The CFR is the set of US FDA regulations that governs activities regulated by the FDA.
Date of Surgery (DOS)	Acronym for the actual date that surgery occurs – DOS.

Electronic Case Report Form (eCRF)	A computerized system designed for the collection of data in electronic form.
Ethics Committee (EC)	Alternate term for Institutional Review Board (IRB) or Research Ethics Board (REB) - see below.
Electronic Data Capture (EDC)	A system designed for the collection of clinical data in electronic format. The EDC system that will be used in this clinical investigation has been validated in accordance with 21 CFR Part 11, European Commission's Directive on Data Protection and US Safe Harbor Certification.
Food and Drug Administration (FDA)	The US FDA is an agency within the Department of Health and Human Services. The FDA is responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, US food supply, cosmetics, and products that emit radiation.
Forgotten Joint Scale (FJS-12)	A patient reported outcome (PRO) tool to provide a more patient-centered view on treatment outcome. The goal of this tool is to assess a patient's ability to forget the artificial joint in everyday life.
Good Clinical Practice (GCP)	A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical studies that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial Subjects are protected.
Harris Hip Score (HHS)	Harris Hip Score (HHS) questionnaire is a tool used to assess the results of hip surgery and is intended to evaluate various hip disabilities. The HHS is a clinical-based outcome measure administered by a qualified health care profession, such as the Principal Investigator (PI) or Sub-Investigator (SI).
Health Insurance Portability and Accountability Act (HIPAA)	Federal legislation, applicable to US sites, Title II of which (in this context) is intended to help people keep their information private, and to address the security and privacy of health data. The legislation requires the establishment of national standards for the handling of health care information.
Hip Disability and Osteoarthritis Outcome Score (HOOS)	A 40-item questionnaire that is used to assess patient-relevant outcomes in five separate subscales (pain, symptoms, activity of daily living, sport and recreation function and hip related quality of life). The HOOS is a patient reported outcome (PRO).
Informed Patient Consent Document (IPC)	An explanation of all relevant aspects and risks of the proposed study, provided in appropriate language so that the Subject can understand and determine whether they wish to participate. See ISO 14155 and 21CFR50.
Independent Radiographic Reviewer (IRR)	An IRR will be used to review radiographic outcomes to help minimize bias in radiographic evaluations.

Institutional Review Board (IRB)	Institutional Review Board (IRB) is a board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of biomedical research involving human Subjects. The primary purpose of such review is to assure the protection of the rights, safety, and welfare of human Subjects. The IRB should be established, operated, and function in conformance with 21 CFR 56. The term has the same meaning as "institutional review committee" in section 520(g) of the FD&C Act or "Ethics Committee" in other jurisdictions. Internationally, this entity may be referred to as an Ethics Committee (EC) or Research Ethics Board (REB).
Investigator's Site File (ISF) (or the Site's Study Binder)	Binder provided to the Principal Investigator by the Sponsor and maintained by the Investigational Site. The binder includes regulatory documents, IRB/REB/EC documents, correspondence, Investigator's responsibilities, study protocol correspondence, Investigators Curriculum Vitae (CV), and other contents deemed applicable by the Sponsor.
International Standard ISO 14155	ISO (the international Organization for Standardization) is a world-wide federation of national standards for clinical investigation of medical devices for human subjects. ISO14155 addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes.
Patient Activity Tracking	Patient Activity Tracking, for the purposes of this study, is a mobile, wearable watch-like device, will be used to gather passive and actively reported aspects of Subject recovery, pain management, activities of daily living (ADLs) and function directly from participating Subjects from the time of consent preoperatively through 3-months postoperatively. A smartphone (*e.g.,* Android or iPhone) is required to receive the download of the ActiTrak™ mobile application (app). If a study Subject wants to participate and does not have a smartphone, the Sponsor can provide an android type tablet for study use only that will be returned at the 3-month postoperative visit.
Clinical or Principal Investigator (PI), or Investigator	Clinical Investigator is interchangeable with Principal Investigator (PI) and/or Investigator and is the individual at an Investigational Site qualified by training and experience who has overall responsibility for the conduct of a clinical investigation at that Site. This individual supervises the Site's team and is responsible for authorizing and delegating duties.
Research Ethics Board (REB)	Alternate term for Institutional Review Board (IRB) or Ethics Committee (EC) - see above.

Source Documents	Original documents, data and records (*e.g.* hospital records, clinical and office charts, laboratory notes, radiographs, other Subject information, etc.) that document Subject care and associated procedures in a clinical investigation. Also, called Source Documentation.
Sub-Investigator (Sub-I)	The Sub-Investigator (SI) is an individual at an investigational site qualified by training and experience to carry out the protocol, and whose activities relative to the protocol are supervised by the PI.

6 SUBJECT MANAGEMENT STUDY SCHEDULE

e-CRF Name	Event / Visit	Pre-op		Operative	6 Week	3 Month	Minimum 1 Year	Minimum 2 Year
		-180 to DOS	-90 to DOS	Day 0	28-70 d	71-132 d	304-668 d	669-1763 d
N/A	Complete Screening Log		✓					
N/A	Obtain Informed Subject Consent		✓					
N/A	Verify Inclusion / Exclusion Criteria		✓					
eCRF DM	Subject History		✓					
eCRF HH	Harris Hip		✓		✓	✓	✓	✓
eCRF HE	Hip Evaluation		✓		✓	✓	✓	✓
eCRF HOOS	HOOS		✓		✓	✓	✓	✓
eCRF FJS	Forgotten Joint Scale (FJS-12)				✓	✓	✓	✓
eCRF SG	Operative Details (Total or Hemi)			✓				
eCRF DX	Device Log			✓				
eCRF PA	Patient Activity Tracking (ActiTrak™) This Optional portion of the study was completed upon the enrollment of 225 THAs (*i.e.*, June 5, 2017)		✓	✓	✓	✓		
eCRF UNS	Unscheduled Visit Report * (Interim Visit)				✓	✓	✓	
eCRF AE	Adverse Event			✓	✓	✓	✓	✓
eCRF DS	End of Study (Withdrawal) Form**				✓	✓	✓	✓
Operative Side Radiographs	*AP Femur*	✓			✓	✓	✓	✓
	Lauenstein Lateral	✓			✓	✓	✓	✓
	AP Pelvis (for leg length discrepancy)	✓			✓	✓	✓	✓
N/A	Advise Subject of next visit		✓	✓	✓	✓	✓	

***To be completed, as applicable, when Subjects return for an unplanned or unscheduled visit between the protocol-defined windows.**
****The End of Study /Withdrawal Form to be completed for all Subjects to document a premature withdrawal or designate end of study/minimum 2-year final endpoint has been completed.**

7 INTRODUCTION

Hip replacement, or arthroplasty, is a surgical procedure in which the diseased or damaged parts of the hip or hip joint are removed and replaced with prosthetic implants in the proximal femur (stem) and the acetabulum (cup or shell). The most common reason that people have hip replacement surgery is the wearing out of the hip joint as a result of osteoarthritis. Other conditions, such as rheumatoid arthritis (a chronic inflammatory disease that causes joint pain, stiffness and swelling), avascular necrosis (loss of bone caused by insufficient blood supply), injury (such as fracture), and bone tumors also may lead to breakdown of the hip joint and the need for hip replacement surgery.

Hip replacement surgery is a reproducible surgical procedure with long-term implant survival. The Actis® Total Hip System is designed to include total hip replacement surgery and is an implant optimized for the anterior (surgical) approach. The anterior approach is a muscle sparing approach, which may allow for faster patient recovery, less pain and complications after surgery, better component placement, and the potential for lower postoperative dislocation and leg length discrepancies. The anterior approach can be performed on a standard operating or fracture table or with the use of a specialized orthopaedic table (*e.g.* HANA Table) that facilitates femoral exposure.

The Actis® Total Hip System is designed to also include hemi-hip (Hemi) arthroplasty, a surgical procedure which replaces one half of the joint with an artificial surface and leaves the other part in its natural (preoperative) state. This class of procedure is most commonly performed on the hip after a sub-capital (just below the head) fracture of the neck of the femur (a hip fracture). The procedure is performed by removing the head of the femur and replacing it with a metal hip prosthesis (or hip stem).

The Actis® Total Hip System consists of a wide range of stem neck designs and sizes allowing an accurate anatomical match for each patient. A list of compatible femoral heads and acetabular cup components are listed in **Appendix E.**

The following information describes the study to be conducted for Actis® Total Hip System. The demonstration of the stability and performance specific to the Actis® Total Hip System medial collared DUOFIX® hip stem is important to survivorship and efficacy of this hip system.

8 RATIONALE

The purpose of this study is to gather information regarding the function, performance and safety of the Actis® Total Hip System (Featuring DUOFIX® Technology).

This is not a hypothesis driven study. Instead it is designed to evaluate clinical outcomes (*i.e.,* Harris Hip Score) with an adequate margin of error, radiographic outcomes and an estimate of device survivorship (please also refer to **Section 16).**

8.1 Duration of Study

The estimated duration of the overall clinical study is 3-years: 1-year for enrollment and 2-years for postoperative follow-up. Although, it is expected that the hemi-hip arthroplasty cohort may take longer than 1-year to enroll. At the minimum 2-year visit, an End of Study eCRF will be completed for every study Subject who has not been prematurely withdrawn, and study participation will conclude.

9 SUBJECT DEFINITION

9.1 Subject Population

For the purpose of this study, a "Subject" is defined as an individual who participates in the study as a recipient of the product (*i.e.,* Actis® Total Hip System). Note: before Informed Patient Consent is obtained, a Subject may be referred to as a "patient".

9.2 Subject Screening

All patients who present for cementless primary total hip arthroplasty (THA) or a hemi-hip arthroplasty who generally meet the study requirements are potential candidates. Potential study patients should be screened for eligibility and listed on the Screening and Enrollment Log (to be provided by the Sponsor) in order to document that the patient selection was unbiased. The date of screening, the results of patient screening (included or not) and the primary reason for not including the patient (*e.g.*, does not satisfy eligibility criteria) will be recorded on this log. Acceptance or declination of participation in the optional Patient Activity Tracking will also be captured on this log. The original log is to be retained at the Site and a copy sent to the Sponsor regularly during enrollment.

9.3 Subject Eligibility (Inclusion and Exclusion Criteria)

The eligibility criteria for inclusion into this clinical investigation are consistent with the approved labeling for the Actis® Total Hip System. Subjects qualify for treatment with the Actis® Total Hip System if they sign consent, and meet inclusion criteria and none of the exclusion criteria described below. Subjects who have qualified for study treatment will also have the opportunity to participate in the parallel and optional Patient Activity Tracking portion of the study. Declining participation in Patient Activity Tracking will not preclude the study Subject from otherwise participating as long as all other eligibility criteria are met. Specific information regarding the Patient Activity Tracking device and the ActiTrak™ mobile application are provided in **Appendix G** and is also disclosed in the informed patient consent (IPC) document (**Appendix B**).

The femoral stem component of the Actis® Total Hip System is optimized for use with the Anterior Approach (AA). However, if an *eligible Subject* has an implantation of the Actis® Total Hip System femoral stem and an anterior surgical approach (AA) has not been utilized the Subject will remain a study Subject and be followed per protocol. These non-anterior approach data will be analyzed as a cohort population.

Subjects who have an existing contralateral total hip replacement ***greater than 6 months*** postoperatively at the time of consent may be entered into this study if they qualify based upon the eligibility criteria and the approved labeling requirements. Simultaneous or staged bilateral patients utilizing the Actis® Total Hip System, or any hip system, are **not** allowed in this study (see **Exclusion Criterion #8**).

9.4 Inclusion Criteria:

The Actis® Total Hip System is indicated for cementless use only, and this is as noted in the package labeling (*i.e.,* Instructions for Use/IFU will be in each Actis® Total Hip System package). Subjects must meet at least one inclusion criterion for *either* total or hemi-hip arthroplasty.

Total primary hip replacement is indicted in the following conditions:

1. A severely painful and/or disable joint from osteoarthritis, traumatic arthritis, rheumatoid arthritis, or congenital hip dysplasia.
2. Avascular necrosis of the femoral head.
3. Acute traumatic fracture of the femoral head or neck.
4. Certain cases of ankylosis.

Hemi-hip arthroplasty is indicated in the following conditions:

5. Acute fracture of the femoral head or neck that cannot be appropriately reduced and treated with internal fixation.
6. Fracture dislocation of the hip that cannot be appropriately reduced and treated with internal fixation.
7. Avascular necrosis of the femoral head.
8. Non-union of femoral neck fractures.
9. Certain high sub-capital and femoral neck fractures in the elderly.
10. Degenerative arthritis involving only the femoral head in which the acetabulum does not require replacement.
11. Pathology involving only the femoral head in which the acetabulum does not require replacement.

    Modular Femoral Heads and Acetabular Components: A DePuy modular femoral head is to be used with the DePuy femoral stem component. The acetabulum is to be replaced with a DePuy 2-piece metal-backed Ultra High Molecular Weight Polyethylene (UHMWPE) or all UHMWPE acetabular cup component with an inside diameter corresponding to the outside diameter of the modular femoral head that is utilized.

    Warning: Use only DePuy modular femoral heads with DePuy femoral stems. The taper size of the femoral head **MUST** be matched to the taper size of the femoral stem.

Further inclusion criteria for individuals who, in the opinion of the Principal Investigator, are suitable candidates for using the devices specified in this protocol and they are as follows:

12. Individuals who can speak, read, and comprehend the informed patient consent (IPC) document, which is in English, and be willing and able to provide informed patient consent for participation in the study and have authorized the transfer of his/her information to DePuy Synthes.
13. Individuals who are willing and able to return for follow-up as specified by the study protocol.
14. Individuals who are a minimum age of 21 years at the time of consent.
15. Individuals who are not bedridden:
    - The intent of "not bedridden" means a permanent situation, not a temporary situation as in a hip fracture or trauma case.
16. Individuals who are willing and able to complete the Subject Hip Outcomes questionnaires (*i.e.,* FJS-12, HOOS and Hip Evaluation) as specified by the study protocol.

9.5 Exclusion Criteria:

Subjects will be excluded if in the opinion of the Investigator, the individual meets any of the following exclusions:

1. Active local or systemic infection.
2. Loss of musculature, neuromuscular compromise or vascular deficiency in the affected limb rendering the procedure unjustified.
3. Poor bone quality, such as osteoporosis, where in the surgeon's opinion, there could be considerable migration of the prosthesis or a significant chance of fracture of the femoral shaft and/or the lack of adequate bone to support the implant(s).
4. Charcot's or Paget's disease.
5. For hemi-hip arthroplasty, any pathological condition of the acetabulum, such as distorted acetabuli with irregularities, protrusion acetabuli (arthrokatadysis), or migrating acetabuli, that would preclude the use of the natural acetabulum as an appropriate articular surface for the hemi-hip prosthesis.
6. The Subject is a woman who is pregnant or lactating.
7. Existing contralateral hip that was implanted *less than* 6 months from the date of surgery at the time of consent into this study.
8. Subjects requiring a **simultaneous** bilateral hip at the time of consent will be excluded; there can be only one Actis® study hip. This also means that even if another hip system is used for the contralateral hip during simultaneous THAs, the Subject will be excluded. As noted above, Subjects who have an existing contralateral total hip replacement ***greater than***

6 months postoperatively at the time of consent may be entered into this study if they qualify based upon the eligibility criteria and the approved labeling requirements.

9. Subject had a contralateral amputation.
10. Subject has participated in a clinical investigation with an investigational product (drug or device) in the last three months.
11. Subject is currently involved in any personal injury litigation, medical-legal or worker's compensation claims regardless of body system.
12. Subject, in the opinion of the Investigator, is a drug or alcohol abuser or has a psychological disorder that could affect their ability to complete patient reported questionnaires or be compliant with follow-up requirements.
13. Subject was diagnosed and is taking prescription medications to treat a muscular disorder that limits mobility due to severe stiffness and pain such as fibromyalgia or polymyalgia.
14. Subject has a medical condition with less than 2 years of life expectancy.

    Note: Diabetes, at present, has not been established as a contraindication. However, because of the increased risk for complications such as infection, slow wound healing, etc., the physician should carefully consider the advisability of hip replacement in the severely diabetic patient.

    Caution: Implants and trial components from different manufacturers or implant systems should never be used together.

9.6 Enrollment & Subject Identification (ID) Number

A study Subject is *enrolled* when they have been properly consented. Once consent is obtained, the Subject must be added to the study electronic data capture (EDC) system, which will automatically generate a unique Subject number. The first two digits of the Subject number represent the site identification number, followed by a hyphen, and three digits representing the sequential identification (*e.g.,* Subject 10-001 is the first subject enrolled at site 10). The Subject's unique identifier assigned in EDC will be recorded on each page of the eCRF and all other clinical investigation documentation relating to that Subject.

Study-specific Subject questionnaires should not be completed until the study Subject has signed and dated the Informed Consent Document *and* has met all other eligibility criteria. Additionally, a Subject must meet the eligibility criteria in order to participate in the optional Patient Activity Tracking (ActiTrak™) part of the study.

The Principal Investigator must document the Subject's participation in this study in the Subject's clinic and hospital notes.

10 OBJECTIVE AND ENDPOINTS

10.1 Primary Objective

Two-year (2 year) information regarding the performance of the commercially available Actis® Total Hip System in order to obtain and evaluate the clinical outcomes on a series of cementless primary total hip arthroplasty (THA) and hemi-hip arthroplasty using clinical, radiographic and device and procedure related adverse event assessments.

10.2 Primary Endpoint

Investigate the minimum 2-year postoperative functional performance for the Actis® Total Hip System as measured with the Harris Hip Score at minimum 2 years postoperatively for cementless primary total hip arthroplasty. All analyses including the primary endpoint analysis will be conducted on primary THA subjects and a summary for hemi-hip arthroplasty Subjects will be provided separately.

10.3 Secondary Endpoints

- Harris Hip score at 3-months and 1-year
- Radiographic evaluation at 2-years postoperatively, inclusive of leg length discrepancy
- Type and frequency of AEs through 2-years postoperatively
- Device survivorship at 2-years postoperatively

10.4 Tertiary Endpoints

- Change in Subject Outcomes (*i.e.,* FJS-12, HOOS and Hip Evaluation) will be measured and compared from preoperative to 6-weeks, 3-months, minimum 1-year and minimum 2-years.
- Patient tracking activities reported from the mobile ActiTrak™ application will be analyzed for pain, location of pain, mood/emotion, and activities of daily living and range of motion. Subject Satisfaction will be asked periodically after surgery. The range of time for these tertiary endpoints will be from the time of consent preoperatively through 3-months postoperatively.

10.5 Study Design

A prospective, uncontrolled, non-randomized, multi-center study with a total of 255 Subjects to include a minimum of 225 Primary THA Subjects and a cohort with a minimum of 30 hemi-hip arthroplasty Subjects. All Subjects will be seen for a preoperative clinic visit at the time of consent, during surgery, and then at 6-weeks, 3-months, minimum 1-year, and minimum 2-years postoperatively.

Each site is expected to implant the number of Subjects as outlined in their clinical trial agreement; however, cohort reallocation (no greater than 40 Subjects per site) is permitted in order to meet timelines. Details regarding sample size are presented in **Section 16.9.**

10.6 Optional (Electronic) Patient Activity Tracking Device

This clinical investigation will provide the opportunity for Subjects who are properly consented and deemed eligible for the study to join in a parallel and optional portion of the study – to electronically capture real-time patient activities of daily living (such as pain, location of pain, mood/emotion, activities of daily living and range of motion, Subject satisfaction will periodically be asked after surgery) from the time of consent preoperatively to 3-months postoperatively. If a Subject is unable or unwilling to provide the preoperative data, this will not preclude or delay them from enrollment. Subjects may also enroll in the Patient Activity Tracking on the day of their surgery and collect activities through the 3-month postoperative visit interval. This optional part of the study will be open for enrollment until 225 THA Subjects are treated; then, this part of the study will be closed. The fulfillment of 225 THA Subjects occurred June 5, 2017 and this portion of the study has now concluded with Version B of the protocol.

Patient Activity Tracking is a combination of a wearable watch-like device and a mobile application, specifically, the ActiTrak™ application. The wearable watch-like Patient Activity Tracking device will be linked (*i.e.,* electronically synced) to a downloaded mobile application (app) on the Subject's own well-functioning (and updated to the most current operating system version) smartphone. If the Subject does not have a smartphone the Sponsor can provide an Android tablet to help Subjects continuously track their postoperative outcomes in their natural environment, in real-time, and in a non-invasive manner. This type of patient direct data collection can improve data quality and method of collection and is potentially more sensitive to the changes in activities preoperatively compared to postoperatively (*e.g.*, not burdensome or possibly inconclusive like a paper diary).

Study sites and study Subjects are not required to join in the optional portion of the study.

For those eligible study Subjects who chose to participate, the wearable Patient Activity Tracking device will be provided to them by the study site (which has been provided by the Sponsor) and will be returned at the 3-month visit. The mobile ActiTrak™ app will linked to their smartphone (or the Sponsor provided Android tablet as noted above) via a downloaded mobile app. The linking of the Patient Activity Tracking device to the ActiTrak™ app on a smartphone or Android tablet is required in order for the collected data to securely import into the study's EDC system.

The combination Patient Activity Tracking device and the ActiTrak™ app will be used to passively (automatically) as well as objectively (manual or active Subject entries into a downloaded mobile application on either a smartphone or Android tablet) in order to collect activities of daily living. Some questions will occur weekly and others only monthly. **Appendix G** provides guidance and support for study sites and Subjects.

10.7 Study Database

The study database has been validated in accordance with 21 CFR Part 11, European Commission's Directive on Data Protection and US Safe Harbor Certification. Prior to being released for importation of patient activity and study data, validation of the study level components will be conducted in

accordance with approved user acceptance testing procedures. Access to this system will be controlled so that only authorized users will have the ability to enter into the system. The system is considered a closed system according to 21 CFR Part 11 Electronic Records; Electronic Signatures.

10.8 Treatment Assignment

The Actis® Total Hip System is the only construct of interest in the study; there will be no control group. This is applicable to the treatment of both total and hemi-hip arthroplasty.

11 RADIOGRAPHS

This study will accept radiographs for the preoperative interval taken prior to the study Subject's participation in this study up to -180 days before surgery as long as the radiographs meet the three protocol required views: Antero-Posterior (AP) Pelvis, AP Femur and Lauenstein Lateral. The -180 days preoperative is allowed to minimize a study Subject's unnecessary exposure to radiation. Further radiographic details are provided in **Appendix D.**

Leg length discrepancy (LLD) will be recorded by the independent radiographic reviewer (IRR) via the radiographs on the Hip Evaluation eCRF (and, optionally by the Principal Investigator, See **Section 16.12** Secondary Endpoints).

12 SUBJECT EVALUATIONS

12.1 Summary of Subject Evaluations

Diagnostic, demographic and operative information, clinical follow-up and applicable unscheduled (*i.e.,* unplanned or unscheduled that occur between the protocol defined visit windows) visits for each enrolled Subject will be documented on electronic case report forms (eCRFs) which have been developed specifically for this study. Subject completed Patient Reported Outcomes or PROs will be completed on source by the study Subject and then entered by the study site into the EDC system. The eCRF details that are to be used to collect and evaluate study Subject outcomes preoperatively, intra-operatively and postoperatively are listed below in **Table 4.** Patient reported outcomes (shaded in light blue) will be provided in hard copy (*i.e.,* paper) printed sets for completion by the study Subject during the clinic visit. Study sites should not enter any data into the EDC system until each potential patient has signed consent and is considered enrolled (**Section 15** defines the consent process and **Section 9.1** defines the Subject population).

12.2 Table 4 Summary of Subject Evaluation and eCRFs

Table 4 Summary of Subject Evaluations and eCRFs	
Subject History **eCRF DM**	Demographic and study entry criteria are documented on Subject History. The preferred timing of the Informed Consent process and preoperative data collection (with the exception of the preoperative radiographs – see **Section 11**) is from -90 to -1 days of the surgical event.
Harris Hip Evaluation **eCRF HH**	The Harris Hip Evaluation will be used to clinically assess each Subject at the preoperative and postoperative intervals specified in **Section 6 Subject Management Study Schedule.** Contained in Section H, Leg length, of the eCRF HH there is an **OPTION** to provide a measurement of each leg (surgical and non-surgical) pre- and postoperatively. This option applies to both cohorts: THA and hemi-hips. If manual leg length measurements are taken, there are checkboxes in Section H to record the measurement method: "Apparent", "True" and "Other". The "Apparent" manual method is measured using a tape measure from the umbilicus to the medial malleolus. The "True" manual method is measured using a tape measure from the anterior superior iliac spine to the medial malleolus (Sabharwal). "Other" consistent and repeatable LLD measurements are acceptable as per each study sites' standard of care. If leg length is manually measured and reported pre-operatively for a Subject, please be consistent and collect it for the entire study for analysis. Leg length discrepancy (LLD) will be analyzed (**Section 16.12**) as a secondary endpoint.
Hip Evaluation **eCRF HE**	Subjects will complete a hip outcomes self-assessment, which includes questions about their satisfaction and hip function starting at the preoperative interval.
HOOS **eCRF HOOS**	Subjects will complete this hip outcomes self-assessment, which includes 40 questions about their activities of daily living and more advanced sports and recreational activities starting at the preoperative interval.

Forgotten Joint Scale (FJS-12) **eCRF FJS**	Subjects will complete this hip outcomes self-assessment, which includes 12 questions about their awareness of their (operative) hip joint and their ability to 'forget' the artificial joint in everyday life.
Pre- and Postoperative Hip Radiographic **No eCRF for Study Site**	Radiographic guidelines are provided in **Appendix D.** High quality Antero-Posterior (AP) Femur, AP Pelvis and Lauenstein Lateral radiographs of the operative hip will be obtained during the same preoperative and postoperative follow-up intervals as for the clinical evaluations. All original radiographs will be retained by the site and digital copies will be sent to the Sponsor through a web-based application. Alternate methods to submit radiographs to Sponsor must be pre-arranged. Analysis of the radiographs by an Independent Radiographic Reviewer (IRR) will involve the use of a web-based application. *Observations by the IRR will be documented on the radiographic eCRF (radiographic eCRF is not provided to study sites) and entered into the study radiographic database by the IRR.*
Operative Details **eCRF OP**	For all Subjects, detailed information related to the primary diagnosis, anesthesia type and time, if a fracture table (*e.g.,* HANA Table) was utilized, and surgical exposure (*e.g.,* anterior approach), and other surgical data will be recorded on the Operative Details eCRF – this includes primary total hip arthroplasty and hemi-hip arthroplasty.
Device Log **eCRF DX**	Labels for each component/device used during the procedure must be recorded.
Unscheduled Visit Report (unplanned or interim) **eCRF UNS**	An unscheduled office visit is defined as any visit at the study site where a study subject is seen by one of the site staff including the principal Investigator (PI), any Sub-investigator (as appropriate), and anyone identified on the PI's team, outside of the scheduled study visit. An unscheduled visit is only to be reported when the visit falls between study intervals as described in **Section 6 Subject Management Study Schedule**. **An unscheduled visit eCRF is not to be completed if the Subject comes in for additional, unplanned visits within the in-window study interval.** If the previous protocol defined study interval visit was missed, the required eCRFs/CRFs in the previously missed interval visit are also required along with the unscheduled visit eCRF.

	If an unscheduled visit is related to a new, worsening, or resolved adverse event, both an AE eCRF and the unscheduled visit eCRF are completed.
Adverse Event (AE) eCRF AE	In the event of a postoperative AE the details will be captured on an AE eCRF. Only one AE can be recorded on an AE eCRF. An AE can be defined as Mild, Moderate or Severe and these terms are defined in **Section 13** (The definitions of Serious Adverse Event and Unexpected Adverse Device Event or UADE are defined in **Section 13**). For a worsening AE, please resolve the previous AE on eCRF and report a "New" AE eCRF for the new Severity.
Patient Activity Tracking (ActiTrak™) **eCRF PA**	The Patient Activity Tracking device is a wearable watch-like device that will be linked with the ActiTrack™ app that is downloaded on to a Subject's own smartphone (iPhone or Android phone, or Sponsor provided Android tablet) and will be used at some sites. It is not mandatory for a study site or a study Subject to participate. For details on the Patient Activity Tracking device *(i.e.,* the wearable watch-like device) and the required downloaded mobile app, refer to **Appendix G**. Preoperatively at from the time of consent through 3 months postoperatively is the preferred timeline for participation. Data collected via the Patient Activity Tracking is a part of the tertiary endpoints (**Section 16)**.
End of Study/ Withdrawal **eCRF DS**	Please complete the End of Study eCRF when a study Subject has either completed the study primary endpoint (2-year follow-up) or for any reason for withdrawal; some examples are listed below: • Withdrawal of consent • Investigator decision • Death (correlate with AE eCRF) • Lost to follow-up • General screen failure (includes intra-operative screen failures) • Study site withdrew/terminated from study • Adverse event related (including revisions postoperative, correlate with AE eCRF) • Other reasons – specify • Revision (correlate with AE eCRF) • Completion of final endpoint at minimum 2 years

	NOTE: AE eCRF will be completed for only ***device and procedure related*** *AEs. For further details and directions regarding revision of any study component please also refer to* ***Table 8 Revisions and Reoperations****.* All screen failures (SFs) are to be reported on the **Screening and Enrollment Log** (Log will be provided by the Sponsor).

12.3 Actions for Screen Failure Subjects

Subjects can be a screen failure prior to surgery (*e.g.,* withdraw of consent) or be considered a screen failure when withdrawn intra-operatively; intra-operative screen failure could be due to the Subject requiring a non-study implant. **Table 5** below provides further examples of screen failures and required actions.

12.4 Table 5 Actions for Screen Failure Subjects

Table 5 Actions for Screen Failure Subjects
(Based on the definition of an Enrolled Subject in Section 9)

Screen Failure Type	Screening/ Enrollment Log?	Data submitted To EDC?	Enrolled Subject?	Example	Action
Pre-operative screen failure	Yes	Yes	Yes	Subject signed IPC, meeting the definition of enrolled, but has withdrawn consent before surgery or no longer meets inclusion/exclusion criteria at time of surgery	Document on Screening & Enrollment Log as Preoperative Screen Failure Complete & enter Preoperative eCRFs if data was collected: DM, HH, HE, HOOS and DS

Intra-operative screen failure	Yes	Yes	Yes	Subject signed IPC, meeting the definition of enrolled, but it was determined during surgery that the Subject would not have the Actis® Total Hip System implanted	Document on Screening & Enrollment Log as Intra-operative Screen Failure Complete & enter Preoperative & Operative eCRFs if data was collected: DM, HH, HE, HOOS, PA and DS
Overall, the number of study Subjects implanted with the Actis® Total Hip System, across all study sites, must meet the total sample size of 255 Subjects that includes a minimum of 225 Primary THA Subjects and a cohort of a minimum of 30 hemi-hip arthroplasty Subjects. Meaning, you can replace Subjects who have screen failed prior to implantation.					

12.5 Actions for Postoperative Withdrawals

A postoperative withdrawal is a Subject who signed the IPC document, was implanted with the study device, and is later withdrawn from study participation (*i.e.,* withdrawal of consent, revision of femoral or acetabular components, death, etc.). **Table 6** provides examples and the actions and eCRF(s) to be completed at the time of withdrawal.

All data up to date of withdrawal will be included in the clinical analysis.

12.6 Table 6 Actions for Postoperative Withdrawal

Table 6 Actions for Postoperative Withdrawal		
Example	**Actions**	**Follow -up**
Subject withdraws consent	• Document Subject's request for withdrawal from the study in the source • Complete End of Study/Withdrawal eCRF • Update Screen/Enrollment Log	Do not continue
Death	• Document in source • Complete Adverse Event eCRF • Complete End of Study/Withdrawal eCRF • Update Screen/Enrollment Log	Do not continue
Revision	**See Section 14.5, Table 9 Revisions and Reoperations**	**Do not** continue if the femoral stem has been removed or revised.

		Please continue to follow if the femoral component has **not** been removed or revised

13 ADVERSE EVENTS (AEs)

An adverse event (AE) is defined as an untoward medical occurrence, unintended disease or injury, or untoward clinical signs (or change or worsening of a pre-existing medical condition) in a patient, which may or may not have an association with the device. In addition, an adverse device effect is defined as "any untoward and unintended response to a medical device". Further types of AEs and definitions are in **Table 7** below. AEs are reported beginning from when the informed consent is signed until Subject participation has ended (study completed or consent withdrawn. This protocol requires each site to report AEs to their respective IRB/REC, EC, per their IRB/REB/EC's respective requirements. Device related AEs will be reviewed by DePuy Synthes and reported, if applicable, to the appropriate regulatory body.

Study Sites have two (2) weeks from when they become aware of device and /or procedure related AEs to inform the Sponsor via the AE eCRF.

For this study, only the AEs related to the study devices (excluding the Patient Activity Tracking devices) or the procedure are to be reported (please refer to Figure 13.1). The determination whether the AE was related to the device or procedure will be based upon whether a causal relationship between the device or procedure and the AE is at least a reasonable possibility, *i.e.*, the relationship cannot be ruled out. A causal relationship cannot be ruled out if, in the medical judgment of the Investigator, the effect follows a reasonable temporal association with the use of the device and/or is confirmed by the improvement of the effect upon discontinuation of the clinical use of the device, and/or the effect is not reasonably explained by the Subject's clinical state.

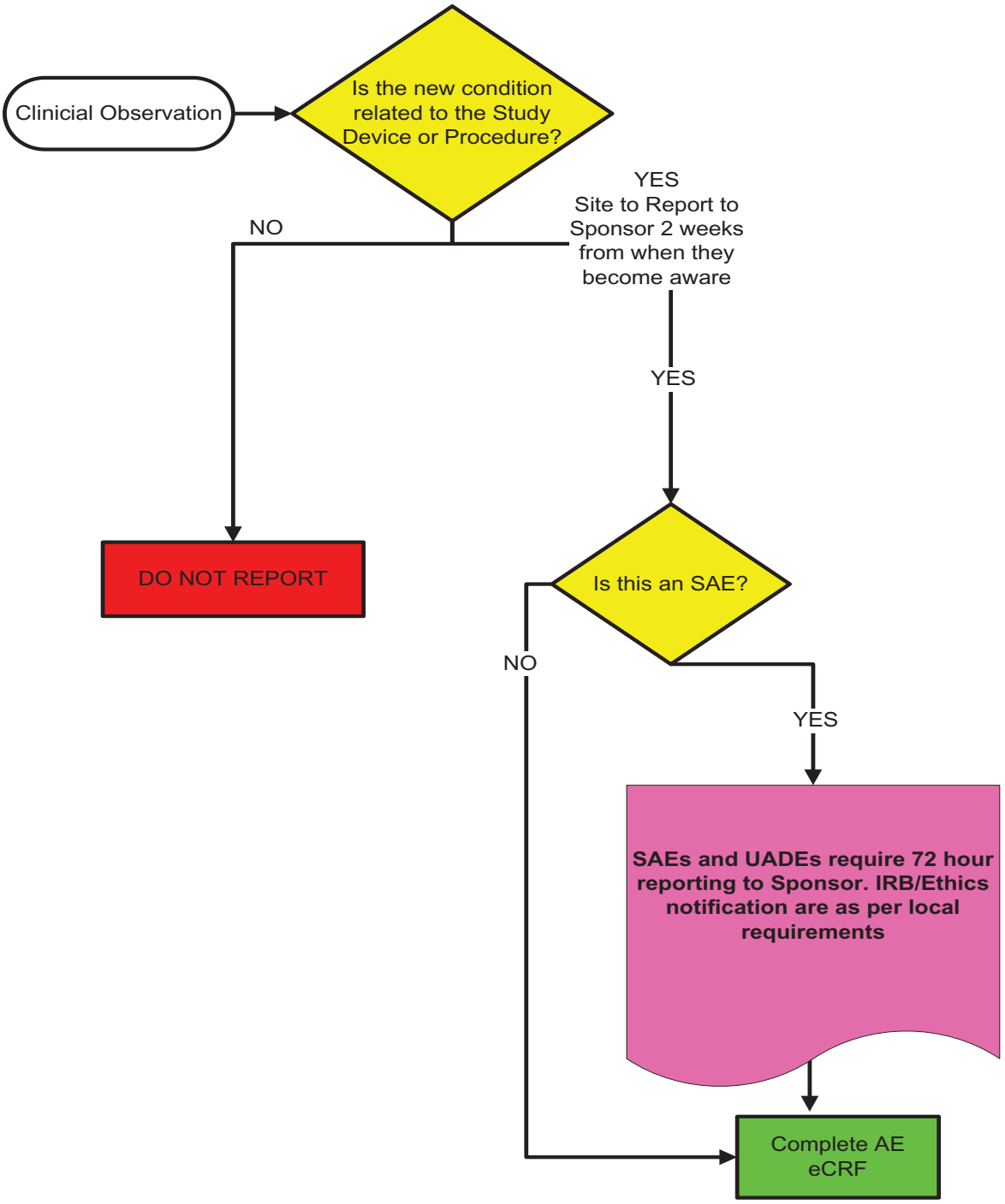
A record of each device or procedure related AE, including details of the nature, onset, duration, severity, relationship to the device, relationship to the operative procedure and outcome, will be made on an AE eCRF. Subjects must be questioned about any new or changed AEs at each subsequent follow-up visit, whether scheduled or not.

AEs must be followed to resolution, or end of subject's study participation. When a Subject ends participation in the trial, all open AE outcomes must be designated in the AE eCRF as either "Recovered/Resolved with no residual effects", "Recovered/Resolved with residual effects", "Ongoing", "Death", or "Unknown" providing a resolution date (if applicable) or ongoing designation.

There is no personal benefit to the Subject for participation in this study. However, data collected in this study will contribute to the safety profile of the Actis® Total Hip System.

Figure 13.1: AE Reporting flowchart illustrates a series of question a site must consider when determining whether a given clinical observation must be reported and which AEs do not need to be reported for this study.

Figure 13.1 AE Reporting Flowchart



Adverse Events (AEs) occurring postoperatively after hip arthroplasty are not unique to the Actis® Total Hip System and are like those that may occur with any THA or hemi-hip arthroplasty. And, per

the Instructions for Use (IFU), which is included in the implant packaging, the following are generally the most frequently encountered AEs and complications in hip arthroplasty.

General:

1. Change in position of the prosthetic components, often related to the factors listed in WARNINGS AND PRECAUTIONS.
2. Early or late loosening of the prosthetic components, often related to factors listed in WARNINGS AND PRECAUTIONS.
3. Fatigue fracture of the femoral stem, often related to factors listed in WARNINGS AND PRECAUTIONS.
4. Excessive wear or fracture of the bearing components due to: intra-operative damage to the prosthetic components, loose cement, bone fragments, metallic particles, ceramic particles or other factors listed in the WARNINGS AND PRECAUTIONS.
5. Early or late infection.
6. Peripheral neuropathies, Subclinical nerve damage may also occur as a result of surgical trauma.
7. Tissue reactions, osteolysis, and/or implant loosening caused by metallic corrosion, allergic reactions, wear or particulate debris (such as loose cement, metallic, polyethylene or ceramic particles).

Intra-operative:

1. Acetabular perforation.
2. Femoral shaft perforation, fissure, or fracture, which may require the use of internal fixation.
3. Trochanteric fracture.
4. Damage to blood vessels (*e.g.,* iliac, obturator and femoral artery).
5. Temporary or permanent nerve damage (*e.g.,* femoral, obturator or isolated peroneal nerve).
6. Subluxation or dislocation of the hip joint due to implant size or configuration selection, positioning of components and/or muscle and fibrous tissue laxity.
7. Breakage or chipping of the ceramic femoral head.
8. Lengthening or shortening of the affected extremity.

Early Postoperative:

1. Cardiovascular disorders including venous thrombosis, pulmonary embolism and myocardial infarction.

2. Hematoma and/or delayed wound healing.

3. Pneumonia and/or atelectasis.

4. Subluxation or dislocation.

Late Postoperative:

1. Trochanteric avulsion from excessive muscular tension, weight-bearing, or inadvertent intra-operative weakening of the trochanter.

2. Aggravation of problems in the ipsilateral or contralateral knee and ankle joints due to leg length discrepancy, femoral medicalization and/or muscular deficiencies.

3. Femoral or acetabular fracture due to trauma or excessive loading, particularly in the presence of poor bone stock caused by sever osteoporosis, bone defects from previous surgery, - reaming procedures, or bone resorption.

4. Bone resorption which may contribute to the deterioration of fixation and eventual loosening of the implant.

5. Peri-articular calcification or ossification which may lead to a decrease in joint mobility and range of motion.

6. Traumatic arthrosis of the ipsilateral knee secondary to intra-operative positioning, of het extremity during surgery.

7. Subluxation or dislocation.

The incidence and severity of complications in hip replacement are usually greater in revisions than in primary operations. Common problems encountered in revision surgery may include difficulty in placement of the incision, removal of ectopic bone and old bone cement, positioning and fixation of components, and/or obtaining adequate bony support. In general, increased operative time, blood loss and risk of infection, pulmonary embolus and wound hematoma can be expected with revision procedures.

WARNING: if postoperative breakage or chipping of the ceramic femoral head component is confirmed, surgery for its removal must be performed as soon as reasonably possible.

13.1 Table 7 Definitions of Adverse Event (AE) Types, Device Deficiency.

For this protocol, the term "expected" will be synonymous with the term "anticipated" and "unexpected" will be synonymous with "unanticipated".

Table 7 Definitions of Adverse Event (AE) Types, Device Deficiency	
Awareness (Date of AE Awareness)	The day, month and year that the study site becomes aware of information from any source that reasonably suggests that an AE has occurred. Note: This date may or may not correspond to the date of onset. The date of awareness is critical to reporting timelines.
Adverse Event (AE)	AE is defined as an untoward medical occurrence, unintended disease or injury, or untoward clinical signs (or change or worsening of a pre-existing medical condition) in a patient, which may or may not have an association with the device. AE is synonymous with "complication" or "medical event".
Adverse Device Effect (ADE)	ADE is defined as an Adverse Event related to the use of an investigational medical device. Notes: This definition includes adverse events resulting from insufficient or inadequate instruction for use, deployment, implantation, installation or operation, or any malfunction of the medical device under study. This definition includes any event resulting from user error or from intentional misuse of the medical device under study).
Serious Adverse Device Effect (SADE)	SADE is defined as an Adverse Device Effect that has resulted in any of the consequences characteristic of a serious adverse event.
Serious Adverse Event (SAE)	SAE is defined as an Adverse event that: • led to a death, • led to a serious deterioration in the health of the Subject that either: o resulted in a life-threatening illness or injury, or o resulted in a permanent impairment of a body structure or a body function, or

	○ required inpatient hospitalization or prolongation of existing hospitalization, or ○ resulted in 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. • Other serious important medical events. Report when the event does not fit the other outcomes, but the event may jeopardize the patient and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. *Examples of procedure related serious AEs (SAEs) may include: stiffness requiring manipulation of the hip under anesthesia, dislocation of hip requiring closed reduction, Deep Vein Thrombosis (DVT) without hospitalization. Examples of device related SAEs may include radiolucent lines around the femoral component or device dislocation.*
Unexpected/Unanticipated Adverse Device Effect (UADE)	Is defined as any serious adverse effect on health or safety, or any life-threatening problems, 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 Clinical Investigation Plan, or application, or any other unanticipated serious problem associate with a device that relates to the rights, safety, or welfare of Subjects. A UADE will not be listed in the Instructions for Use (IFU). All potential UADEs that occur during this investigation must be reported by the Investigator **no later than 72 hours** from the time when the Investigator is aware of the event to the Sponsor by telephone (800) 829-7003, electronic correspondence, or facsimile (574) 371-4950.

	In the event of a UADE or serious adverse *device* effect, the Investigator should institute appropriate therapeutic and follow-up measures in accordance with good medical practice and notify the local IRB/REB/EC. The Investigator must document follow-up treatment in the "comment" section of the AE eCRF. *A full written report of the event must be forwarded to DePuy Synthes within 10 working days of the discovery.* DePuy Synthes must notify FDA, all reviewing IRB/REB/EC's and all participating Clinical Investigators of all UADEs within 10 working days of first receiving notice of the event. In addition, the event will be reported to the DePuy Synthes Complaint Handling Unit (CHU) for investigation.
Device Deficiencies	Are defined as in adequacy of a medical device with respect to its identity, quality, durability, reliability safety or performance. Device deficiencies include malfunctions, use errors and inadequate labeling. Device deficiencies should institute appropriate therapeutic and follow-up measures in accordance with good medical practice and notify the IRB/REB/EC as applicable. The Investigator must document follow-up treatment of the AE and the Sponsor will report the event to the DePuy Synthes Complaint Handling Unit for investigation.

13.2 Definition of AE Severity

An adverse event (AE) or an adverse device effect (ADE) may be:

- **Mild**: Easily tolerated and transient in nature with minimal or no impairment of normal activity. Intervention is not indicated. Clinical or diagnostic observations only and no impairment of normal activity.

- **Moderate**: Poorly tolerated, sustained and interferes with normal activity and requires medical attention. Intervention is either noninvasive or not indicated. Activities of daily living can be sustained.

- **Severe**: Poorly tolerated, requires intervention and significantly affects activities of daily life; or places the Subject at immediate risk or harm.

14 DETERMINATION OF RELATIONSHIP TO DEVICE AND/OR PROCEDURE AND ADES AND SADES

14.1 Device or Procedure Related

As noted in **Section 13**, for this study, only the AEs related to the study devices or the procedure are to be reported and the determination of whether the AE is related to the device or procedure is based on the definition provided in that section.

Relationship to study device ***or*** procedure should both be rated as follows: "Definitely", "Probably", "Possibly", "Remote Possibility", or "Definitely not".

Table 8 Definitions of Device-Relatedness and Procedure-Relatedness for AEs

Term	Description
Definitely	The relationship between study device or procedure and event does exist and is confirmed upon further investigation by the Investigator
Probably	The relationship between study device or procedure may exist if other causes are unlikely
Possibly	The relationship between study device or procedure could exist; however, other causes are possible
Remote Possibility	There is minimal chance that a relationship exists between the study device and/or procedure
Definitely Not	There is definitely no relationship between study device or procedure and the event

14.2 Worsening Adverse Events

For a worsening AE, resolve the original AE on an AE eCRF and complete an additional AE eCRF for the new Severity. Examples of this exercise will be included in the eCRF Completion Instructions (CCIs), a tool which will be provided to site to help aid in entering data into the EDC system. A simple example is that if a Subject has a superficial wound infection with oral medication as a treatment that progresses to a deep wound infection with additional treatment (*e.g.,* inpatient hospitalization for an irrigation and debridement). The study site must resolve the superficial wound infection and report the worsening on an additional AE eCRF. Each AE will be counted individually – as in one superficial wound infection and one deep wound infection AE/SAE.

14.3 Pre-existing Medical Conditions

Pre-existing medical conditions or symptoms reported prior to device implantation are to be recorded as history and not to be recorded as AEs (*e.g.*, History of Asthma or existing osteoarthritis in contralateral knee would be recorded on the Subject History eCRF). In the event there is an

exacerbation of the pre-existing medical condition or symptoms, related to the device or procedure, *an AE must be reported*.

14.4 Minimization of Risks

The Sponsor will further minimize the identified and/or emergent risks throughout the study, by reviewing the reported complications and adverse effects. Device related adverse events will be reviewed and reported to the FDA as part of the Medical Device Reporting (MDR) requirements (http://www.fda.gov/cdrh/mdr/). Based upon an evaluation of such events, the Sponsor may either amend the investigational plan or terminate the investigation to protect the rights, safety and welfare of the study Subjects. Investigators will be provided periodic reports of all adverse events.

Should an IRB/REB/EC decide to suspend or withdraw its approval for a PI to conduct the study at that institution, based on unacceptable risks to the study Subjects, the study Sponsor will notify all reviewing IRB/REB/ECs, and PIs of this action. To further minimize risks, any new information obtained during the course of the study relating to unanticipated adverse findings will be provided to all Subjects, PIs, and IRB/REB/ECs.

The study has been designed to minimize the number of Subjects, yet provide sufficient numbers of Subjects for valid scientific analysis of the compiled study data. The study design, the procedures for oversight and the documentation, reporting and evaluation of the results from its surgical use will further control risks.

14.5 Table 9 Revisions and Reoperations

A "**revision"** is defined as a surgical procedure of the affected study hip where any Actis® Total Hip System component for any reason is removed. A revision algorithm specifically for this study is as follows:

Table 9 Revisions and Reoperations		
Component(s) revised/removed	**eCRFs to be completed**	**Actions**
All 4 components removed: femoral stem and head, acetabular cup and liner	AE eCRF End of Study eCRF	Subject is revised and withdrawn from the study
Exchange of only the polyethylene acetabular liner (*only poly liners are allowed in the study*)	AE eCRF	Subject is categorized as revised but not withdrawn from study Continue to follow through the 2-year endpoint
Removal of only the femoral stem and head (acetabular cup and liner remain in place)	AE eCRF End of Study eCRF	Subject is revised and withdrawn from the study
Removal of only the acetabular cup and liner (femoral stem and head remain in place)	AE eCRF	Subject is categorized as revised but not withdrawn from study Continue to follow through the 2-year endpoint

A "**re-operation"** is defined as any surgical procedure of the affected study hip in which **NO THA components are removed.** These subjects are **not to be withdrawn**. An **AE eCRF must be completed** (*e.g.,* reoperation could occur to treat an infection).

All removed components are subject to further evaluation. If the implant is known to be available, the Sponsor will encourage the Investigator to preserve the prosthesis alone. In the event of a death, the excised hip joint with the implant in place should be provided to the Sponsor if possible. Please contact the Sponsor for details should a retrieved study implant become available.

15 INFORMED PATIENT CONSENT (IPC) PROCESS

In compliance with ISO 14155 and 21CFR50, no Subject shall be enrolled in an investigation without provision of adequate informed consent. The Principal Investigator is responsible for ensuring that no Subject is included in the study without adequate informed consent being provided. Failure to obtain and properly document this process is in violation of ISO 14155, the Declaration of Helsinki, and this study protocol.

All Informed Patient Consent (IPC) documents must have favorable opinion of the IRB/REB/EC. Many institutions request modification of the IPC to satisfy specific institutional requirements. The use of a modified or unique IPC is permitted provided that all the requirements of ISO 14155 are met and the document is approved before use by the Sponsor.

Subjects who agree to participate in the study will complete an IRB/REB/EC approved IPC document that documents his or her willingness to take part in this study. Each potential Subject will have the nature and the purpose of this study explained to him or her by the Principal Investigator (PI) or another delegated member of the investigative team at the study Site. The PI or designee will explain the following features of the study to the patient thoroughly and will offer to answer any questions the patient may have.

- The purpose of the study
- The potential risks or adverse events that are posed by their treatment
- The potential risks or adverse events related to study participation
- Possibility of failure and the need for subsequent treatment(s)
- Alternative procedures/treatments available to the Subject
- Requirements of the study follow-up visits
- All the Subject's rights as a participant in the clinical investigation
- The plan to perform retrieval analysis in the event of an explanted device
- A modest payment may be provided to cover Subject travel expenditures associated with study participation up to 2 years postoperatively
- Voluntary participation in the Patient Activity Tracking portion of the study, and the details associated with this portion of the study.

Consent must be given by the Subject, or by a Legally Authorized Representative as applicable, and documented on an Informed Patient Consent Document in the primary language of the Subject. A copy of the IPC is to be provided to the Subject. An IPC must be obtained for all Subjects *prior* to the Subject completing any study-specific assessments or procedures that are not standard of care. *A study Subject is considered enrolled in the study once they have signed the IPC.*

Obtaining Consent Day of Surgery: If the IPC document signatures are acquired on the day of surgery a **time stamp** on the signature page is required to support consent was obtained from the study Subject prior to any treatment related and/or mood-altering medications being administered.
No dates should be pre-populated, or completed by someone other than the person providing the signature.

Subjects will be made aware that their personal data will be collected and processed in accordance with data protection legislation including Health Insurance Portability and Accountability Act of 1996 (HIPAA - refer to **Section 5, Table 3, Definition of Terms**). The release of Personal Health Information (PHI) for the purpose of this clinical investigation will be included in the informed patient consent. Results from this clinical investigation may be published, however, subject confidentiality will be maintained at all times and it will not be possible to identify them from any data presented.

16 STATISTICAL METHODOLOGY

Statistical analysis will be performed using SAS® (SAS Institute Inc., SAS Campus Drive, Cary, North Carolina 27513) software version 9.3 or higher. Any further software that may be necessary will be described in the final study report.

16.1 Study Design

The study design is a prospective, uncontrolled, non-randomized, multicenter study.

A minimum of 255 Subjects that includes a minimum cohort of 225 Primary THA and a cohort of a minimum of 30 hemi-hip arthroplasty Subjects, will be prospectively enrolled into the study. All Subjects will be seen for a preoperative clinic visit at the time of consent, and evaluated at the time of surgery, 6 weeks, 3 months, minimum 1 year, and minimum 2 years postoperatively.

16.2 Treatment Assignment

The Actis® Total Hip System, specifically the medial collared DUOFIX® hip stem, is the **only** device of interest in the study; there will be no control group. Two cohorts of Subjects will be enrolled:

- Subjects who receive a primary THA
- Subjects who undergo a primary hemi-hip arthroplasty.

16.3 Levels of Significance

There are no pre-specified hypotheses, and all analyses are exploratory. Confidence intervals and p-values may be provided to facilitate clinical judgement. Unless otherwise stated, p-values will be 2-sided and confidence intervals will be 2-sided 95% confidence intervals with no adjustments for multiplicity.

16.4 Interval Windows

See **Section 6 Subject Management Study Schedule** above.

16.5 Handling of Missing Data

. Only actual subject data which is collected will be utilized in analyses.

16.6 Primary and Secondary Endpoints

See **Sections 10.2 and 10.3**

16.7 Hypotheses

This is not a hypothesis driven study.

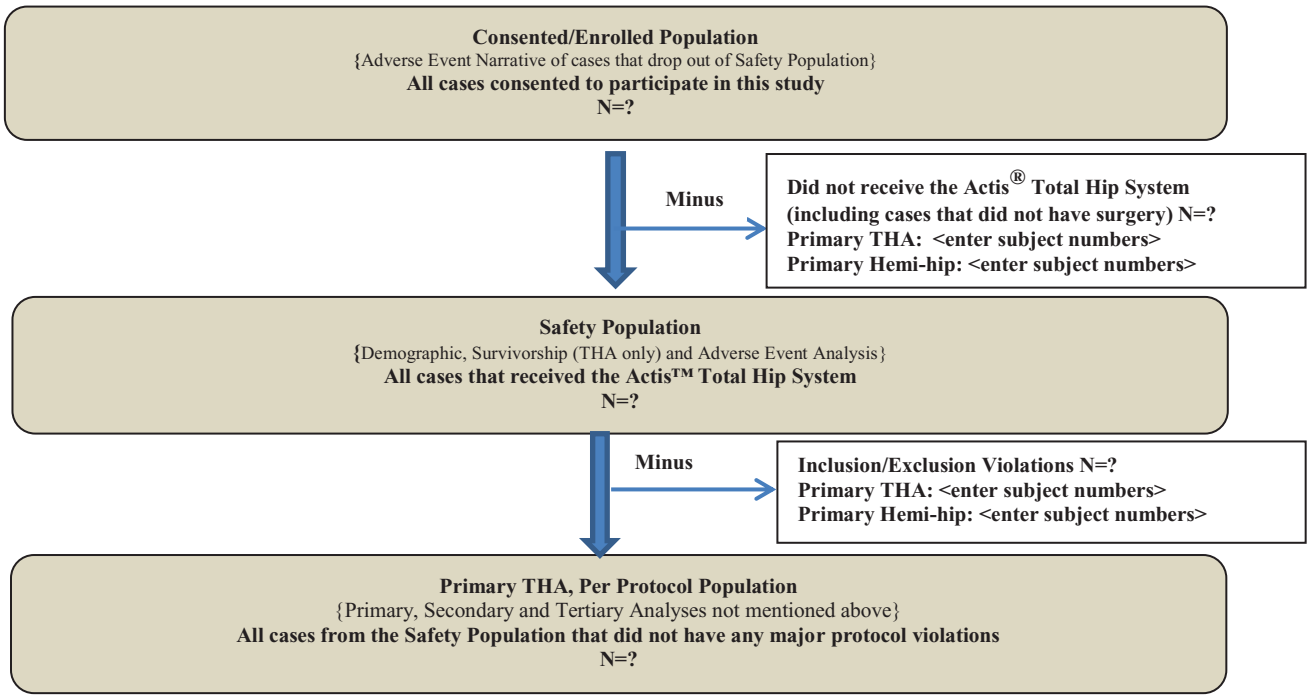
16.8 Analysis Sets

- This study will have 3 analysis sets which will be determined for both THA and hemi-hip Subjects as defined below and illustrated in the Data Flow Diagram: Enrolled Set is defined as all cases consented to participate in this study. The Enrolled Set will be used for the summary of disposition.

- Safety Set is defined as all cases that received the Actis® Total Hip System. The Safety Set will be used to summarize demographic characteristics, adverse events and survivorship;

- Per Protocol Set is defined as all Safety Set subjects without major protocol violations. The Per Protocol Set will be used for the summary of primary, secondary and tertiary endpoints.

Figure 16-1: Analysis Set Flowchart



16.9 Sample Size Justification

The primary endpoint in this study is the Harris Hip Score at minimum 2-year postoperative. It is anticipated that this primary outcome measurement will be obtained on approximately 200 primary THA Subjects due to anticipated attrition. The standard deviation in this outcome will be approximately 10 points (based on historical hip studies). It is therefore anticipated that the margin of error on the mean Harris Hip Score estimate at minimum 2-years postoperatively will be approximately 1.4 points. The study team believes this margin of error is sufficient for this 2-year outcomes and follow-up study. A sample size of N=30 hemi-hip arthroplasty procedures was established as a feasible number.

16.10 Analysis Plan

Results for the cohorts of Subjects who were enrolled with a primary THA, and who were enrolled with a primary hemi-hip arthroplasty procedure will be summarized side-by-side, and overall, unless otherwise stated. Demographics, baseline subject characteristics, procedure characteristics and the primary and secondary endpoints will be presented overall (pooled) and by study site. Descriptive statistics for dichotomous/categorical variables will include the number and percentage of subjects. For categorical endpoints, 2-sided 95% confidence intervals around observed percentages will be based on the binomial exact method. Descriptive statistics for continuous variables will include the number of subjects, mean, standard deviation, median, minimum, and maximum. For continuous endpoints, 2-sided 95% confidence intervals around the mean will be computed using the t-distribution.

16.11 Primary Endpoint

The primary endpoint is the total Harris Hip Score at minimum 2 years after cementless primary total hip arthroplasty (THA) or hemi-hip arthroplasty. This primary endpoint analysis will be conducted on both groups combined (primary THA and primary hemi-hip arthroplasty); however, results will also be analyzed separately for each cohort. Descriptive statistics that include the number, per group, of study hips, mean, standard deviation, median, minimum, and maximum will be presented. A 2-sided 95% confidence interval around the mean will be computed using the t-distribution.

16.12 Secondary Endpoints

- Harris Hip score at 3 months and 1 year. The same methods as described for the primary endpoint will be utilized for this secondary endpoint.
- Radiographic evaluation at 2 years post-operatively. Radiographs will be read by an independent radiographic reviewer (IRR) at 6 weeks to act as a baseline measurement to be compared to radiographs taken at later time points (3 months, 1 year, and 2 years). Parameters measured include stem subsidence, shell migration, shell inclination angle, osteolytic lesions, radiolucencies, heterotopic ossification, demarcation lines (sclerotic lines), porous coating integrity (delamination/bead shedding), calcar remodeling, femoral stem tilt (appearance), and leg length discrepancy. Please refer to the Radiographic Parameters **Appendix D** for details on how these measurements are taken. For analysis purposes, minimum change from baseline thresholds are defined below for several of these parameters; These threshold levels are considered to be clinically important change from baseline thresholds:
    - Femoral stem Subsidence – greater than 2 mm
    - Acetabular shell Migration – greater than 2 mm
    - Acetabular shell Inclination angle – change greater than 4 degrees
    - Osteolysis – greater than 5 mm in the greatest dimension
    - Radiolucencies – greater than 2 mm in width

    The percentage of cases that exceed the thresholds provided above will be presented by visit for each radiographic parameter, along with the number of cases and 2-sided 95% confidence intervals based on the binomial exact method. A listing of the cases exceeding the thresholds will also be provided along with the corresponding numerical measurement (i.e. radiolucency width measured in mm). Further, the number and percentage of the other radiographic parameters will be presented along with a listing of cases with undesirable results (*i.e.* cases with Heterotopic Ossification not equal to 'None').
- Leg length discrepancy (LLD) will be analyzed by study visit in several ways:

- Analysis of "True" versus "Perceived" LLD: Each subject will be asked, yes or no, if they Perceive that they have LLD both before and after undergoing hip replacement. Percentages will be presented along with 95% binomial exact confidence intervals.
- Radiographic measurements will provide True LLD by measuring each leg to the nearest millimeter. A LLD of 3 cm or greater will be considered a true LLD. A McNemar's test of discordant pairs will be utilized to compare perceived vs. actual LLD before surgery, and also to compare perceived vs. actual LLD after surgery.
- Analysis of Change (post-surgical – pre- surgical) of True LLD: Compare the difference between the absolute true LLD before and after hip replacement surgery for those cases that had a true LLD prior to hip replacement surgery (using a definition of 3 cm or greater as the threshold). The analysis variable will be the absolute value of the difference between the right and left knee and a paired t-test will be used to assess this difference.
- Analysis of proportion of cases that have true LLD after surgery will be presented and this will be compared to the proportion that had true LLD prior to surgery; McNemar's test of discordant pairs will be conducted.

- The type and frequency of AEs through 2 years post-operatively will be presented in table form and via a listing. Frequencies and listing of AE's seriousness, severity, whether unanticipated, outcome, and treatment will also be presented.
- Device survivorship at 2 years post-operatively. Kaplan-Meier survivorship will be conducted with removal of any component, defined as revision, for any reason specifying the event of interest. Cases not revised will be censored at their date of last follow-up, death, or withdrawal from the study. Survivorship point estimates and 95% confidence intervals will be presented when 40 subjects are left being followed. Survivorship analysis is not planned for the cohort of hemi-hip subjects as the sample size is insufficient; however, a listing will be provided to present all subjects requiring removal of any component.
- Stem Revision at 2 years post-operatively.
- Kaplan-Meier survivorship will be conducted with removal specifically of the femoral stem component, defined as revision, for any reason specifying the event of interest. Cases not revised will be censored at their date of last follow-up, death, or withdrawal from the study. Survivorship point estimates and 95% confidence intervals will be presented when 40 subjects are left being followed. Survivorship analysis is not planned for the cohort of hemi-hip Subjects as the sample size is insufficient; however, a listing will be provided to present all Subjects requiring removal of the femoral stem component.

16.13 Tertiary Endpoints

- Change in Subject Outcomes (*i.e.,* FJS-12, HOOS and Hip Evaluation) will be measured and compared from preoperative to 6 weeks, 3 months, minimum 1 year and minimum 2 years.
    - Raw measurements and change from baseline (pre-op) scores will be presented for FJS-12 and HOOS scores and will include number of subjects, mean, standard deviation, median, minimum, and maximum. Two-sided 95% confidence intervals around the mean will be computed using the t-distribution.
    - Frequency tables will be provided for the following Hip Evaluation outcomes and include 2-sided 95% confidence intervals based on the binomial exact method: satisfaction, procedure again, and groin and buttock pain.
- Voluntarily participating study Subjects utilizing the wearable Patient Activity Tracking device and will provide the Sponsor with data on daily activity (*e.g.,* pain, location of pain, mood/emotion, activities of daily living and range of motion, and after surgery Subject satisfaction will be asked periodically) from the time of consent preoperatively (if possible) through 3 months postoperative.
    - The number of subjects participating, and the completeness and cleanliness of those data will impact analysis methods. At minimum, pain level before and after surgery will be summarized and presented by the corresponding category. Pain, location of pain, mood/emotion, activities of daily living, range of motion and Subject satisfaction will also be summarized.

16.14 Interim Analysis

Ad hoc interim analyses may occur as required for either THA or the hemi-hip arthroplasty populations. There are no planned interim analyses for the purpose of stopping the study early.

17 DATA MANAGEMENT

17.1 Data Management for Subject Operative Details and Follow-up Evaluations

Electronic Case Report Forms (eCRFs) entered into an electronic data (EDC) system will be used to collect all Subject data once a Subject is enrolled in the study. Study sites will be asked to enter Subject data into the eCRFs via the EDC web based database portal promptly after each study visit.

The patient-reported outcome measures (*i.e.,* FJS-12, HOOS and Hip Evaluation) will be recorded on paper-based questionnaires. The data will then be entered into the respective eCRF within the EDC system by the PI or designee. The patient-reported outcomes measures captured on paper-based questionnaires must be stored in the Subject's medical notes, as these are the source document. Any errors on paper-based questionnaires should be crossed out with a single stroke, initialed and dated by the Subject; a study site must not alter any data entered on the paper-based questionnaires. Typing correction fluid must not be used. The PI will retain one copy of each completed paper-based

questionnaires (*e.g.*, HOOS) in the medical notes and another copy will be kept in the site study file (*e.g.,* individual study Subject binder or Subject specific tab if contained within a single binder).

For all Subjects, detailed information related to the primary diagnosis, anesthesia type and time, if a specific kind of fracture table (*e.g.,* HANA Table) was utilized, and surgical exposure (*e.g.,* anterior approach), and other surgical variables will be recorded on the Operative Details eCRF. Any occurrence of an operative complication must be recorded on the AE eCRF. An intra-operative device or procedure related complication is defined as a complication that occurs from the start of anesthesia to when the Subject returns to their room. Please complete a separate AE eCRF for each intra-operative complication. Labels for each device or component used during the procedure must be recorded on Device Log eCRF.

Data collected during the study for each Subject will be maintained as accurately and completely as possible with entries into an EDC system provided by DePuy Synthes. The personal data recorded on all documents, including copy documents, and within the system will be regarded as confidential. The PI will be responsible for the timing, completeness and accuracy of the details entered within the EDC system. All data entered in the database must have source documents in the Subject's medical records.

The Investigator should retain copies of all documents pertaining to this study (including source documentation, the informed consent document and any other documents to identify the Subjects) for at least two years after this clinical investigation is completed. In addition, if the PI moves/retires, etc., she/he should provide DePuy Synthes with the name and address of the person who will look after and be responsible for the Subjects' study related records.

18 CLINICAL MONITORING

Actis® is a minimal risk study not regulated by 21 CFR Part 812, and due to the level of risk, onsite interim monitoring is not required; however, to further increase confidence in the quality of this post-market study data, targeted monitoring activities at clinical sites may be conducted. If on-site monitoring activities are determined necessary, they will be conducted as outlined in a study specific Monitoring Plan.

19 STUDY DEVICES

The Actis® Total Hip System (Actis®) is indicted for cementless use for primary total hip arthroplasty (THA) and hemi-hip arthroplasty.

A total hip prosthesis is composed of individually packaged titanium (Ti-6A1-4V) femoral hip stem, modular metal or ceramic femoral head, and a two-piece metal-backed Ultra High Molecular Weight

Polyethylene (UHMWPE), acetabular components designed to replace the natural articular surface of the hip joint.

Hemi-hip prosthesis is comprised of a titanium (Ti-6A1-4V) femoral stem and a metal head designed to replace the natural femoral head and neck in hemi-arthroplasty.

The Actis® medial collared DUOFIX® hip stem is manufactured from forged titanium alloy (Ti-6A1-4V) and has a sintered commercially pure titanium bead porous coating (POROCOAT®), and a thin layer of plasma-sprayed hydroxyapatite (HA) coating. Refer to **Appendix E** for a complete listing of the Actis® Total Hip System and compatible component product codes.

Only the compatible acetabular cups, acetabular liners and femoral heads listed in Appendix E are allowed for use in this clinical investigation.

20 DEVIATIONS & NON-COMPLIANCE HANDLING

With the exception of emergency situations, no deviations to this clinical investigational plan will be permitted. In the event of an emergency situation the Principal Investigator must notify the Sponsor immediately. A full written report of the situation must be forwarded to the IRB/REB/EC Committee who approved the original CIP and DePuy Synthes promptly.

20.1 Lost to Follow-up

There may be study Subjects who will not or cannot return for follow-up examinations as prescribed in this clinical investigation. These individuals will **not** be considered as "lost to follow-up", but as **non-compliant** with the study protocol and thus entered into a missing data category. This group includes:

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

Subjects that are considered "lost to follow-up" cannot be considered withdrawn from the study. The PI must continue efforts to schedule the Subject until study closure or the Subject provides communication (preferably written) of a desire to withdraw from study participation. Both oral (telephone) and written (email or letter) correspondence should be employed to schedule the Subject. If a Subject does not respond, a registered letter should be sent to the Subject indicating the importance of the follow-up visits and to contact the office immediately. Each PI will maintain a record of communications and/or attempts at communications in the source documentation.

21 ETHICAL PRINCIPLES

This clinical investigation shall be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. The Declaration of Helsinki and other guiding principles are also noted above in the protocol signature page.

22 PRINCIPAL INVESTIGATOR RESPONSIBILITIES

An Investigator's responsibilities in conducting clinical investigations of a medical device are described below. Additionally, a signed agreement between the Investigator and Sponsor will be in place prior to consent of the first subject into the study.

In conducting this medical device clinical investigation, the Investigator is responsible for:

1. Ensuring that a clinical investigation is conducted according to applicable regulations, the signed Investigator agreement, and the investigational plan;
2. Protecting the rights, safety, and welfare of subjects under the Investigator's care.

22.1 Institutional Review Board Approval (IRB or REB or EC)

Each Investigator must obtain IRB/REB/EC approval prior to the consent of the first Subject; no study-related procedures can occur without the approval and oversight of a registered IRB/REB/EC.

All Principal Investigators must submit for initial review a copy of the clinical investigational plan (CIP) and a sample Informed Patient Consent Document (IPC) to their institution's IRB/REB/EC. Initial approval must be documented; originals of correspondence and approvals are to be filed by the Investigator and copies forwarded to the Sponsor.

Continuing review and any other additional required submissions will be forwarded for IRB/REB/EC review according to their policies and procedures. Approval or acknowledgement must be documented; originals of correspondence and approvals are to be filed by the Investigator and copies forwarded to the Sponsor.

22.2 Informed Patient Consent (IPC)

The Principal Investigator is responsible for ensuring that no Subject is included in the study without adequate informed consent being provided. Source documents must be maintained, evidencing informed consent was obtained prior to participation in the study. Failure to obtain or properly document this process is in violation of ISO 14155, 21CFR50, the Declaration of Helsinki and this study protocol.

See descriptions of the Informed Consent process in **Section 15** and a sample Informed Patient Consent Document in **Appendix B.** Each subject is entitled to withdraw from this clinical investigation for any reason without obligation and/or prejudice to further treatment.

The Investigator will clearly document the date and reason(s) for the subject's withdrawal from this clinical investigation, and submit the appropriate eCRFs to DePuy Synthes.

22.3 Source Documentation

The Investigator will maintain source documentation records of each Subject's case history. Case histories include the case report forms and medical records, including progress notes, hospital charts, nurses' notes, etc.

Records shall include:

- Documents evidencing informed consent
- All relevant observation concerning adverse events
- Subject history of each Subject upon entering the study
- Information on the condition of the Subject during the course of the study.

22.4 Electronic Case Report Form (eCRF) Completion

Electronic Case Report Forms (eCRFs) in an electronic data collection (EDC) system will be used to collect all Subject data once a Subject is enrolled in the study. Investigative study sites will be asked as a *best practice* to enter Subject data into the eCRFs no later than 2 to 4 weeks from the time the Subject was seen for their scheduled study visit.

Detailed description of the eCRF components and eCRF completion guidelines are included in the User Instructions available in the MediData Rave System and eCRF Completion Instructions (CCIs), which will be provided to the Investigators and applicable site staff to aid in data entry in the EDC system. The respective eCRFs must be fully completed for each Subject and signed electronically by the Investigator.

The patient reported outcome measures (*i.e.,* FJS-12, HOOS and the Hip Evaluation) will be recorded on paper questionnaires (*i.e.,* source documentation). The data will then be entered into the respective eCRF within the EDC system by the PI or a properly delegated designee. The patient reported outcomes measures captured on paper-based questionnaires must be stored in the Subject's medical notes, as these will be considered to be the source document. Any errors on paper-based forms should be crossed out with a single stroke, initialed and dated. Typing correction fluid must not be used.

22.5 Clinical Investigation Plan (CIP) Adherence

The Investigator must not deviate from the investigational plan without first receiving approval from the Sponsor and reviewing IRB/REB/EC, except when necessary to eliminate apparent immediate hazards to a subject.

Except for emergency situations, no deviations to this CIP will be permitted; please refer to **Section 20** for further details regarding protocol deviations and non-compliances.

The Investigator will notify the Sponsor and the reviewing IRB/REB/EC of any deviation from the investigational plan.

22.6 Clinical Investigation Plan (CIP) Amendments

Applicable IRB/REB/EC approvals will be obtained prior to implementation of changes in the Clinical Investigational Plan that may affect the scientific soundness of the investigation or the rights, safety or welfare of study subjects. Administrative changes must also be submitted to the reviewing IRB/REB/EC.

22.7 Investigator Reporting Responsibilities

The Principal Investigator is responsible for submitting complete, accurate and timely reports as described below in **Table 10**.

22.8 Table 10 Principal Investigator Reporting Responsibilities

Table 10 Principal Investigator Reporting Responsibilities	
Report	**Description**
Withdrawal of IRB/REB/EC Approval	The Investigator will notify the Sponsor of a withdrawal of approval by the reviewing IRB/REB/EC of the Investigator's part in an investigation **within 5 working days**.
Reports of Deviations from the Clinical Investigational Plan (CIP)	Investigator will **promptly** report deviations from the CIP to the Sponsor via the EDC system, and to the reviewing IRB/REB/EC (as applicable per the requirements).
Other	The Investigator will, **upon request** by a reviewing IRB/REB/EC, provide accurate, complete, and current information about any aspect of the investigation.

Serious Adverse Event (SAE defined in **Section 13**)	The Investigator will notify the Sponsor, and their reviewing IRB/REB/EC's as applicable, of all SAEs upon receiving notice or discovery of the event.
Unexpected/Unanticipated Adverse Device Effect (UADE defined in **Section 13**)	All potential UADEs that occur during this investigation must be reported by the Investigator **no later than 72 hours** from the time when the Investigator is aware of the event to the Sponsor by telephone (800) 829-7003, electronic correspondence, or facsimile (574) 371-4950. In the event of a UADE or serious adverse *device* effect, the Investigator should institute appropriate therapeutic and follow-up measures in accordance with good medical practice and notify the local IRB/REB/EC. The Investigator must document follow-up treatment in the "comment" section of the AE eCRF. *A full written report of the event must be forwarded to DePuy Synthes within **10 working days of the discovery.***

22.9 Investigator Site Files (ISF or Regulatory Binder)

Each Investigator must maintain accurate, complete, and current information about all aspects of this clinical investigation. This includes documentation relating to the Investigator's participation, and all correspondence relating to the clinical investigation. Correspondence consists of, but is not limited to, written and verbal correspondence with other participating Investigators, the reviewing IRB/REB/EC, and the Sponsor.

23 SPONSOR OBLIGATIONS

23.1 Ethics (IRB/REB/EC) Approval

Each Investigator must obtain Institutional Review Board (IRB)/Research Ethics Board (REB)/Ethics Committee (EC) approval prior to consent of the first Subject. Each Investigator must also maintain continuous approval. Documentation of initial approval, subsequent renewals and IRB closure must be provided to the Sponsor, and filed on site in the Investigator Site File (ISF). Additionally, amendments to the protocol will be submitted for review before implementation, and copies of the submissions and approvals provided to the Sponsor.

The Sponsor will maintain copies of all site IRB/REB/EC documentation in the Trial Master File.

23.2 Investigator Training

Prior to enrolling Subjects in this study, the Investigator and/or appropriate Site personnel will be trained in general aspects of study administration, content and manner of administration of the Subject questionnaires, all procedures in the protocol, and the procedure for e-data acquisition and radiographic transmission.

Training will be done through a combination of teleconferences, Web-Ex conferences and on-site training as appropriate. Site visits, if required, will be arranged once IRB/REB/EC approval is obtained and the Clinical Research Agreement is executed.

23.3 Sponsor Reporting Responsibilities

This is not a regulated study and reporting to regulatory agencies is not required.

The Sponsor will provide regular reports directly to the study Site in order to communicate study progress and Site study conduct periodically throughout the study. In general, these reports are provided quarterly; however, this frequency may be modified based upon enrollment rate and phase of project.

Additional reports the Sponsor is responsible for preparing and submitting are as described below in **Table 11.**

Table 11 Sponsor Reporting Responsibilities

Report	Description
Withdrawal of IRB/REB/EC Approval	The Sponsor shall notify all reviewing IRB/REB/ECs and participating Investigators of any withdrawal of approval of the investigation by a reviewing IRB/REB/EC within 5 working days after receipt of notice.
Unanticipated Adverse Device Effect (UADE)	The Sponsor must notify FDA, all reviewing IRB/REB/EC's and all participating Clinical Investigators of all UADEs within 10 working days of first receiving notice of the event. In addition, the event will be reported to the DePuy Synthes Complaint Handling Unit for investigation.
Other	The Sponsor will, upon request by a reviewing IRB/REB/EC provide accurate, complete, and current information about any aspect of the investigation.

23.4 Insurance

The Sponsor recognizes its liability in law to compensate for any injury sustained by a Subject participating in this clinical investigation because of negligence or breach of duty of care; adequate insurance provisions have been made by DePuy Synthes to compensate any Subject so injured.

23.5 Financial Agreement

Funding of this clinical investigation will be the subject of a separate agreement between the Sponsor and the Institution where the clinical investigation is being conducted and the Principal Investigator (where permitted by the Institution).

23.6 Sponsor Study Termination

The Sponsor may prematurely terminate or suspend the clinical study as a whole or at an individual investigational site for significant and documented reasons. Reasons for premature termination or suspension include, but are not limited to safety, inadequate recruitment, Principal Investigator issues, and device related problems, alignment with business strategy or administrative issues.

If suspicion of an unacceptable risk to Subjects arises during the clinical study, or when instructed by an IRB/REB/EC or a Regulatory Authority, the Sponsor shall suspend the clinical study at all active sites while the risk is assessed. The Sponsor shall terminate the clinical study if an unacceptable risk is confirmed, or resume the clinical study following appropriate communication and approval from the IRB/REB/EC and a Regulatory Authority as required.

In terminating the clinical study, the Sponsor and the Principal Investigator will assure that adequate consideration is given to the protection of the subject's interests. All documentation is archived and the appropriate bodies such as the IRB/REB/ECs and any Regulatory Authorities are informed as appropriate.

24 PUBLICATION PLAN

All manuscripts of data obtained from this clinical investigation will be reviewed and approved by the Sponsor, and each author, prior to any submission. And, current and applicable Medical Device & Diagnostic (MD&D) Publication Policy will be followed.

DePuy Synthes will require a written agreement for any external author(s) prior to initiating any publication. All authors must disclose financial or personal affiliations that could be considered a conflict of interest.

25 STUDY SUMMARY STATEMENT

In summary, this study will provide 2-year safety and performance data and outcomes for the Actis® Total Hip System. For a given Subject, their study participation will end when they have reached the final endpoint; that is, each Subject will reach "end of study" when they have had the minimum 2-year clinical evaluation. For Subjects participating in the optional and parallel Patient Activity Tracking portion of the study (ActiTrak™), their participation in that particular aspect of the study will be completed when they have 3-months of postoperative data collected.