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DePuy Synthes Clinical Research	
CLINICAL INVESTIGATION PLAN (CIP)	
36 mm CERAMAX® Ceramic Hip System PMA POST-APPROVAL STUDY: Short to Mid-Term Follow-up of New Study Subjects	
Clinical Investigation Plan Number:	12017
Country:	U.S.
CIP Prepared By:	PPD
CIP Version:	**Revision D: May 11, 2020**
Clinical Investigation Sponsor:	Medical Device Business Services, Inc. (hereafter referred to as DePuy Synthes) 700 Orthopaedics Drive P.O. Box 988 Warsaw, IN 46581
Medical Director	PPD

PROTOCOL SIGNATURE PAGE

I have read this protocol and agree to conduct this clinical investigation 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, local regulations, 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), or other oversight committee, to ensure complete and continual oversight of this clinical investigation.

I will use an Informed 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, in particular, 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, FDA, the IRB/EC, or other regulatory authorities' direct access to all records, including source data/documents, relating to the clinical investigation, whether paper-based or electronic data capture.

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, Inc.

PRINTED OR TYPED NAME	SIGNATURE	DATE
Principal Investigator		

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3 TABLE 1 STUDY SUMMARY

Title:	***36 mm CERAMAX® Ceramic Hip System PMA POST-APPROVAL STUDY: Short to Mid-Term Follow-up of New Study Subjects***
Short Title:	COC36 Post Approval Study-New Subjects
Treatment Device:	36 mm Delta CERAMAX® Ceramic-on-Ceramic Acetabular Cup Prosthesis System
Control Device:	None; this is a non-comparative study
Intended Use:	The Ceramic on Ceramic Hip System is indicated for primary, unilateral, cementless total hip replacement surgery in skeletally mature patients with non-inflammatory degenerative joint disease or any of its composite diagnoses of osteoarthritis, avascular necrosis and post-traumatic arthritis.
Objective:	This study is intended to gather short and mid-term information regarding the performance and safety of the commercially available 36 mm CERAMAX® Ceramic on Ceramic Total Hip System from a cohort of new study subjects that were not previously involved in the IDE study for this device. The compiled information will be included in the annual post-approval study (PAS) reports for the approved PMA (P070026).
Study Design:	A prospective, non-controlled, non-randomized, multicenter study. A minimum of 170 subjects will be prospectively enrolled into the study. Study sites will be comprised of both IDE study sites, as well as newly recruited sites. Subjects will be seen for a preoperative (pre-op) clinic visit at the time of consent, and then at 6-weeks, 1-year, 2-years, 3-years, 4-years and a minimum of 5-years postoperatively (post-op). If Subjects are not willing or able to return for a clinical and radiographic follow-up in the 3- and/or 4-year interval, then a telephone interview may be utilized for the purpose of determining device survivorship/patient satisfaction and case report form (CRF) 4b will be used. It is anticipated that a minimum of 136 unrevised subjects in this PAS will have a minimum 5-year post-op clinic evaluation.
Number of Sites:	Up to fifteen (15) sites will participate, consisting of up to 5 sites who participated in the IDE study and the remainder being newly recruited sites.
Subject Population:	Newly enrolled subjects at participating sites who meet the inclusion/exclusion criteria for this study.
Sample Size:	Sites will prospectively enroll a minimum of 170 new subjects into this PAS.

Title:	***36 mm CERAMAX® Ceramic Hip System PMA POST-APPROVAL STUDY: Short to Mid-Term Follow-up of <u>New Study Subjects</u>***
Study Duration:	The anticipated duration of this investigation is approximately seven years from the time of study initiation given that • It may take up to a minimum of 2-years from the time of study initiation to enroll new subjects. • Each subject will be followed until they have completed their minimum 5-year follow-up. • The study will be closed when all subjects are at 5-years post-operatively.
Endpoints:	Primary endpoint: • Device survivorship, which will be estimated with a Kaplan-Meier survivorship analysis at 5-years post-operatively. Secondary endpoints: • Device survivorship will also be estimated at each year post-operatively. • Harris Hip scores, Subject-hip outcomes, radiographic evaluation, and type and frequency of AEs will also be estimated at each year post-operatively.
Procedure Schedule:	Subjects will be assessed at the following intervals: pre-op, operative, 6-weeks, 1-year, 2-years, 3-years, 4-years, and a minimum of 5-years post-operatively.
Safety:	All adverse events (AEs) reported throughout the PAS will be summarized in annual study reports.

4 TABLE 2: SUBJECT MANAGEMENT STUDY SCHEDULE

Case Report Form (CRF) Number	Event / Visit	Pre-op		Operative	6 Wk	1 Yr	2 Yr	3 Yr	4 Yr	5 Yr Min
		-90 days of surgery	-180 days of surgery	Day 0	1– 92 d	275-455 d	640-820 d	1,005-1,185 d	1,370-1,550 d	1,825– Section 9.10 d
N/A	**Complete Screening Log**	✓								
N/A	**Obtain Informed Patient Consent (IPC)**	✓								
N/A	**Verify Inclusion / Exclusion Criteria**	✓								
"STATUS"	**Identify Protocol, Confirm Eligibility, Confirm Consent**	✓								
1	**Subject History**	✓								
2	**Harris Hip**	✓			✓†	✓	✓	✓	✓	✓
4a	**Subject Hip Outcomes (Clinic)***					✓	✓	✓	✓	✓
4b	**Subject Hip Outcomes (Phone)***							✓	✓	
6	**Operative Details**			✓						
7	**Device Log**			✓						
8	**Interim Visit Report††**				✓	✓	✓	✓	✓	
9	**Adverse Events****	✓			✓	✓	✓	✓	✓	✓
10	**Withdrawal Form*****	✓			✓	✓	✓	✓	✓	✓
Radiographs	Antero-Posterior *(AP)* ****	✓			✓	✓	✓	✓	✓	✓
	*AP femur*****	✓			✓	✓	✓	✓	✓	✓
	Lateral	✓			✓	✓	✓	✓	✓	✓
	Cross-Table Lateral				✓					

† Range of motion is an **optional** assessment at the 6-week interval.

* If subjects are not willing or able to return for a clinical and radiographic follow-up visit in the 3- and/or 4-year interval, then a telephone interview may be utilized for the purpose of determining device survivorship/patient satisfaction and CRF 4b will be used.

†† **To be completed, as applicable when subjects return for an unplanned visit (only** between the protocol-defined windows).

** When applicable

*** The Withdrawal Form will be completed for **all subjects** either to document a premature withdrawal or to designate that the end of study/ 5-year final endpoint has been completed

**** For pre-op films **only**, the visit window can be -180 days before surgery

***** The AP femur view is required only when the distal end of the femur is not visible on the AP view

5 INTRODUCTION

The following information describes a post-approval study (PAS) to be conducted for the 36 mm DePuy Synthes CERAMAX® Ceramic Total Hip System with BIOLOX delta® advanced composite ceramic. This study is being conducted in accordance with *21 CFR Part 814, Subpart E- Post-approval Requirements* of the United States Code of Federal Regulations covering post-approval studies for premarket approval (PMA) applications approved by the Food and Drug Administration.

6 PURPOSE

This study is intended to gather short and mid-term information regarding the performance and safety of the commercially available 36 mm CERAMAX® Ceramic Hip System from a cohort of new study subjects that were not previously involved in the IDE for this device. The compiled information will be included in the interim and annual post-approval study reports for the approved PMA (PMA P070026) submitted to the FDA.

This is not a hypothesis driven study. Instead it is designed to estimate device survivorship with an anticipated margin of error.

7 DEVICE DESCRIPTION

A detailed listing of permitted product codes is included in **Exhibit D** (Surgical Technique, pages 40-46) and **Exhibit K** (Device Codes). A brief description of the permitted components is included in this section. Please note, the direct anterior surgical approach is not permitted in this protocol.

7.1 The 36 mm CERAMAX® Ceramic Hip System consists of:

- a modular 36 mm inner diameter ceramic bearing insert that secures to a titanium metal alloy PINNACLE™ Acetabular Shell via a taper locking mechanism; and
- a 36 mm outer diameter ceramic femoral head that is attached to a conventional femoral stem to complete the total hip prosthesis device configuration.

7.2 36 mm CERAMAX® Ceramic Acetabular Bearing Insert

The 36 mm ceramic acetabular bearing insert component is manufactured from high purity, dense alumina matrix composite ceramic. CCI [redacted] The insert is available in several inner diameter sizes, including 36 mm; only 36 mm inserts will be utilized in this PAS. The inserts secure to DePuy Synthes' PINNACLE acetabular shells by means of an interlocking mechanical taper. The PINNACLE Tamp Extractor can be used to reposition and or remove a ceramic PINNACLE insert that has not yet been seated. Instructions to use the Tamp Extractor are as noted in the **Exhibit D** (Surgical Technique, pages 34-35).

7.3 PINNACLE Metal Outer Shell

The shells are designed to assemble to the ceramic insert components described above. The styles utilized in this clinical investigation are the POROCOAT-coated PINNACLE 100, PINNACLE 300, Sector II, and Multi-Hole Series shells.

7.4 Ceramic Femoral Head

The 36 mm BIOLOX delta® ceramic femoral head components are manufactured from the same ceramic material as the acetabular bearing insert components. The femoral head is secured to the femoral stem component with an interlocking taper. There are two taper sizes: 11/13 and 12/14 and these sizes correspond to the appropriate femoral stem. The femoral head is available in several outer diameter sizes and multiple offsets; only 36 mm heads will be utilized in this PAS to match the inner diameter of the ceramic bearing insert.

7.5 Femoral Stem

The stems with the 36 mm CERAMAX® device include the SUMMIT® POROCOAT®, Tri-Lock® Bone Preservation Stem (BPS) and the S-ROM® devices only. Refer to **Exhibit K** for a complete listing of permitted stems.

8 STUDY DESIGN, IRB REVIEW, INFORMED PATIENT CONSENT (IPC), FINANCIAL DISCLOSURE

8.1 Study Design

This is a prospective, non-controlled, non-randomized, multicenter study of the 36 mm Ceramic on Ceramic (COC) device.

A new enrollment cohort of a minimum of 170 subjects will be prospectively enrolled into the study. Study sites will be comprised of both IDE study sites, as well as newly recruited sites. These subjects will be seen for a pre-op clinic visit at the time of consent, and then at 6 weeks, 1 year, 2 years, 3 years, 4 years, and a minimum of 5 years. The purpose of the pre-op visit will be to obtain patient medical history and baseline information. At the post-op clinic visits the following information will be obtained: a Harris Hip evaluation, radiographic evaluation, subject evaluation and adverse event information (if applicable). The primary endpoint in this study is device survivorship at 5 years post-op. A minimum of 80% of enrolled subjects will be confirmed to either have a surviving implant or to have had a revision at a minimum of 5 years post-op with a clinical evaluation.

For a given Subject, their study participation will end if they withdraw consent, as per PI decision, undergo a revision of either the acetabular shell and/or liner, are reported as deceased or when they have reached the final endpoint at 5 years.

8.2 Primary Endpoint

Device survival at 5 years post-op is the primary endpoint in this study. A revision is defined as the removal of any THA component(s), and device survival is defined as the lack of revision. A 5-year Kaplan-Meier survivorship estimate of COC 36 mm implanted hips will be estimated.

8.3 Primary Endpoint Justification

The maximum acceptable hazard of revision for the COC 36 mm system is assumed to be a constant 1% per year, that is, *h(t) = 0.01.* The survival function for this hazard is

$$S(t) = exp\left[-\int_0^t h(u)du\right] = \exp(-0.01t),$$

so at 5 years, a minimally acceptable level of survival is assumed to be

$$S(10) = exp[-0.05] = 0.951.$$

It will be demonstrated that the Kaplan-Meier 5-year point estimate of survival is at, or higher than this minimally acceptable level of 95.1%.

8.4 Sample Size

The sample size will be a minimum of 170 prospectively enrolled subjects. This sample size will provide data upon which to obtain a 5-year survivorship estimate from newly enrolled subjects who did not participate in the COC36 IDE study. The sample size of 170 subjects in this PAS is approximately the same sample size of COC36 IDE investigational subjects, and hence will provide sufficient data on a new cohort of subjects to further support mid-term clinical success.

The objective of this study is to obtain an estimate of device survivorship at 5-years post-operatively. The enrolled 170 enrolled subjects will provide a minimum of 136 subjects (80% of enrolled subjects) with 5-year follow-up. This will yield a 5-year survivorship estimate that has an approximate 3.6% margin of error. In particular, Peto's estimate[1] for the variance of a Kaplan-Meier survival estimate is

$$var\big(\hat{S}(t)\big) = \frac{\big(\hat{S}(t)\big)^2\big(1-\hat{S}(t)\big)}{n(t)}$$

where $\hat{S}(t)$ is the estimate of survival at time *t* and $n(t)$ is the number of unrevised subjects at risk (still being followed) at time, and *t*. Hence, if it is assumed that the point estimate of survival is at a minimally acceptable level of 95.1% for subjects in this PAS, and there is a minimum of 136 subjects (80% of enrolled subjects) at 5-years post-operatively upon which this estimate is based, then an estimate for the variance of the Kaplan-Meier survival estimate at 5 years is

$$var\big[\hat{S}(5)\big] = \frac{[0.951]^2(0.049)}{136} = 0.00034\,,$$

and a two-sided 95% confidence interval margin of error for survival at 5 years is anticipated to be approximately

$$1.96 * \sqrt{0.00034} = 3.6\%.$$

A sample size of 170 enrolled subjects is therefore justified in order to obtain a 3.6% margin of error on a 5 year survivorship estimate.

8.5 Anticipated Number of Subjects with Minimum 5 Year Follow-up

A minimum of 80% of enrolled subjects (136 subjects) will be confirmed to either have a surviving implant or to have had a revision at a minimum of 5 years post-op with a clinical evaluation.

8.6 Treatment Assignment

The 36 mm COC device is the only device configuration of interest in the study.

[1] Cantor, A. Estimates of the Variance of the Kaplan-Meier Estimator. In: *Extending SAS® Survival Analysis Techniques for Medical Research.* 2nd ed., Cary NC: SAS Institute, 2003:24.

8.7 Secondary Endpoints

Secondary endpoints include Harris Hip score and sub-score means, radiographic evaluations, device survivorship, and adverse event outcomes at each protocol defined post-op interval. Cumulative results of these endpoints will be reported in each interim PAS report to FDA.

8.8 Interim Analysis

There are no planned interim analyses for the purpose of terminating the study early. However, some statistical analyses may be performed for conference presentations or abstracts prior to the primary endpoint being reached.

Interim analyses of the primary and secondary endpoints will be carried out for each interim PAS report to FDA.

8.9 Analysis Plan

At the time of each interim PAS report, the following analyses will be presented for all subjects combined, as well as separately for each individual stem type that is represented in the PAS, and also separately for each individual cup type that is represented in the PAS:

- Baseline summary statistics will be calculated for age, weight, BMI, race, ethnicity and pre-op Harris Hip Scores for both cohorts. The proportion of each gender will be calculated.
- Harris Hip score summary statistics and change from baseline statistics will be reported for each protocol defined post-op visit interval. These will be provided for total Harris Hip score as well as the Harris Hip sub-scores (pain, function, activity, deformity, and range of motion). These will be provided for total Harris Hip score as well as the Harris Hip sub-scores. Results will be presented overall, as well as stratified by obesity (non-obese vs. obese) according to BMI (subjects with BMI < 30 and with BMI ≥ 30, respectively)[2].
- Subject-reported outcomes will be reported for each protocol defined post-op visit interval.
- Radiographic analysis will be reported for each protocol defined post-op visit interval.
- Tabular displays of all cumulative reported adverse events will be provided by adverse event, as well as by category (intraoperative, postoperative-operative site, systemic, and overall). Tables will also be provided of adverse events over time.
- A Kaplan-Meier survivorship analysis will be provided, with device survivorship as a function of post-op time. A proportional hazards model will be provided, in which device survivorship is a function of post-op time, and with BMI (at the time of index surgery) as a covariate. Implant survival will be reported over time where greater than 40 hips are still at risk of revision.
- For Subjects that are not able to return to clinic at the 3- or 4-year interval, device survivorship information will be obtained through telephone interviews and will be utilized in the Kaplan-Meier analysis of device survivorship for the primary endpoint analysis in the study.

[2] Obesity is defined as BMI ≥ 30 According to the World Health Organization: http://www.who.int/mediacentre/factsheets/fs311/en/

8.10 Institutional Review Board

Prior to enrolling subjects into the study, each participating Investigator will be required to obtain approval from the reviewing institutional review board (IRB) at each institution where the study will be conducted. It is the Investigator's responsibility to submit and obtain IRB approval of the study plan, the Informed Patient Consent form (IPC), and any relevant study related information.

Revisions or amendments to the study plan and/or the IPC form that affect the scientific soundness of the post-approval study or the rights, safety or welfare of the participating subjects require approval by the reviewing IRB and the study sponsor prior to being implemented.

8.11 Informed Patient Consent (IPC) and Authorization for Release of Medical Records

An informed patient consent must be obtained for all subjects in person prior to enrollment into this 36 mm COC Post-Approval Study. Subjects who agree to participate will complete an IRB-approved IPC that documents his or her willingness to take part in this post-approval study. Each potential subject will have the nature and the purpose of this clinical investigation explained to him or her by the Clinical Investigator or another member of the investigative team at the site. The investigator 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
- Possibility of failure and subsequent treatment(s)
- Alternative procedures
- Requirements of the study (follow-up visits)
- 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 to 5-years.

Prior to entry into this clinical investigation the patient must give voluntary, written informed patient consent to participate by signing the IPC. A copy of the IPC is to be provided to the subject. A study subject is enrolled once they have signed the IPC and had the study device implanted.

8.12 Financial Disclosure

Each Investigator participating in the study will complete a financial disclosure form at the beginning of the study and then per DePuy Synthes' policy thereafter. Per FDA requirements, an additional financial disclosure must be completed one year after the study has concluded.

9 POST APPROVAL STUDY PLAN

9.1 Subject Population

For the purpose of this study, a Subject is defined as an individual who participates in the clinical study as a recipient of the investigational product. Note: before the IPC is obtained, a Subject is referred to as a "patient".

The post-approval study (PAS) will be comprised of:	Prospectively enrolled subjects in this COC36 PAS study who meet the eligibility criteria described below and are willing to provide written informed consent.

The Investigator or designee will solicit the IPC of any patient meeting the eligibility criteria and will explain the features of the study and answer any questions from the patient.

9.2 Indication for Use

Subjects will be entered into this study if they meet the criteria for inclusion described below. Subjects who have an existing contra-lateral total hip replacement at the time of consent may also be entered into this study if they qualify based upon the criteria for inclusion and the approved labeling requirements.

9.3 Subject Eligibility

The eligibility criteria will be consistent with the approved labeling for the COC36 device (**Exhibit H**).

Individuals meeting all of the following specific criteria will be considered for participation in the study:

9.4 Inclusions:

1. Males and females between 21 - 75 at the time of surgery.
2. Individuals, who in the opinion of the investigator, are suitable candidates for primary total hip replacement using the devices specified in this protocol.
3. Individuals with non-inflammatory degenerative joint disease (NIDJD) or any of its composite diagnoses of osteoarthritis, avascular necrosis, and posttraumatic arthritis.
4. Individuals who are willing and able to provide informed patient consent for participation in the study;
5. Individuals who are willing and able to return for follow-up as specified by the study protocol; and
6. Individuals who are willing and able to complete the Subject Hip Outcomes questionnaire as specified by the study protocol.

9.5 Exclusions:

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

1. Skeletally immature patients (tibial and femoral epiphyses not closed)
2. Evidence of active infections that may spread to other areas of the body (*e.g.,* osteomyelitis, pyogenic infection of the hip joint, overt infection, urinary tract infection, etc.)

3. The presence of any known neoplastic (tumor-causing) or metastatic (spread of cancerous cells) disease
4. Significant neurologic or musculoskeletal disorders or diseases that may adversely affect gait, weight bearing or postoperative recovery (*e.g.,* muscular dystrophy, multiple sclerosis)
5. Presence of highly communicable disease(s) that may limit follow-up (*e.g.,* immuno-compromised conditions, hepatitis, active tuberculosis, etc.)
6. Any condition that may interfere with postoperative recovery (*e.g.,* Paget's disease, Charcot's disease)
7. Inadequate bone stock to support the device (e.g., severe osteopenia or osteoporosis)
8. Poor skin coverage around the hip joint
9. Use in patients with known allergies to the implant materials
10. Marked atrophy (muscle and/or tissue loss) or deformity in the upper femur such as a birth defect affecting the leg bones.
11. Inflammatory degenerative joint disease (*e.g.,* rheumatoid arthritis)
12. Subject has participated in an IDE/IND clinical investigation, other than the COC28/COC36 IDE or PAS for their contralateral hip, with an investigational product in the last three months.
13. Subject is currently involved in a personal injury litigation, medical-legal or worker's compensation claims.
14. Subject is a known drug or alcohol abuser or has a psychological disorder that could affect their ability to comply with protocol procedures and/or subject-completed questionnaires.
15. The Subject is a woman who is pregnant or lactating.
16. The Subject has a medical condition with less than 2 years of life expectancy.

9.6 Recruitment Strategy

Sites will be recruiting potential study subjects from their population of primary total hip arthroplasties. Sites will provide screening/enrollment logs to the Sponsor so that the Sponsor can monitor progress and reallocate cohorts as needed. Sites will be instructed to begin actively recruiting all subjects upon receipt of the IRB approval letter. Screening results are documented on the screening and enrollment log.

9.7 Enrollment & Subject Identification Number

A study subject is **enrolled** when they have met eligibility criteria, been consented and had the THA procedure and study device implanted per protocol. Once enrolled, the site assigns the subject ID number which is comprised of a two-digit site code followed by a 4- digit subject specific code. For example, the first three enrolled subjects at site #06 would be: 06-0401, 06-0402, 06-0403.

9.8 Subject Evaluations and Follow-up

Diagnostic, demographic and operative information and clinical follow-up for each enrolled Subject will be documented on case report forms which have been developed specifically for this study. Examples of the case report forms for this post-approval study are provided in **Exhibit A**. The "Status" case report form (CRF) is completed for all subjects to identify which protocol each subject is participating. Details of subject evaluations are summarized in **Table 3** below.

9.9 Table 3 Subject Evaluations.

Table 3 Subject Evaluations	
Diagnostic, demographic & Study entry	Diagnostic, demographic and study entry criteria are documented on the Subject History case report form.
Clinical Assessment	The modified Harris Hip Evaluation will be used to clinically assess each subject at the pre-op and post-op intervals specified in the **Table 4** below. Also note, range of motion (ROM) at the 6 Week follow-up interval is an ***optional assessment***.
Subject Self-Assessment	Subjects will also complete hip outcomes self-assessment, which includes questions about their satisfaction and hip function starting at the 1 year post-op interval.
Radiographic	High quality antero-posterior (AP) and lateral radiographs of the operative hip will be obtained during the same post-op follow-up intervals as for the clinical evaluations (*i.e.,* 6 weeks, 1-5 years). Of note, for pre-op films only, the visit window can be -180 days before surgery. An additional AP femur view is required **only** if the distal tip of the femoral stem cannot be seen and/or assessed on the AP view. Also, at the first post-op visit, at 6 Weeks, a Cross-Table Lateral film will be collected to permit assessment of cup positioning. 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) may involve the use of a web-based application. Observations will be documented by the IRR on to the radiographic CRFs and entered into the study database.
Risk Analysis (Safety)	See **Section 10.**

Interim Visits	An interim 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 interim visit is **only** to be reported when the visit falls between study intervals as described in **Table 4**. An Interim Visit CRF is not to be completed if the Subject comes in for additional, unplanned visits in the "in-window" study interval. If the previous protocol-defined, study interval visit was missed, the required CRFs in that previously-missed interval visit are also required along with the Interim Visit CRF. If the interim visit is related to a new, worsening, or resolved adverse event, both an Adverse Event CRF and Interim Visit CRF are completed.
End of Study/ Withdrawal	**This form must be completed for all enrolled subjects to either reflect"** • **Completion of final endpoint (Minimum 5 years)** • **Premature withdrawal** Study participation may be prematurely discontinued through revision of acetabular components (shell and/or liner), withdrawal of consent, or death. ➢ *NOTE: A **revision** is defined as a surgical procedure of the affected hip where one or more of the THA components (femoral stem, femoral head, acetabular shell and/or acetabular liner) are removed. Of note, if both the acetabular shell and ceramic liner remain intact, the Subject will continue to be followed in the study.* ➢ *NOTE: Should it be necessary for the Subject to undergo a revision of either the acetabular shell and/or the acetabular liner between the date of the enrollment and the completion of the study data acquisition, **the Subject is withdrawn from study participation. Thus, both an Adverse Event (AE) CRF and an END of Study/Withdrawal CRF would be completed.***

Electronic Case Report Forms (CRFs) entered into an electronic data capture (EDC) system will be used to collect all Subject data once a Subject is enrolled in the study. Study sites will be instructed to enter Subject data on to the CRFs via the EDC web-based database portal.

The patient-reported outcome measure, CRF 4a, Subject Hip Outcomes (Clinic) will be recorded on a paper-based CRF. The data will then be entered into the respective CRF within the EDC system by the PI or designee. The patient-reported outcomes measure captured on paper-based CRFs must be stored in the Subject's medical notes, as these are considered to be the source document.

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. The Postoperative visit intervals will be assigned the following schedule:

9.10 Table 4: Postoperative Visit Intervals

	6 Week	1 Year	2 Year	3 Year	4 Year	5 Year Min
One Event / Visit	*1– 9 2 d	275-455 d	640-820 d	1,005-1,185 d	1,370-1,550 d	1,825–2,555 d

*6-Week follow-up ROM is an **optional** assessment, based on standard of care procedures at each study site.

Follow-up of orthopaedic patients is known to be a challenge, particularly after the 2-year postoperative visit. Ideally, all subjects are to be seen in clinic at the intervals described in the above table so that they may be physically assessed, and radiographs obtained per this protocol. In order to optimize mid-term follow-up compliance, site personnel are permitted to contact the study subject in the 3- and 4-year intervals by phone (in place of a clinic visit) to assess the current status of the hip. For these limited circumstances, the site shall complete CRF 4b - Subject Hip Outcomes (Phone), which will provide information regarding survivorship and safety, in addition to patient satisfaction via direct data entry. In the event that a subject discloses a safety event, such as a hip problem, they should be encouraged to return to clinic for assessment.

10 RISK ANALYSIS

10.1 Potential Adverse Events (AEs)

Adverse Events (AEs) must be reported for all Subjects and AE determination will be done by the Principal Investigator, or appropriate designee.

Potential AEs include:

- Excessive wear of the ceramic components secondary to damage of mating wear surfaces or debris particles;
- Metal sensitivity reactions;
- Possible detachment of the coating(s) on the femoral stem or acetabular shell components, potentially leading to increased debris particles;
- Device related noise such as, clicking, popping, squeaking or grinding;
- Pain;
- Femoral or acetabular perforation, or bone fracture while seating the device;
- Damage to blood vessels resulting in hematoma;

- Temporary or permanent nerve damage resulting in pain or numbness of the affected limb;
- Undesirable shortening or lengthening of the limb;
- Traumatic arthrosis of the hip from intraoperative positioning of the extremity;
- Cardiovascular disorders including venous thrombosis, pulmonary embolism, or myocardial infarction;
- Temporary or permanent neuropathies;
- Delayed wound healing;
- Infection;
- Osteolysis;
- Fracture, migration, loosening, subluxation, or dislocation of the prosthesis or any of its components, any of which may require a second surgical intervention or revision;
- Periarticular calcification or ossification, with or without impediment to joint mobility;
- Inadequate range of motion due to improper selection or positioning of components, by femoral impingement, and periarticular calcification; and
- Death.

These possible AEs are not unique to the CERAMAX® Ceramic Hip System and, as stated above, may occur with any total joint replacement surgery.

10.2 Potential Adverse Events (AEs) Associated with the CERAMAX® Ceramic Hip System

The most commonly reported adverse events related to the DePuy Synthes CERAMAX® Ceramic Total Hip System are:

- Wear of the ceramic acetabular components has been reported following total hip replacement. Higher rates of wear may be initiated by particles of cement, metal, or other debris that can cause abrasion of the articulating surfaces. Higher rates of wear may shorten the useful life of the prosthesis, and lead to early revision surgery to replace the worn prosthetic components.
- While rare, fatigue fracture of the prosthetic component can occur as a result of improper assembly, trauma, strenuous activity, improper alignment, or duration of service.
- Component dissociation.
- Breakage or chipping of the ceramic femoral head and/or ceramic acetabular insert.

There are no additional risks to the subject associated with participation in this study. The evaluations included in the study are considered to be the standard of care for following total hip replacement patients. Likewise, 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 this Ceramic on Ceramic articulation.

10.3 Table 5 Definitions of Adverse Events (AE) Types

For this protocol, the term “expected’ will be synonymous with the term “anticipated” and “unexpected” will by synonymous with “unanticipated”.

This protocol requires each study site to report AEs, serious adverse events (SAEs), adverse device effects (ADEs), serious adverse device effects (SADEs), and unexpected (unanticipated) adverse device effects (UADEs) to their respective IRB/EC per their IRB/EC requirements.

Table 5 Definitions of Adverse Event (AE) Types	
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). 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/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/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 (CHU) for investigation.

10.4 Definition of AE Severity

An AE 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.

10.5 Adverse Event (AE) Reporting

The definition of an AE is provided above in **Table 5**. Pre-existing medical conditions or symptoms reported prior to the surgical event are to be recorded as part of the medical history and not be recorded/reported as AEs. The only exception would be in the event there is an exacerbation of a pre-existing medical condition or symptom(s) in the post-operative time frame, then an AE must be reported.

A record of each AE, except for those anticipated AEs listed in **Exhibit L**, including details of the AEs are reported beginning from surgery and until Subject participation has ended (study completed, or consent withdrawn). Study sites have two (2) weeks from when they become aware of AEs to inform the Sponsor via the

AE CRF. If unable to enter the AE CRF you must contact the Sponsor directly or your Clinical Research Associate (CRA) to report.

AEs must be followed to resolution, or until the study completion or consent withdrawal. When a Subject ends participation in the study (either completion or consent withdrawal) AEs must be reviewed and designated, if applicable, as "resolved" and an end date provided. If AEs are not resolved at the end of a Subject's participation, they will be considered ongoing.

An AE should be reported for each AE – meaning, if edema and bleeding occur secondary to a fall there will be two (2) AEs reported that can be attributed to a fall. Subjects should be encouraged to report AEs spontaneously and may volunteer AE information at any time. At each evaluation, the Subject should be asked if any AEs have occurred since their last evaluation. If an event occurs at an outside institution, the Investigator should attempt to obtain, if possible, required AE information.

The Investigator will record the nature, severity, treatment and outcome of the AE, and will determine their association to the device and/or the study procedure (see **Section 10.6** below).

All UADEs, SADEs and SAEs, defined in **Table 5** above, 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 via the AE CRF. If unable to enter the AE CRF you must contact the Sponsor directly or your CRA to report.
In the event of a UADE the investigator should institute appropriate therapeutic and follow-up measures in accordance with good medical practice and notify their IRB/EC. The investigator must document follow-up treatment in the "comment" section of the AE CRF. 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'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 immediately and electronically reported to the DePuy Synthes Complaint Handling Unit (CHU) for investigation.

10.6 Determination of Relationship to Device and/or Procedure

The determination whether the AE is related to the device and/or procedure will be based upon whether a causal relationship between the device or procedure and the AE a reasonable possibility is, *i.e.,* the relationship cannot be ruled out. A causal relationship cannot be ruled out if, in the medical judgement 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.

Device related AEs will be reviewed by DePuy Synthes and reported, if applicable, to the appropriate regulatory body.

10.7 Minimization of Risk

Only trained orthopaedic surgeons with expertise in treating total hip conditions will participate in this study.

Investigators should refer to the instructions for use (package insert, **Exhibit H**) for additional information and reference the surgical technique (**Exhibit D**).

The Sponsor will further minimize the identified and/or emergent risks throughout the study, by reviewing the reported complications and adverse effects. All AEs, SAEs, ADEs, SADEs and UADEs will be reviewed and evaluated by the Medical Monitor assigned to this study.

11 STUDY SUMMARY STATEMENT

In summary, this PMA Post-Approval Study for the 36 mm CERAMAX® Ceramic Hip System will support short and mid-term safety and performance with an expanded pool of clinical investigators. The newly enrolled subjects will expand information contained in the original PMA submission by supporting survivorship at 5 years post-op.

For a given subject, their study participation will end if they withdraw consent, as per PI decision, undergo a revision of either the acetabular shell and/or liner, are reported as deceased or when they have reached the final endpoint at 5 years.

12 IMPLANTS RETRIEVALS

Any prosthesis that may be made available because of a removal or revision surgery or subject death will be submitted for detailed evaluation. A protocol for device explanation and retrieval analysis is included (**Exhibit M**).

If the implant is known to be available, the sponsor will encourage the investigator to preserve the prosthesis alone, or, in the event of a death, if possible, provide the excised hip joint with the implant in place.

Retrieval analysis will be completed by one or more independent reviewers as outlined in the **Exhibit M**. In addition, DePuy Synthes and/or CeramTec may perform analyses, as appropriate.

13 CLINICAL MONITORING

Monitoring activities will follow the Sponsor standard operating procedures (SOPs), applicable FDA regulations and good clinical practices (GCPs). Given that this is a regulated study and the level of risk to Subject safety and data integrity, and criticality of ensuring compliance, monitoring will include onsite monitoring visits. Remote monitoring may be conducted if deemed appropriate by the Clinical Study Lead and Clinical Operations lead (*e.g.*, if sites have not enrolled (consented) any Subjects).

14 REPORTING

Reports of this study will be prepared according to the Guidance for Industry and FDA Staff: Clinical Data Presentations for Orthopaedic Device Applications.

Per the Guidance for Industry and FDA Staff- Procedures for Handling Post-Approval Studies Imposed by PMA Order http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm071013.pdf), the applicant will provide a report to the FDA every 6 months for the first 2 years following device approval and annually thereafter until the end of the study (see **Section 16.2**).

The reports will include:

- A complete listing of all sites and IRBs.
- Enrollment updates (during enrollment) – screening/recruitment logs from all sites
- Site follow-up compliance to clinical investigation plan,
- Clinical Results- Overall Harris Hip Scores and Harris Hip sub-scores (pain, function, activity, deformity, and range of motion)
- Radiographic Results
- Safety Summary- documentation and compilation of all adverse events
- Survivorship at each year post-operatively for which there are sufficient subjects to compute survivorship

15 PUBLICATION POLICY

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.

16 PROJECTED TIMELINES FOR POST APPROVAL STUDY

16.1 Overall Study Projected Timeline

The anticipated duration of this investigation is approximately seven years from the time of study initiation.

- It may take up to a minimum of 2 years from the time of study initiation to enroll new subjects.
- Each subject will be followed until they have completed their minimum 5 year follow-up.

All timeline information is reflected as “deltas” compared to previous column.

Expected # of Study Sites	*Expected Date of Study Initiation	Expected Date of Obtaining IRB Approval for all Sites	Expected Date of Completion of Subject Enrollment**	Final Endpoint
Up to 15 (up to 5 original IDE + up to 10 new sites)	6 months after agency approval of PMA	+ 3-6 months	+ 24 months	+ 5 years

* Defined as submission for approval of study by a reviewing IRB

** It is anticipated that it will take up to a minimum of 24 months to enroll new subjects. Approximately 7 subjects will be enrolled monthly.

16.2 Annual/Interim Reports Projected Timeline

Interim Reports will be provided to FDA every six months for two years following the date of final PMA approval. Reports will then be submitted annually until completion of the post-approval study. The contents of the reports are described above in **Section 14**. The schedule of dates for the reports to be provided is noted in the following table:

INTERIM / ANNUAL REPORT DUE DATES (based on April 2, 2013 PMA approval)
October 2, 2013
April 2, 2014
October 2, 2014
April 2, 2015
April 2, 2016
April 2, 2017
April 2, 2018
April 2, 2019
April 2, 2020
Annual Interim Reports to continue as required, based on 5-year follow-up Final Report will follow FDA reporting requirements