DePuy Synthes Joint Reconstruction
CLINICAL RESEARCH

CLINICAL INVESTIGATION PLAN (CIP)

TITLE

Comparison of Alignment achieved using Single-Use versus Reusable Instrumentation in Total Knee Arthroplasty (TKA): A Prospective, Non-Randomized Multi-Center Investigation.

Clinical Investigation Plan Number:	10002
Country:	Worldwide Study
CIP Prepared By:	[redacted]
CIP Version:	Revision B
Clinical Investigation Sponsor:	DePuy Synthes Joint Reconstruction a division of DePuy Orthopaedics, Inc. PO Box 988 700 Orthopaedic Drive Warsaw, IN 46581-0988 [redacted]

PROTOCOL SIGNATURE PAGE

Comparison of Alignment achieved using Single-Use versus Reusable Instrumentation in Total Knee Arthroplasty (TKA): A Prospective, Non-Randomized Multi-Center Investigation.

PROTOCOL 10002

Document Type/Revision		Protocol/Exhibit	Effective Date
Original	#1	Protocol/Exhibits Rev A	May 28, 2015
Administrative	#2	Protocol/Exhibits Rev B	February 19, 2018

Principal Investigator:

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

I understand the protocol and I understand I am solely responsible to ensure the investigation is conducted in accordance with Good Clinical Practices (GCP), applicable country regulations, the Declaration of Helsinki, the signed clinical study contract with DePuy Synthes Joint Reconstruction, and with the protocol outlined herein.

I will conduct this study as outlined therein and will make reasonable effort to complete the study within the time period designated by DePuy Synthes Joint Reconstruction.

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)/Ethics Committee (EC), 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 Joint Reconstruction and my reviewing IRB/EC.

I agree to report all information or data in accordance with the protocol and I agree to report any serious adverse events, device related adverse events, or procedure related adverse events as defined in this protocol to DePuy Synthes Joint Reconstruction and comply with all adverse events reporting requirements of my reviewing IRB/EC.

I agree to permit DePuy Synthes Joint Reconstruction, its authorized representatives, my reviewing IRB/EC, and any regulatory authority/body access to all records relating to the clinical investigation.

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

_____ _____

Principal Investigator Date

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1 LIST OF ABBREVIATIONS

ADE	Adverse Device Effect
AE	Adverse Event
AP	Anterior-Posterior
BS	ENBritish Standard European Norm
21 CFR	Code of Federal Regulation: Title 21
CE	Conformité Européenne
CIP	Clinical Investigational Plan
CR	Cruciate Retaining
CRF	Case Report Form (paper)
DVT	Deep Vein Thrombosis
EC	Ethics Committee
eCRF	Electronic Case Report Form
EMEA	Europe/Middle East/ Asia-Pacific
EU	European Union
FB	Fixed Bearing
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HTO	High Tibial Osteotomy
ICD	Informed Consent Document
IRB	Institutional Review Board
ISO	International Organization for Standardization
IRR	Independent Radiographic Reviewer
ITT	Intent To Treat
MEDDEV	Medical Device Guidance Document(s)
NIDJD	Non-inflammatory Degenerative Joint Disease
OR	Operating Room
PHI	Personal Health Information
PI	Principal Investigator
PMCF	Post-Market Clinical Follow-up
Post-op	Post-operative
PP	Per Protocol Analysis

Pre-op	Pre-operative
RUI	Reusable Instruments
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SAS®	Statistical Analysis System
SUI	Single Use Instruments
TKA	Total Knee Arthroplasty
UADE	Unanticipated Adverse Device Effect
UK	United Kingdom
US	United States
USADE	Unanticipated Serious Adverse Device Effect
UTO	Upper Tibial Osteotomy (See also HTO)

2 SUMMARY

TITLE:	***Comparison of Alignment achieved using Single-Use versus Reusable Instrumentation in Total Knee Arthroplasty (TKA): A Prospective, Non-Randomized Multi-Center Investigation.***
Short Title:	SUI vs. RUI
Protocol Number:	10002
Treatment Device:	**Single Use Instruments (SUI)** for implantation of ATTUNE® primary TKA. Four implant configurations are permitted: Cruciate Retaining Fixed Bearing (CR FB), Cruciate Retaining Rotating Platform (CR RP), Posterior Stabilizing Fixed Bearing (PS FB) and Posterior Stabilizing Rotating Platform (PS RP) configurations. Each site will be restricted to using either Cruciate Retaining configurations or Posterior Stabilizing Configurations for both treatment and control groups.
Control Device:	**Reusable Instruments (RUI)** for implantation of ATTUNE primary TKA. Four implant configurations are permitted: Cruciate Retaining Fixed Bearing (CR FB), Cruciate Retaining Rotating Platform (CR RP), Posterior Stabilizing Fixed Bearing (PS FB) and Posterior Stabilizing Rotating Platform (PS RP) configurations. Each site will be restricted to using either Cruciate Retaining configurations or Posterior Stabilizing Configurations for both treatment and control groups.
Intended Use:	The intended use for the instrumentation and device, applicable to this study, is as follows: Candidates for total knee replacement include patients with severely painful and/or severely disabling Non-inflammatory Degenerative Joint Disease (NIDJD) resulting from osteoarthritis (OA) or post-traumatic arthritis.
Primary Objective:	To determine whether the mechanical axis alignment achieved with SUI instrumentation is non-inferior to the alignment achieved with RUI instrumentation.
Secondary Objectives	• To compare individual component alignment achieved with SUI vs. RUI of individual components in the frontal and sagittal planes, specifically: distal femoral varus-valgus (FM), proximal tibial varus-valgus (TM), femoral component flexion and tibial slope. • To compare the type and frequency of adverse events
Study Design:	Prospective, comparative, sequential, non-randomized, multi-center, controlled study design. Level of evidence: Level III[A]
Number of Sites:	4 Centers Worldwide
Subject Population:	Male and female Subjects who are candidates for primary, total knee arthroplasty between 22 and 80 years of age, inclusive, with noninflammatory degenerative joint disease (NIDJD) resulting from osteoarthritis (OA) or post-traumatic arthritis.
Sample Size:	A total of 88 Subjects will be enrolled in the investigation (44 treatment Subjects and 44 control Subjects).

[A] Levels of Evidence for Primary Research Question

TITLE:	***Comparison of Alignment achieved using Single-Use versus Reusable Instrumentation in Total Knee Arthroplasty (TKA): A Prospective, Non-Randomized Multi-Center Investigation.***
Study Duration:	The estimated duration of this study is 13 months: 8 months for enrollment and 5 months for post-operative follow-up.
Procedure Schedule:	Demographic data will be collected preoperatively. Surgical data will be collected intraoperatively. Post–operatively, radiographic data will be collected at approximately 90 days.
Safety:	All adverse events will be collected from the time of surgery through to the end of the study or the time when that Subject is withdrawn from the study. A listing of expected, procedure-related, early postoperative adverse events (AEs) will be provided and such events will not need to be recorded.The type and frequency of recorded AEs will be analyzed.

2.1 Time and Events Table

Event / Visit	Pre-Op	Surgery	Post-Op
Required Timing (days)	-180d to include day 0	0	30 -150
Discuss Study with Subject	Yes		
Screening Log	Yes		
Informed Consent	Yes		
Enrollment	Yes		
Complete Subject History eCRF	C		
Surgical Procedure • **Complete** Operative Details eCRF • **Complete** Device Log eCRF		 C C	
Radiographs • Hip to Ankle Long Film			 R*
• AP View	R		R
• Lateral View			R
Complete Adverse Event eCRF		A	A
Complete End of Study/Withdrawal	A	A	C
Advise the Subject when they will next be seen	Yes	Yes	

C= Case Report Form to be completed and submitted in the Electronic data capture system
R= Radiograph obtained and submitted
R*, For the purposes of this investigation this radiograph will only be performed when the Subject can achieve full leg extension (±5°).
A= As needed

3 INTRODUCTION

3.1 Background

Alignment

Successful total knee arthroplasty relies on proper positioning of prosthetic components to restore the mechanical axis of the lower extremity. It is widely accepted that proper alignment is an important factor in the success and longevity of total knee arthroplasties [1-4]. Mechanical axis alignment is defined as the line drawn from the center of the femoral head through the center of the knee and ankle. The knee is in proper alignment when these three points are collinear in the frontal plane [1] . Many authors have observed that the correct alignment of the lower limb is correlated with clinical success in total knee arthroplasty [2-7].

Operating Room (OR) Efficiency
In this era of capitated reimbursement and managed care, cost containment is assuming greater importance in health care. Consequently, operating room efficiency has become higher priority for many institutions [8]. As patient volume increases and hospital resources are strained the OR can become a bottleneck in providing efficient, high quality patient care. Optimizing OR performance without compromising safe and high-quality health care for patients is an important goal.
There are a number of studies aimed at increasing operating room efficiency and controlling operating room costs while striving to provide high-quality, technologically advanced surgical services. Often the focus is on streamlining the existing steps that are involved in delivering patient care preoperatively, intraoperatively, and postoperatively [10]. This need for improved delivery of care is further critical when one recognizes the increasing number of patients needing TKA. Improved surgical instruments are one factor that may improve OR efficiency and an approach is to introduce Single-Use instruments.

An important aspect of the delivery of surgical care is the time required to prepare the operating room prior to the procedure as well as the turnover time at the conclusion of the surgery. Preparation timeline for every surgical procedure is at risk from various delays. Unwanted delays have occurred related to unavailable sterile instruments, holes found in the sterile wrap of sterilized instruments, the time required to flash sterilize an instrument requested last minute, etc. Prepackaged sterilized Single-Use instruments may help to resolve some of these unwanted delays. Additionally, when single use instruments are combined with preoperative templating to define implant sizing, there should be a substantial reduction in the quantity of instruments brought to the OR (Figure 1). Single use instruments provide a completely clean and sterile instrument for every patient, which is used once and disposed of, removing the need for lengthy decontamination processes[13].

Figure 3-1: ATTUNE TKA Instrumentation (left to right):Reusable instrumentation; and Single Use instrumentation shown

4 RATIONALE

4.1 Study Rationale

A pre-requisite for SUI adoption is to confirm that the mechanical axis alignment achieved with single use instruments is non-inferior to the alignment achieved with ATTUNE reusable instruments .

4.2 Study Design Rationale

The study was designed as comparative, sequential, non-randomized, multi-center, such that each site has an equal number of Subjects in each treatment group, SUI and RUI. The follow-up period of approximately 90 days was selected due to the time required for most Subjects to be able to achieve full leg extension (within ± 5°), a requirement for obtaining suitable weight-bearing hip-to-ankle radiographs for analysis of alignment. The mechanical axis alignment will be assessed at the 3 month follow-up by independent radiographic review. The sequential design (that is at each site all RUI cases will be completed before doing any of the SUI cases) is set up to ensure that with the control group (RUI), current status of OR efficiency is captured rather than this being influenced by any efficiencies learned from use of the SUI.

4.3 Rationale of Endpoints

Successful total knee arthroplasty relies on proper positioning of prosthetic components to restore the mechanical axis of the lower extremity. It is widely accepted that proper alignment is an important factor in the success and longevity of total knee arthroplasties [1-4]. A goal of 0° ± 3° mechanical axis alignment was chosen because the Investigators in this study confirmed they regularly aim for this target.

4.4 Rationale of Study Population

Subjects with NIDJD and determined to be suitable for a cemented, primary TKA with the ATTUNE implant are targeted as this study is on surgical instruments to implant a cemented, primary ATTUNE implant. Narrowing the indications to exclude inflammatory arthritis was done to have more homogeneity in the population, including bone quality that could possibly influence bone resections with the two instrument types.

5 SUBJECT DEFINITION

Male and female Subjects, aged 22-80 years, inclusive, with Non-Inflammatory Degenerative Joint Disease (NIDJD) resulting from osteoarthritis (OA) or post-traumatic arthritis and suitable candidates for primary, total knee arthroplasty using an ATTUNE system are eligible for enrollment in this study.

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

- Surgeon preference/medical opinion (under very limited conditions not to introduce Investigator bias).
- Withdrawal of consent from study participation.

5.1 Inclusion Criteria

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

a) Subjects with severely painful and/or severely disabling Non-inflammatory Degenerative Joint Disease (NIDJD) resulting from osteoarthritis (OA) or post-traumatic arthritis.

b) Subject is male or female and between the ages of 22 and 80 years old, inclusive.

c) Subject requires a primary total knee replacement and is considered by the Investigator to be suitable for the specific knee prosthesis identified in the protocol.

d) Subject, who, in the opinion of the Investigator, is suitable for implantation using either RUI or SUI instrumentation.

e) Subject is able to speak and read English to facilitate comprehension of the Informed Consent Document.

f) Subject has given voluntary, written informed consent to participate in this clinical investigation and has authorized the transfer of his/her information to DePuy Synthes Joint Reconstruction.

g) Subject, in the opinion of the Investigator, is able to understand this clinical investigation and is willing and able to perform all study procedures and follow-up visits and co-operate with investigational procedures.

5.2 Exclusion Criteria

Subjects will be excluded from participation if they meet **any** of the following criteria:

a) The Subject has, in the opinion of the Investigator, a severe deformity that will hinder achieving a mechanical axis alignment target of 0° ± 3°.

b) The Subject has, in the opinion of the Investigator, an existing condition that would compromise their participation and follow-up in this study.

c) The Subject has, in the opinion of the Investigator, a flexion deformity that will not allow for 0° extension postoperatively.

d) The Subject is a woman who is pregnant or lactating.

e) The Subject, in the opinion of the Investigator, is a drug or alcohol abuser (in the last 5 years) or has a psychological disorder that could affect follow-up care or treatment outcomes.

f) The Subject has participated in a clinical investigation with an investigational product in the last 3 months.

g) The Subject is currently involved in any personal injury litigation, medical-legal or worker's compensations claims.

h) The Subject has previous prosthetic knee replacement (any type including unicompartmental, total knee arthroplasty, patellofemoral arthroplasty or ipsilateral UTO/HTO) of the affected knee or a previous patellectomy.

i) The Subject presents with ankylosis of the hip joint on the side to be treated.

j) The Subject had a contralateral TKA and that knee was previously entered into the study.[B]

k) The Subject requires simultaneous bilateral total knee replacements.[C]

l) Any case in which Computer-Assisted Surgery (CAS) or TruMatch (or any other type of Custom Patient Instruments) is to be used, or any additional instrumentation are to be used for bone resections that are not provided as part of the ATTUNE RUI or SUI Instrument kits.

m) The Subject requires a device not specified in the protocol or the surgeon determines that the ATTUNE Knee System is not a suitable treatment.

5.3 Definition of Subject Enrollment

As described in additional detail in Section 8.2 a patient will be considered **enrolled** when they have:

✓ Provided written informed consent to participate in this Investigation, which includes authorization of the release of their Personal Health Information (PHI).

B Having both knees from one Subject in the study could confound the data.
C As the study involves measuring the time taken for stages of surgery a simultaneous bilateral procedure would confound this dataset (would always take longer)

6 OBJECTIVES AND HYPOTHESIS

6.1 Primary Objective

To determine whether the mechanical axis alignment[D] achieved with SUI instrumentation is non-inferior to the alignment achieved with RUI instrumentation. Mechanical axis alignment is defined as the line drawn from the center of the femoral head through the center of the knee and ankle and will be measured from weight bearing long-leg (51") Anteroposterior (AP) radiographs, taken approximately 90 days post-op (when subject has reached full knee extension) and read by an independent radiographic reviewer.

6.2 Secondary Objectives

- To compare alignment achieved with SUI vs. RUI of individual components in the frontal and sagittal planes, specifically: distal femoral varus-valgus (FM) , proximal tibial varus-valgus (TM), femoral component flexion and tibial slope.
- To compare the type and frequency of adverse events, from the time of surgery through to withdrawal of a subject or the end of the study (includes serious adverse events, and device and/or procedure-related adverse events), between the SUI and RUI instrument groups.

6.3 Exploratory Objectives

- To compare SUI and RUI operating room times from OR set-up through OR clean down as detailed in Table 8-3 of Section 8.3.3.
- To determine whether SUI provides opportunity to reduce the incidence of minor procedural obstacles during the time in the OR.
- To compare Surgeon satisfaction of SUI instrumentation to RUI instrumentation.

The primary and secondary clinical endpoints and the relevant statistical analyses are described in Section 10.6

6.4 Hypothesis

Hypothesis: If Single Use Instruments are used to implant an ATTUNE Total Knee, the alignment achieved will be non-inferior to that achieved with Reusable Instruments for the same procedure.

See Section 10.7 for further details on study hypotheses.

[D] *During preparation of this protocol discussions with the sites to be involved in this study confirmed that all 4 sites regularly plan to achieve 0° ± 3° mechanical axis alignment. Exceptions to this are only in rare cases of extreme deformity. The study has therefore been designed with this in mind and collection of pre-operative plans are not required for the study.*

7 STUDY DESIGN

This study is designed as a prospective, comparative, sequential, non-randomized, multi-center, controlled clinical investigation.

There will be 4 centers worldwide that will recruit a total of 88 Subjects (44 Treatment Subjects and 44 Control Subjects). A complete description of the methods for determining sample size is contained in Section 10.9. Initially, the Subjects will be evenly distributed across the four sites; therefore it is expected that each site will recruit 22 Subjects (11 Control followed sequentially by 11 Treatment Subjects). In between the Control and Treatment Subjects, a learning curve is permitted for the use of SUI.

- The **Control group** will consist of 44 Subjects, 11 per site and the surgical procedure for these Subjects will be performed using Reusable Instruments (RUI).
- The **Treatment group** will consist of 44 Subjects, 11 per site and the surgical procedure for these Subjects will be performed using Single Use Instruments (SUI).

At each site the 11 Control Subjects will be enrolled and operated on prior to performing the first surgery in the Treatment group. For a given site, either Cruciate Retaining or Posterior Stabilising configurations will be used; consistent with their standard of care. Within a given CR site, the Investigator may choose to implant either the CR FB or CR RP. Similarly, within a given PS site, the Investigator may choose to implant either the PS FB or PS RP. Randomization is not being applied in this study in order to isolate and learn if there are changes in OR efficiency with SUI under normal operating room procedures.

One surgeon at each site will complete all RUI and SUI surgical cases including the learning curve. No Sub-Investigators will be permitted to perform surgery to avoid possible confounding issues with varying surgical process. All sites will have previously completed their learning curve with the ATTUNE Primary Implant implanted using RUI prior to enrolling the 1st patient. Then after the completion of all RUI study cases, a learning curve will be permitted for the use of SUI. The duration of the SUI learning curve is anticipated to be approximately 5 cases and is at the discretion of the Principal Investigator. These early cases that are within the learning curve will not be enrolled into this study at each site.

Both resurfaced patellae and non-resurfaced patellae are permitted in this investigation, consistent with site standard of care. TruMatch technology or any other type of Custom Patient Instruments are not permitted. Similarly Computer-Assisted Surgery (CAS) is not permitted within the study. The procedures must be performed using only the instrumentation provided (SUI or RUI) and standard surgical methods, without additional tools that could confound the key research question of this study (for example, instrumentation that helps perform bone resections).

The Sponsor will monitor overall project enrollment. Cohort reallocation during the RUI phase only may be done in order to maintain project timelines. The Sponsor can authorize a shift of a group of Subjects from one site to another to maintain project timelines. For example, the Sponsor can reduce the cohort of a slow-enrolling RUI site to a faster-enrolling RUI site and the faster-enrolling RUI site will assume responsibility for the reallocated RUI cohort and the same number of SUI Subjects.

8 PROTOCOL

8.1 The sequence of events for a Subject are as follows:

- If the Patient is thought to be generally eligible, the Patient is invited to participate and the informed consent procedure is followed
- The Subject is screened for eligibility against the Protocol Inclusion/Exclusion criteria
- If the Subject meets the Protocol Inclusion/Exclusion criteria, a subject history is taken
- Within 180 days from initiating the consent procedure TKA surgery is performed during which operative details, timepoints of key stages of the procedure, instrument and device details, and any intraoperative complications are captured on eCRFs for submission and subsequent analysis.
- Approximately 90 days (+/-60 days) post-surgery weight bearing long-leg (51") Anteroposterior (AP) radiographs are taken and any postoperative complications collected. Radiographs are to be anonymized and sent to the Independent Radiographic Reviewer (IRR) for analysis.

8.2 Subject Enrollment

No study-related procedure or form associated with this study can be completed until written informed consent is obtained for that Subject. (see Section 5.3 Definition of Subject Enrollment).

8.2.1 Subject Screening

All Patients who present with NIDJD affecting the knee, and are candidates for primary, cemented TKA, and who generally meet the study requirements, will be screened for eligibility and will be listed on the Screening and Enrollment Log in order to document that the Subject selection was unbiased. The date of screening, the results of screening (included or not) and the primary reason for not including the patient (*e.g.*, does not satisfy eligibility criteria, not interested in participating) will be recorded on this log. The original log is to be retained at the Site and a copy sent to the Sponsor regularly during enrollment. A flowchart demonstrating the screening process and definition of enrollment is illustrated in Figure 8-1.

Eligible Patients who agree to participate in the study will be required to sign an Informed Consent Document prior to any study related procedures being done. ***After signing the Informed Consent, study Subjects are defined as "enrolled" and site will complete the non-standard of care pre-operative data collection.***

It is expected that complete data collection will be obtained for all enrolled Subjects, with the only exception being a Subject who is subsequently withdrawn. See Section 8.4 Discontinuation of Subject Participation (Withdrawal) for details.

8.2.2 Subject Informed Consent

In compliance with BS EN ISO 14155, and the Declaration of Helsinki, 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 BS EN ISO 14155, the Declaration of Helsinki, and this study protocol.

All informed consent documents (ICD) must have favorable opinion of the IRB/EC (Section 12.1). Consent of a Subject needs to be from the subject themselves and documented on an Informed Consent Document in the primary language of the Subject.

Screening, consenting and enrollment are illustrated in Figure 8-1. The Investigator or trained designee preliminarily screens to determine if a patient generally meets the eligibility criteria for the study (*item 2 in flowchart*, Figure 8-1). If so, the Investigator or trained designee shall offer study participation to those patients (*item 3 in flowchart*, Figure 8-1). If the patient agrees to participate s/he signs the informed consent document.

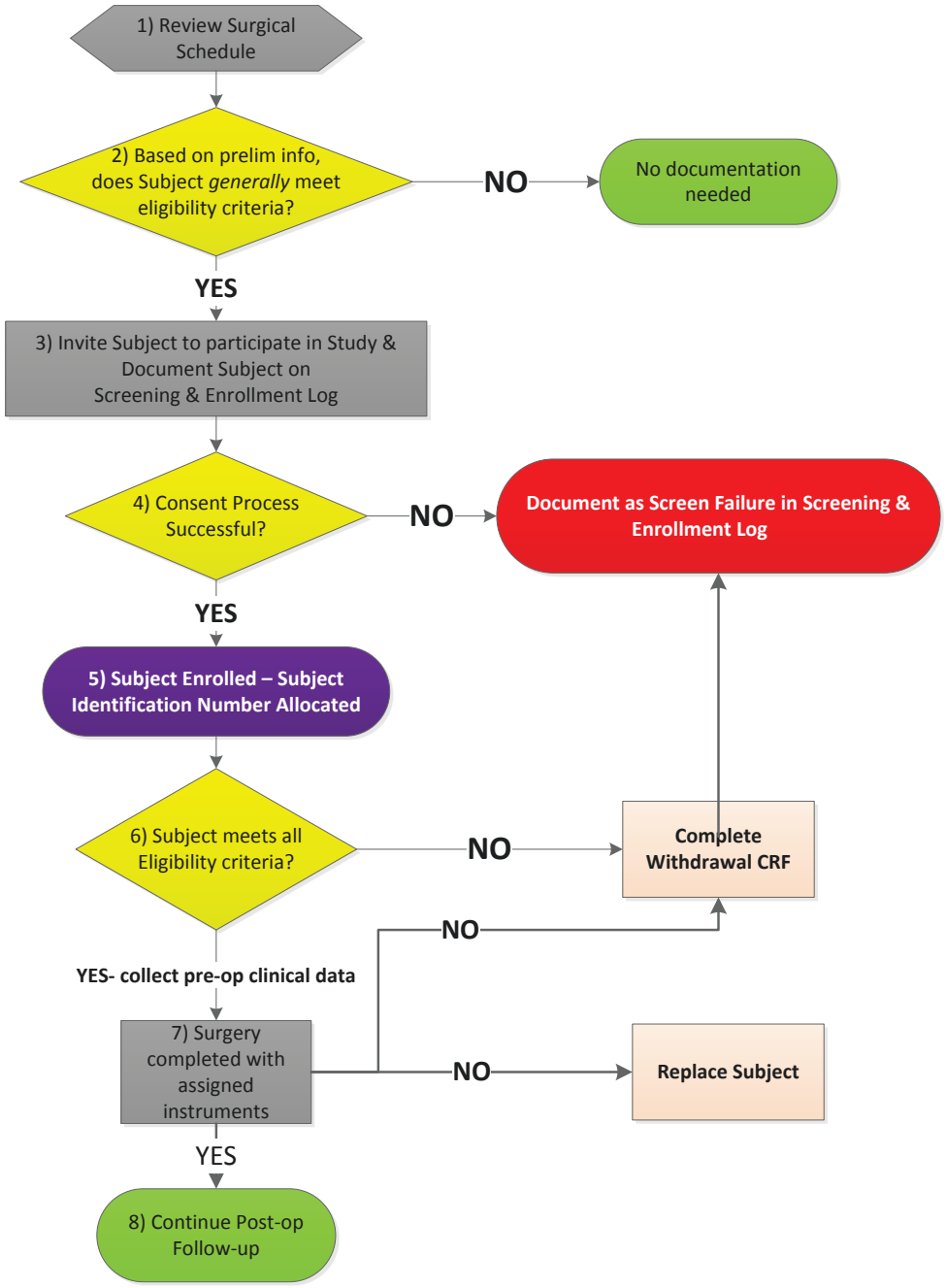
Table 8-1: Key Elements of Consent Process

Key Element of Consent Process *(item 4 of flowchart)*
The Investigator or designee shall confirm the Subject understands each of the following points of the study: • The purpose of the study, • The potential risks or adverse events that are posed by their treatment, • The potential risks or adverse events directly 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 including rehabilitation and follow-up visits, • All of the Subject's rights as a participant in the clinical investigation. Following the explanation of the study intent, the Investigator or trained designee shall offer to answer any of the Subject's questions. If the Subject then agrees to participate, his or her willingness must be documented via a signature and date on the IRB/EC's approved ICD and this document countersigned and dated by the person taking consent.

Upon successful completion of consent process, the Patient is enrolled and is identified as a Study Subject (*items 5 in flowchart*, Figure 8-1). The Investigator or trained designee will assess eligibility per Sections 5.1 & 5.2 (*item 6 in flowchart*, Figure 8-1).

Acquiring Consent on Day of Surgery: If the Informed Consent Document signatures are acquired on the day of surgery, a time stamp on the signature page is required to support that consent was obtained from the study Subject prior to any treatment related and/or mood altering medications being administered. A time stamp is not required where consent is obtained on a day prior to surgery.

Figure 8-1: Screening and Enrollment Process



8.2.3 Subject Identification Numbering

The **database assigns** Subject ID numbers after consent is obtained.

Each site is identified uniquely , e.g., 01-, 02- through 04, followed by 0001 for the first Subject, at the site, 0002 for the second Subject, and so on. For example, the first (3) three Subjects enrolled at Site #1 will be identified as 01-0001, 01-0002, 01-0003. Together the Site number and the Subject number will then become the unique identifier of the Subject and will be recorded on each page of the eCRF and on the Subject Screening & Enrollment Log.

In the instance of a Subject being enrolled, a number assigned and subsequently the Subject is deemed ineligible prior to receiving the ATTUNE knee, the Subject will be recorded as a screen failure on the screening/enrollment log. Once a Subject identification number is assigned, it may not be reused. Refer to Sections 8.4 Discontinuation of Subject Participation and 8.4.1 Enrollment Replacement Rules.

8.3 Study Procedures

This section is applicable to individuals who have undergone screening, have signed an Informed Consent Document, and have otherwise been found eligible to participate in this study per the Protocol's Inclusion/Exclusion criteria. This section details the pre-operative, operative, and post-operative management of Subjects. Visit evaluations include radiographic evaluations. Sample Case Report Forms (CRFs) are located in Exhibit A. eCRFs must be submitted to DePuy Synthes Joint Reconstruction as outlined in Section 12.7 Case Report Form Completion and Data Submission.

8.3.1 Subject Evaluation Tools

No Patient Reported Outcome Measures are included in this study.

8.3.2 Pre-operative Management

Prior to surgery, the evaluations in Table 8-2 must be completed for each enrolled Subject. The interval for obtaining pre-op assessments is - 180 days to day 0 (day of surgery) as designated on the Time & Events Table 2.1. The pre-surgery management of each Subject enrolled in this investigation will be according to the standards of care used at the study site.

Table 8-2: Pre-operative Data Collection and eCRF

Evaluation	Details of Evaluation
Subject History	**For all Subjects** the Investigator or designee must confirm consent has been given, record the Subject's demographic details and details of their previous medical history, and confirm eligibility on Subject History eCRF.
Radiographs	Pre-operative radiographs will be obtained.

8.3.3 Intra-operative Management

The surgical process is to follow site standard of care.
This investigation allows the Investigator to follow their current standard of care with respect to patellar resurfacing. Specifically the Investigator can choose to:

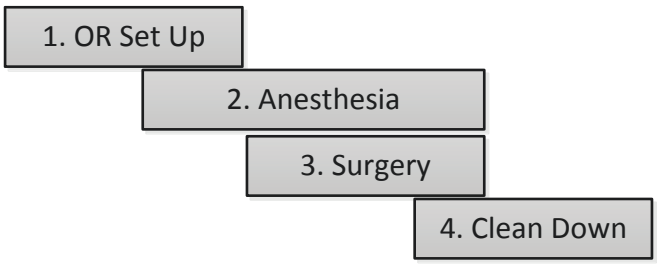
- Resurface the patella
- Leave the patella unresurfaced.

This investigation does NOT permit the Investigator to use TruMatch (or any other PSI instrumentation) or CAS for any Subjects, whether they are in the RUI or SUI arms of the study.

Products supplied by DePuy Synthes must be used in accordance with the manufacturer's instructions unless an alternative technique is medically necessary.

Each Investigator or designee will collect information as noted in Table 8-3 below. The detailed surgical procedure is provided in Exhibit B. Data collection will begin at the time the OR is being set up for a study Subject procedure and will continue until the room is cleaned up and ready for the next case.

Table 8-3: Intra-operative Data Collection and eCRFs

Evaluation	Details of Evaluation
Operative Details eCRF	**For all Subjects**, detailed surgical information and time information relating to the duration of 4 key elements of the surgical procedure will be recorded on the Operative Details eCRF. These 4 elements are OR Set Up, Anesthetic, Surgery & Clean Down. Definitions of each element will be provided as part of the training for individuals who will be capturing time data. Note there is likely to be overlap in time between some of these elements (possible scenario illustrated below).  In addition to the start and stop times for the 4 key elements, the occurrence of various incidents that can introduce delays or interruptions to the surgical flow will also be recorded.

Evaluation	Details of Evaluation
Device Log eCRF	**For all Subjects,** each component used during the procedure should be documented on the **Device Log** eCRF. The required product codes and catalog numbers can be found on pre-printed labels provided in the sterile implant boxes. **Retain a copy of each label to facilitate data entry into the eCRF**
Intra-operative Complications (if applicable) Adverse Event eCRF	**In the event of an intraoperative complication,** an **Adverse Event** eCRF is completed. An intra-operative complication is defined as a complication that occurs between the start of anesthesia and up to the time the Subject is moved to the recovery room. Complete a separate form for each intra-operative complication.

8.3.4 Post-operative Management

Immediate post-operative management is at the discretion of the Principal Investigator and should follow each Site's standard of care.

The one(1) postoperative study follow-up visit will be conducted according to the Time and Events Table 2.1. Each Investigator or designee will collect information as noted in Table 8-4 below. At this visit radiographs will be collected as detailed in the Radiographic Protocol (Exhibit F). An independent radiographic reviewer (IRR) will evaluate all radiographs. Copies of the evaluations will be available to Investigators upon request.

Table 8-4: Post-operative Data Collection and eCRFs

Evaluation	Details of Evaluation
Radiographs	**For all Subjects** post-operative radiographs will be obtained.
End of Study Completion or Subject Withdrawal	**For all Subjects** the Investigator or designee must complete an **End of Study/Subject Withdrawa**l eCRF to confirm the Subject is no longer in the study.
Post-operative Complication(s) (if applicable)	**In the event of a post-operative complication** an **Adverse Event** eCRF is completed. A post-operative complication is defined as a complication that occurs at any time from the time the Subject is in the recovery room up through the time a Subject withdrawal form is submitted ending the Subject's study participation. Complete a separate form for each post-operative complication.

8.3.5 Radiographic Procedures

Weight bearing long-leg, hip-to-ankle (51" = 129.54 cm) Anteroposterior (AP) radiographs will be taken, as well as standard AP and lateral view radiographs, following the detailed instructions presented in the Radiographic Protocol (Exhibit F). While Patellar Skyline/Merchant view radiographs may be standard of care at some sites, they are not a requirement of the study and they do not need to be submitted to the IRR. All radiographs **must** be de-identified by the site prior to making them available for review by the Independent Radiographic Reviewer (IRR).

8.3.6 Management of Bias

To avoid potential bias and ensure consistency, an Independent Radiographic Reviewer (IRR) will be used to evaluate the post-op 90 day radiographs. This is an open investigation by design. Only the independent radiographic reviewer will be blinded regarding the instrumentation. The X-ray images will be provided with all Subject PHI information removed prior to assessment by the IRR. Data from the IRR radiographic evaluations (not the Investigators) will be used for determination of radiographic success criteria. Details of the radiographic assessment and means of submitting radiographs for review are detailed in Exhibit F, the Radiographic Protocol.

8.4 Process for Discontinuation of Subject Participation

A Subject is considered enrolled after signing the Informed Consent Document, as described in Section 5.3, Definition of Valid Subject Enrollment. Subject participation may discontinue through screen failure, withdrawal, or death. In all instances of Subject discontinuation after obtaining Informed Consent, an End of Study/Withdrawal eCRF is required to be submitted to the Sponsor supporting the study Subject's study discontinuation/withdrawal.

8.4.1 Preoperative Screen Failures/Withdrawals

A Subject may withdraw consent at any time during the study, even before surgery. The Investigator may withdraw the Subject preoperatively for safety reasons due to eligibility, for example, a patient may become pregnant during the window between giving consent and the planned surgery.

In all instances when a Subject is declared a **screen failure**, the Subject Screening and Enrollment Log must be updated to reflect that Subject's removal/withdrawal from the study. Occasionally, a screen failure (after obtaining consent) will also require and an End of Study/Withdrawal eCRF submitted to DePuy Synthes. Please refer to table 8-5 for further guidance.

Table 8-5: Pre-operative Screen Failure/Withdrawal examples

Screen Failure	Potential Subjects determined to be ineligible for study participation preoperatively, and should not be implanted with study device.	
Example	**Action**	**Follow-Up**
Before consent and before surgery, patient is determined to be ineligible	Update Screening/Enrollment Log as "Screen Failure" and document reason	Do not continue
After consent and before surgery, Subject is determined to be ineligible	Update Screening/Enrollment Log as "Screen Failure" and document reason Submit **Subject History** and **End of Study/Withdrawal** eCRFs to Sponsor	Do not Continue
Subject Withdrawal	Potential Subject withdraws consent prior to receiving the study implant.	
Example	**Action**	**Follow-Up**
After consent but before surgery, patient withdraws consent	Update Screening/Enrollment Log as "Withdrawal" and document reason Submit **Subject History** and **End of Study/Withdrawal** eCRFs to Sponsor	Do not continue

8.4.2 Intra-operative Withdrawal

The Investigator may withdraw the Subject intraoperatively for safety reasons, for example, it may become clear that the patient is not suited to receive the implant to be used for the study or the surgeon did not used the assigned instruments for whatever reason. Please refer to table 8-6 for further guidance.

Table 8-6: Intraoperative Withdrawal example

Intraoperative Withdrawal: Potential Subjects to be withdrawn from study participation intraoperatively.		
Example	**Action**	**Follow Up**
Intraoperatively determined to be ineligible (example, ATTUNE primary implant not suitable)	Update Screening/Enrollment Log as "Intraoperative Withdrawal" and document reason Submit **Subject History,** and **End of Study/Withdrawal** eCRFs to Sponsor Inform Subject that they were withdrawn	Do not continue
Example	**Action**	**Follow-Up**
Intraoperatively the assigned instruments are not used to perform the proximal tibia and/or distal femoral resections	Update Screening/Enrollment Log as "Intraoperative Withdrawal" and document reason Submit **Subject History, Operative Details, Device Log** and **End of Study/Withdrawal** eCRFs to Sponsor. Submit Adverse Event as applicable. Inform Subject that they were withdrawn	Do Not continue
Intraoperatively the ATTUNE implant is attempted but not retained	Update Screening/Enrollment Log as "Intraoperative Withdrawal" and document reason Submit **Subject History, Operative Details, Device Log** and **End of Study/Withdrawal** eCRFs to Sponsor. Submit Adverse Event as applicable. Inform Subject that they were withdrawn	Do Not continue

8.4.3 Enrollment Replacement Rules

Since Subjects are enrolled at the time of consent, any Subject that is withdrawn preoperatively or intraoperatively prior to receiving the study implant will be replaced with subsequent Subjects. Overall, the number of Subjects who received an ATTUNE implant using a study device (with either the RUI or SUI instrumentation), across all sites must meet the sample size of 88.

8.4.4 Postoperative Withdrawal

A postoperative withdrawal is a Subject who has signed the Informed Consent Document, has received an ATTUNE implant using a study device (with either the RUI or SUI instrumentation), and is later withdrawn from study participation (i.e., withdrawal of consent, revision, death, etc.). Please refer to table 8-7 for further guidance.

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

Table 8-7: Post-operative Withdrawal Examples

Example	Action	Follow-Up
Subject withdraws consent	• Study site documents Subject's request for withdrawal from study. • Complete **End of Study/Withdrawal** eCRF • Update Screen/Enrollment Log.	Do not continue
Death	• Complete **Adverse Event** eCRF • Complete **End of Study/Withdrawal** eCRF • Update Screen/Enrollment Log	Do not continue
Revision	See Section 8.4.5 and Table 8-8 Revision/Re-Operation Examples	Do not continue if metal tibial base or femoral component revised. Continue to follow if neither the metal tibial or femoral components have been revised.

8.4.5 Revisions / Reoperations

A revision is defined as a surgical procedure of the affected knee where one or more of the TKA components (femoral and/or tibial base, polyethylene insert, or patella polyethylene resurfacing component) are **removed**. Should it be necessary for the Subject to undergo a revision of either the **femoral or metal tibial base components** between the date of the enrollment and the completion of the study data acquisition, **the Subject is to be withdrawn from study participation. Thus, both an Adverse Event (AE) eCRF and an End of Study eCRF would be completed.** If possible, long leg x-rays should be captured prior to revision to permit analysis of the primary objective.

A **re-operation** is defined as any surgical procedure of the affected knee in which **no TKA components are removed.** These subjects are **not to be withdrawn**. An **Adverse Event (AE) eCRF must be completed.** Several examples for revision/reoperations are shown in **Table 8-8**.

Table 8-8: Revision/Re-operation Examples

Revision	A surgical procedure of the affected knee where one or more of the TKA components (femoral and/or tibial base, polyethylene insert, or patella polyethylene resurfacing component) are removed. If either femoral or metal tibial base components are revised, the Subject is to be withdrawn from study participation.	
Example	Actions	Follow Up
Removal or revision of either metal tibial base and/or femoral component	Complete **Adverse Event** eCRF Complete **End of Study/Withdrawal** eCRF	Do not continue
Tibial polyethylene exchange	Complete **Adverse Event** eCRF	Continue
Revision of a patella which was resurfaced in the index TKA	Complete **Adverse Event** eCRF	Continue
Re-operation	Any surgical procedure of the affected knee in which no TKA components (femoral and/or tibial base, polyethylene insert, or patella polyethylene resurfacing component) are removed.	
Example	Actions	Follow Up
Irrigation & debridement without tibial insert exchange	Complete **Adverse Event** eCRF	Continue
Resurfacing of previously unresurfaced patella	Complete **Adverse Event** eCRF	Continue

8.4.6 Minimization of Subjects Lost to Follow-up

Although follow-up compliance is essential to study quality, some Subjects may not be able or willing to return for follow-up evaluations as prescribed in the protocol. Given the short duration of follow-up in this study, this is not expected to occur often.

Sites should make every effort to ensure complete follow-up whenever possible through phone calls and written requests to a Subject. Each Investigator will maintain a record of communications and/or attempts at communications in the source documentation. This record will be used to obtain an indication or report on the current status of the study device (e.g., still in place and functioning satisfactorily; painful; revised; etc.).

A Subject can be classified as "lost-to-follow-up" and withdrawn from the study only after the visit window has closed and the site has documented in the medical record at least two (2) unsuccessful attempts of contact. Please refer to table 8-9 for further guidance.

Table 8-9: Recommended Contact Attempts

If	Then
A response is not received from phone calls	the Investigator should send a letter to the Subject explaining the follow-up agreement per the informed consent.
A response is not received from the Investigator's letter and/or all attempts to contact the Subject are unsuccessful or the Subject is contacted and chooses to withdraw from the study	the End of Study/Withdrawal eCRF will be completed and will specify why the Subject is no longer participating in this study.

9 RISK ANALYSIS

9.1 Adverse Event Determination

Adverse Event determination will be done by the Principal Investigator, or appropriate designee.

9.2 Non-Reportable Adverse Events - Sponsor ONLY

There are immediate post-operative events that are changes from the baseline condition of the Subject, but are expected events resulting from the surgery. If these events occur, they should be recorded in the Subject's medical record per standard medical practice, but it is not necessary to report them as AEs in the eCRF or to the Sponsor (please refer to Exhibit E-2 for listing of Non-reportable AEs).

9.3 Study Related Risks / Reportable Adverse Events

Any surgical procedure poses a potential risk and the procedures undertaken as part of this clinical investigation are no exception.

The surgical risks associated with the use of the Single Use Instruments for implanting the ATTUNE cemented primary TKA system are similar to those with the Re-usable instruments for implanting the ATTUNE cemented primary TKA system when used for the same clinical indication. Additionally, the surgical risks are the same whether or not the Subject participates in this study for a number of reasons:

- It is assumed that the Investigator and patient have mutually decided that primary TKA is an appropriate treatment for the patient's condition and that the patient would have a TKA whether or not they choose to take part in this study;
- The same implant is used with both RUI and SUI instrumentation;
- Both types of instruments have to meet the same design control requirements/standards prior to market availability as do all surgical instruments on the market;
- Participating Investigators in this study are already implanting the ATTUNE TKA system with the re-usable instruments and will obtain training on the single use instruments prior to enrolling study Subjects.

Study related risks are categorized as those anticipated to be related to general surgical risks, total knee arthroplasty risks, or those potential risks associated with the study implant system. Unanticipated Adverse Events may occur as well.

This protocol requires each site to report AEs, SAEs, ADEs, and SADEs to their respective IRB/EC per their IRB/ECs respective requirements

A summary of risks is described below, please refer to the printed IFU for additional details (Exhibit D).

A. General Surgical Risks

General surgical risks and post-operative adverse events can occur with any surgery and include, but are not limited to:

- Anesthetic complications/reactions
- Bleeding and/or excessive blood-loss
- Transfusion reaction
- Post-operative infection
- Vascular injury
- Delayed wound healing
- Deep vein thrombosis (DVT)
- Nerve injury
- Death

B. Risks Associated with Total Knee Arthroplasty Procedure/Study Device/Instruments

Potential adverse events associated with primary total knee arthroplasty include, but are not limited to:

- Early or late loosening of the prosthetic component(s)
- Tibial subsidence
- Bending, cracking, fracture, deformation of the prosthetic components
- Excessive wear of the polyethylene articulating surface
- Progressive bone resorption (osteolysis) as a result of foreign-body reaction to wear debris
- Early or late infection
- Delayed wound healing or wound dehiscence
- Pain
- Dislocation or joint instability of the knee
- Subluxation of the knee
- Flexion contracture
- Varus-valgus deformity
- Malalignment
- Decreased range of motion
- Leg length discrepancy
- Soft tissue impingement or damage
- Bone fracture(s)
- Nerve damage
- Localized swelling
- Vascular injury
- Temporary or permanent neuropathies
- Cardiovascular disorders including venous thrombosis, pulmonary embolism, or myocardial infarction
- Histological reactions resulting in inflammation
- Metal sensitivity
- Corrosion of metal components (the significance and long-term implications are uncertain and await further clinical evidence and evaluation)
- Re-usable or single use instrument breakage

9.4 Minimization of Risk

Risks have been minimized by designing the device under evaluation (total knee arthroplasty surgical instruments) to be similar to commercially available total knee arthroplasty surgical instruments used for the same indication. The ATTUNE surgical instruments have been functionally tested to verify performance characteristics and biocompatibility. In addition, only trained orthopaedic surgeons with expertise in treating this condition will participate in this study.
Investigators should refer to the ATTUNE implant system package insert for additional information and instructions for use (Appendix D) and the surgical technique (Appendix B).

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

9.5 Benefit Analysis

There are no potential benefits to study Subjects from participation in this study. The knowledge gained from this investigation may help future TKA patients.

9.6 Adverse Event

9.6.1 Categories and Definitions

Table 9-1: Adverse Event Categories

<table>
<tr><th>ADVERSE EVENTS</th><th>Non-Device Related</th><th colspan="2">Device- and/or Procedure-related</th></tr>
<tr><td>Non-Serious</td><td>Adverse Event (AE)</td><td colspan="2">Adverse Device Effect (ADE)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)</td><td colspan="2">Serious Adverse Device Effect (SADE)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
</table>

Table 9-2: Adverse Event Definitions

Term	Details
Adverse Event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. Adverse Event is synonymous with complication or medical event.

Term	Details
Serious Adverse Event (SAE)	An Adverse Event that: leads to death, leads to a serious deterioration in the health of the subject that ○ resulted in a life –threatening illness or injury, ○ resulted in an impairment of a body structure or a body function, required in-patient hospitalization or prolongation of existing hospitalization, resulted in medical or surgical intervention to prevent permanent impairment to body structure or a body function, leads to fetal distress, fetal death or a congenital abnormality or birth defect. **Note:** Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.
Adverse Device Effect (ADE)	An adverse event related to the use of an investigational medical device. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition includes any event that is a result of a user error.
Anticipated AE	An effect which by its nature, incidence, severity or outcome has been previously identified in the Instructions for Use for the medical device.
Anticipated Adverse Device Effect (AADE)	An adverse event related to the use of an investigational medical device **is previously** identified in nature, severity, or degree of incidence in the current version of the Instructions for Use. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition includes any event that is a result of a user error.
Unanticipated Adverse Device Effect (UADE)	An adverse event related to the use of an investigational medical device not previously identified in nature, severity, or degree of incidence in the current version of the risk analysis report. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition includes any event that is a result of a user error.
Serious Adverse Device Effect (SADE)	An adverse event related to the use of an investigational medical device that has resulted in any of the consequences characteristic of a serious adverse event.
Anticipated Serious Adverse Device Effect (ASADE)	A **serious** adverse device effect which by its nature, incidence, severity or outcome has been identified in the current version of the Instructions for Use/risk analysis report. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition includes any event that is a result of a user error.

Term	Details
Unanticipated Serious Adverse Device Effect (USADE)	A **serious** adverse device effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis. This definition includes any event resulting from insufficiencies or inadequacies in the instructions for use or the deployment of the device. This definition includes any event that is a result of a user error.
Site 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 Adverse Event has occurred. Note: This date may or may not correspond to the date of onset. The date of awareness is critical to reporting timelines (see Section 9.8).

9.7 Adverse Event Reporting Guidelines

9.7.1 AE Reporting by Site to the Sponsor

For AEs to be reported through this protocol, a record including details of site awareness, the nature, onset, duration, seriousness, relationship to the device, relationship to the procedure, treatment given (if any) and outcome, will be entered into the subject's eCRF.

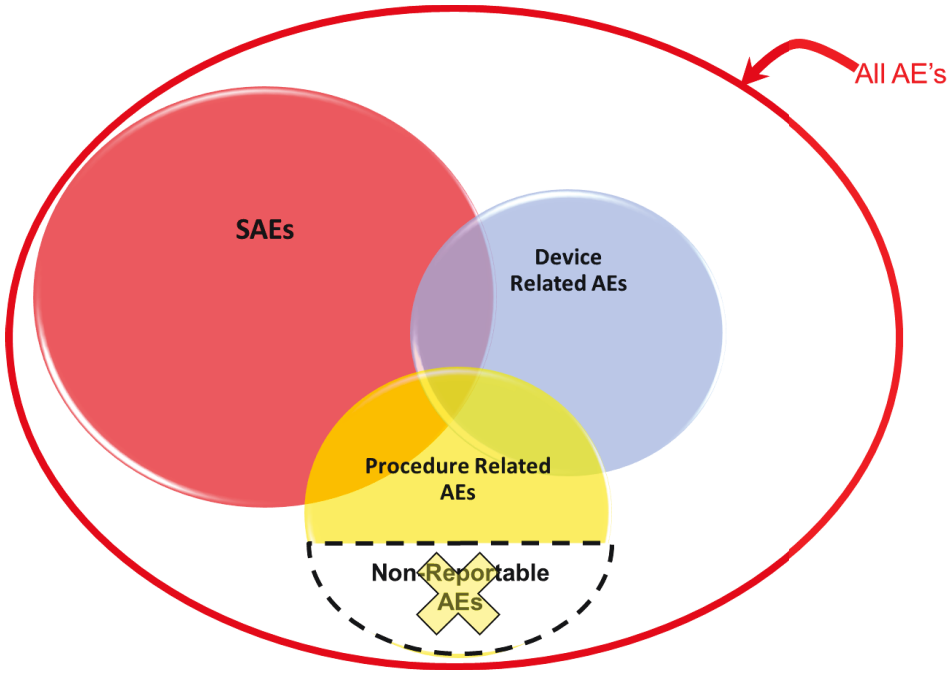
For this study, only serious AEs and those AEs related or possibly related to either the device and/or the procedure are to be reported to the SPONSOR (Please see Figure 9-1).

The outer circle (Figure 9-1) represents all AEs that could possibly be observed. For this protocol, not all AEs are required to be reported. The below list are the reportable AE's that must be recorded on the eCRF and submitted to the Sponsor by entering into EDC per the reporting timelines detailed below:

- Any AE classified as '**Serious'** (SAEs, SADEs, SUADEs) to include Serious procedure related AEs – report to Sponsor as soon as able but **no later than 72 hours from site awareness***.
- All UADEs – report to Sponsor as soon as able but **no later than 72 hours from site awareness*.**
- All non-Serious Device Related (ADE) – report to Sponsor as soon as able but **no later than 2 weeks from site awareness*.**
- All non-Serious Procedure Related AEs, except for selected events (see Exhibit E-2: Non-reportable list) - report to Sponsor as soon as able but **no later than 2 weeks from site awareness*.**

***NOTE: Not meeting the above reporting timelines to the Sponsor will result in a protocol deviation.**

Figure 9-1: Adverse Event Reporting for this Study Protocol



Pre-existing medical conditions or symptoms reported prior to the surgical event are not to be recorded as AEs[E]. 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.

AEs are reported beginning from surgery and until Subject participation has ended (study completed or consent withdrawn). AEs must be followed to resolution, or until the study completion or consent withdrawal. When a Subject ends participation in the study (either study completion or consent withdrawal) an AE must be designated either as "resolved" (end date must be provided), or as "ongoing."

Subjects should be encouraged to report AEs spontaneously and may volunteer AE information at any time. At each evaluation, the Investigator will determine whether a study reportable AE has occurred. If it is determined that such an AE has occurred, the Investigator should obtain all the information required to complete the appropriate AE form eCRF. 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.

[E] An example could be pre-existing contralateral knee osteoarthritis with a planned TKA intervention after the index knee surgery.

9.7.1.1 Determination of AE Severity

Refers to the intensity of the symptoms experienced by the study subject and can be used with any event, without regard to whether or not the adverse event is classified as Serious.

Please refer to Table 9-3 in determining intensity of symptoms of the reportable AE.

Table 9-3: Definitions of Severity of AEs

Term	Description
Severe Symptoms	The intensity of the symptoms are severe and poorly tolerated, requiring intervention, and significantly affect activities of daily life; or place the Subject at immediate risk or harm.
Moderate Symptoms	The intensity of the symptoms are moderate. Intervention is either noninvasive or not indicated. Activities of daily living can be sustained.
Mild Symptoms	The intensity of the symptoms are mild, transient or asymptomatic. Intervention is not indicated. Clinical or diagnostic observations only and no impairment of normal activity.

9.7.1.2 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 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.

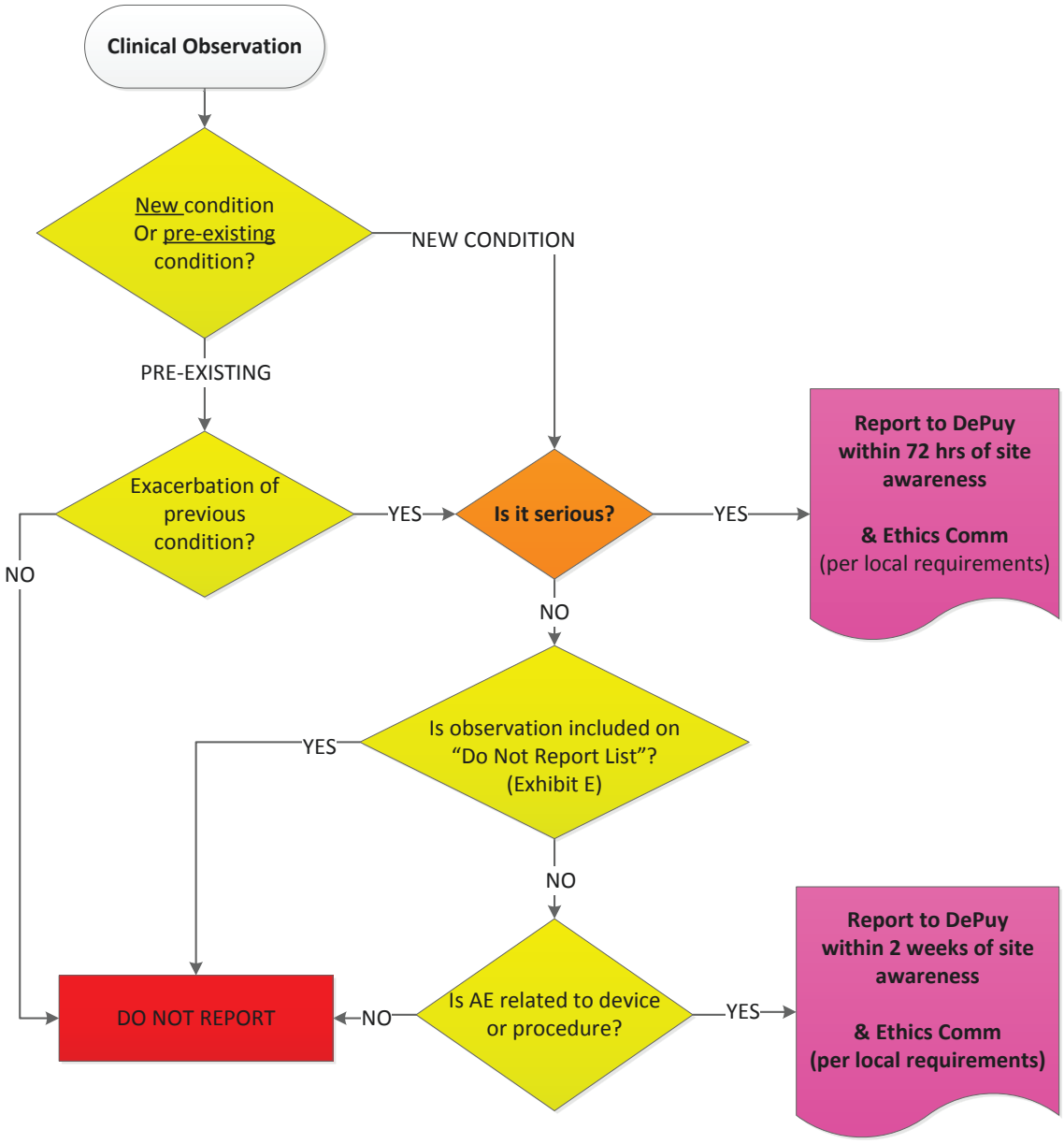
Please refer to Table 9-4 in determining if an AE is related to the study device or procedure.

Table 9-4: 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

The AE Reporting flowchart (Figure 9-2) illustrates a series of questions a site must consider when determining whether a given clinical observation must be reported and which AE's do not need to be reported for this CIP.

Figure 9-2: AE Reporting Flowchart



9.7.2 Institutional Review Board (IRB) / Ethics Committee (EC) Reporting.

This protocol requires each site to report AEs, SAEs, ADEs, SADEs and UADEs to their respective IRB/EC, per their IRB/EC's respective requirements.

9.7.3 Regulatory reporting requirements

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

10 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.

10.1 Study Design

This study is a prospective, comparative, sequential, non-randomized, multi-center, controlled clinical investigation; see Section 7 for further details on study design. Reassignment of Subjects from one site to another may occur under circumstances defined in Section 7. The schema defined for reassigning Subjects is designed to keep RUI and SUI treatment groups balanced and to minimize potential bias.

10.2 Treatment Assignment

See Section 7.

Randomization will not be employed in this study. Each site will consecutively enroll all RUI cases prior to enrolling consecutive SUI cases.

10.3 Levels of Significance

Unless otherwise stated, confidence intervals will be 2-sided 95% confidence intervals, and p-values below 0.05 will be deemed to be statistically significant. Unless otherwise stated, there will be no adjustment of significance levels because of testing multiple hypotheses.

10.4 Interval Windows

The pre-operative window will be from 180 days prior to surgery up to the day of surgery, which is defined to be Day 0. The 3 month post-operative interval will be defined as 90 days plus or minus 60 days.

Table 10-1: Interval Windows

Follow-up [days]			
Pre-Op	**Surgery**	**Immed Post-op**	**3 Month**
-180 to 0	0	1 to 29	30 to 150

10.5 Handling of Missing Data

Subjects with no post-op alignment data at 3 Months post-op will be considered missing at random. Only actual Subject data which is collected will be utilized in analyses; no imputation of missing data will be performed.

10.6 Primary and Secondary Endpoints

The primary endpoint in this study is mechanical axis alignment, and the primary endpoint analysis will be to determine whether the alignment achieved with SUI instrumentation is non-inferior to the alignment achieved with RUI instrumentation. Mechanical axis alignment is defined as the angle between the line drawn from the center of the femoral head through the center of the knee and line drawn from the knee center to the ankle center. Mechanical axis alignment will be measured from weight bearing long-leg (51") Anteroposterior (AP) radiographs, taken approximately 90 days post-op (when Subject has reached full knee extension, within 5 degrees) and read by an independent radiographic reviewer. The non-inferiority margin was set at 1.5^o because the study team felt this was the maximum non-meaningful difference when thinking about absolute mechanical axis alignment differences between the RUI and SUI groups. A standard deviation between 1.5^o to 2^o is anticipated based on previous studies conducted by the sponsor that had the same primary endpoint (Protocol ID #'s 04023, 08003).

The secondary endpoints are as follows:

- To compare alignment achieved with SUI vs. RUI of individual components in the frontal and sagittal planes, specifically: distal femoral varus-valgus (FM) , proximal tibial varus-valgus (TM), femoral component flexion and tibial slope.
  To compare the type and frequency of adverse events, from the time of consent through to withdrawal of a Subject or the end of the study (includes pre-operative, intraoperative and early postoperative device-related adverse events), between the SUI and RUI instrument groups.

Exploratory endpoints

- To compare SUI and RUI operating room times. Specifically the duration of the four key steps in the procedure (possibly overlapping) will be compared. See Table 8-3.
- To determine whether SUI provides opportunity to reduce the incidence of minor procedural obstacles during the time in the OR.
- To compare Surgeon satisfaction of SUI instrumentation to RUI instrumentation.

10.7 Hypotheses

The null (H_o) and alternate (H_A) hypotheses are as follows:

H_o: $\mu_{SUI} \geq \mu_{RUI} + 1.5^o$

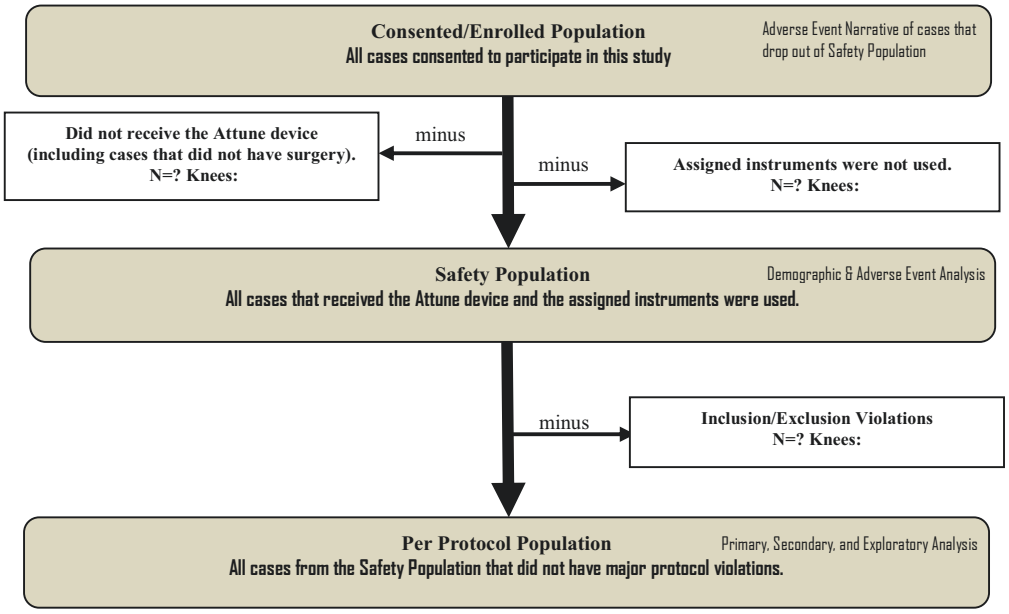
H_A: $\mu_{SUI} < \mu_{RUI} + 1.5^o$,

where μ_{RUI} is the absolute value of mechanical axis alignment angle sample mean of Subjects being operated upon using reusable instruments (RUI), and μ_{SUI} is the absolute value of mechanical axis alignment angle sample mean of Subjects being operated upon using single use instruments (SUI).

10.8 Analysis Sets

Below is a flow chart showing the analysis sets.

Figure 10-1: Analysis Populations Flowchart



The primary analysis dataset will be the Per Protocol population.

Adverse event comparisons will be conducted using the Safety population.

10.9 Sample Size Justification

The primary endpoint will be a non-inferiority test of absolute value mechanical axis alignment, comparing single use instrument results with reusable alignment results.

A standard deviation of 1.870^{o} for this absolute value of mechanical axis was established in a previous DePuy Study (ID # 04023). Assuming that this is a good estimate, a sample size of 35 per group will yield statistical power of 95% for a 1-sided test with a non-inferiority margin of 1.5^{o} and $\alpha = 0.05$. This power estimate was calculated with the following SAS code:

Figure 10-2: SAS Code for Power Estimation

```
proc power;
twosamplemeans
        meandiff= 1.5
        stddev=1.87
        groupweights=(1 1)
        power= .
        alpha=0.05
        sides=1
        ntotal=70;
run;
```

This sample size is increased to 44 per group to account for attrition and possible problems with xray quality.

10.10 Analysis Plan

The primary endpoint is a non-inferiority test of mean absolute mechanical axis angle, comparing single use and reusable instrument results with a non-inferiority margin of 1.5° using a 1-sided independent means t-test and $\alpha = 0.05$. The primary endpoint analysis null hypothesis will be rejected and non-inferiority will be concluded if the 1-sided upper 95% confidence limit for $\mu_{SUI} - \mu_{RUI}$ is less than 1.5°.

Preoperative demographics will be compared to determine whether differences exist between treatment groups. Age and BMI will be compared using two-tailed independent means t-tests. Gender distribution will be compared with a Fisher's exact test.

Secondary analyses include:

- Tests of differences for individual component alignment in the frontal and sagittal planes, specifically: distal femoral varus-valgus (FM), proximal tibial varus-valgus (TM), femoral component flexion and tibial slope using (independent means two-tailed t-tests).
- The types and frequencies of adverse events will be tabulated for all enrolled knees. The proportion of each complication will be compared using a Fisher's Exact Test (2 x 2 only) and Chi-square.

Exploratory analyses will be conducted to see if SUI improves OR efficiency compared to conventional (RUI) instruments. Exploratory analyses will also be conducted to investigate OR step times, inter-site differences in OR times, and issues that potentially introduced delays or interruptions in the surgical flow.

The Following Table presents a summary of the planned statistical tests:

Table 10-2: Planned statistical comparisons

Comparison	Purpose	Expected Result
Mean absolute mechanical axis non-inferiority	Primary efficacy	SUI Non-inferior to RUI
Demographic comparisons	Test comparability	No difference
Distal Femoral Varus-Valgus (FM)	Secondary efficacy	No difference
Proximal Tibial Varus-Valgus (TM)	Secondary efficacy	No difference
Femoral flexion	Secondary efficacy	No difference
Tibial slope	Secondary efficacy	No difference
OR Efficiency	*Exploratory Analysis*	No difference

10.11 Interim Analysis

No interim analyses are planned for the purpose of stopping the study early.

11 DEVICE DESCRIPTION

All products used in this CIP have the appropriate regulatory approval, FDA clearance/approval for commercial distribution and bear the CE mark. The 'devices' under study are the surgical instruments.

11.1 Instruments

The instruments to be used in this study are detailed below. Different sets of instruments will be used for each treatment group of this study. Please refer to Exhibit B, Surgical technique for details.

11.1.1 Reusable Instruments

The ATTUNE Reusable Instruments (INTUITION), as used on the Control group, will be used on multiple patients, going through a process of decontamination and sterilization after each surgical procedure in preparation for the next procedure. Reusable instruments are manufactured from a combination of engineering grade polymers and metals and are supplied non-sterile.

11.1.2 The ATTUNE Single Use Instruments (SUI)

The ATTUNE Single-Use Instruments (SUI), which are also referred to as SOLO, as used on the Treatment group, will be used on a single patient and then disposed of. Single-Use instruments are manufactured from engineering grade polymers and supplied sterile packed to hospitals. Kits consist of 5 packs, which contain all of the necessary instruments to perform a Total Knee Arthroplasty. The pack details are outlined in Table 11-1 below. Once a procedure is complete the packs of instruments are disposed of in clinical waste. Details of the Packs and their function are outlined below.

Table 11-1: Detailed Instrument Information by Pack

Single Use Instruments: Complete set is delivered in 5 Packs	
1 – Primary Cuts & Sizing	Indication: Enables distal femoral and proximal tibial cuts, plus sizing of both femur and tibia.
2 – Tibial Preparation	Indication: Provided in 6 sizes, with one pack being opened once the patient anatomy is defined.
3 – Femoral Finishing	Indication: Provided for both CR and PS configurations, each available in 6 sizes. The specific size and configuration dictates which pack is opened.
4 – Patella Preparation	Indication: Used to size the patella and fix the patella implant component.
5 – Pin Pack	Indication: Used for pinning throughout the procedure.

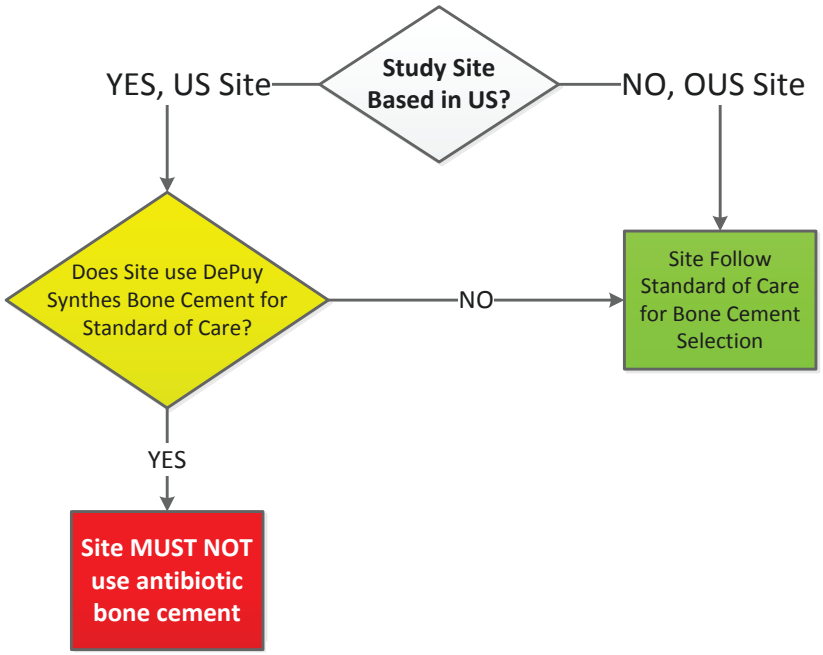
11.2 Implants

All components will be cemented. The implants specified in Table 11-2 below will be used for all study Subjects during this investigation. The intended purpose, indications, contraindications and population are described in the Instructions for Use (IFU), see Exhibit D. Product codes for each component are provided in Exhibit C.

Table 11-2: Detailed Device Information for ATTUNE Implants

Device Component	Component offerings		Details
Femoral Components	Cruciate Retaining (CR)		ATTUNE femoral components are available in **cruciate retaining (CR)** and **posterior stabilized (PS) configurations**. The femoral components are manufactured from cast Co-Cr-Mo alloy conforming to ASTM standard F-75. They are available in lefts and rights. Fourteen sizes are available including standard sizes 1-10 and narrow sizes: 3N, 4N, 5N, 6N. Femoral components are sterilized using gamma irradiation. **They are available for cemented use only.** The PS femoral components have a cam mechanism that articulates with a corresponding spine on the PS tibial insert.
	Posterior Stabilized (PS)		
Tibial Bases	Fixed Bearing (FB)		The FB tibial bases are manufactured from Co-Cr-Mo alloy conforming to ASTM standard F-75. The proximal surface has a universal locking feature that is used for securing the FB tibial insert and permits up-sizing and downsizing. Ten sizes are available including 1-10. The FB base is offered only in a keeled cemented version. The cemented components have a blasted finish to provide for enhanced cement fixation. FB Tibial Bases are sterilized using gamma irradiation. **They are available for cemented use only.**
	Rotating Platform (RP)		The RP tibial bases are manufactured from Co-Cr-Mo alloy conforming to ASTM standard F-75. The metal bases have a hollow, conical intramedullary stem. The flat superior surface of the base has a central hole continuous with the hollow conical medullary stem which receives the conical spike of the RP tibial insert components. The RP tibial insert component is not secured to the metal base, but rotates axially to maintain congruent contact with the femoral prosthesis. Ten sizes are available including 1-10. The RP base is offered only in a keeled cemented version. The RP base articulates with the RP CR and RP PS tibial inserts. The cemented components have a blasted finish to provide for enhanced cement fixation. RP Tibial Bases are sterilized using gamma irradiation. **They are available for cemented use only.**
Tibial Inserts	Fixed Bearing (FB)	Cruciate Retaining (CR)	The CR and PS tibial inserts are manufactured from UHMWPE and are available in sizes 1-10 and thicknesses from 5, 6, 7, 8, 10, 12, 14, 16, 18mm. Additional thicknesses 20 & 22mm are available for the PS inserts. The distal surface has features that secure the insert to the FB tibial base. Tibial inserts are sterilized using gas plasma sterilization. The PS insert has a spine which articulates with the cam on the corresponding PS femoral component.
		Posterior Stabilized (PS)	
	Rotating Platform (RP	Cruciate Retaining (CR)	CR and PS inserts are manufactured from UHMWPE and are available in sizes 1-10 and thicknesses from 5, 6, 7, 8, 10, 12, 14, 16, 18mm. Additional thicknesses 20 & 22mm are available for the PS inserts. RP inserts should be the same size as the selected femoral component. The RP inserts articulate with the RP primary bases and should be within 2 sizes of the RP tibial base. Tibial inserts are sterilized using gas plasma sterilization. The CR RP insert can be used with or without an intact PCL. The PS insert has a spine which articulates with the cam on the corresponding PS femoral component.
		Posterior Stabilized (PS)	
Patellae	Medial Offset		Patellar components are manufactured from UHMWPE. They are available in two styles, medialized dome and medialized anatomic. They are available in 5 sizes with proportionally increasing thicknesses from 8.5 to 10.5 mm. **They are available for cemented use only.**
	Anatomic		
Bone Cement	**FOR US SITES:** DePuy CMW **Antibiotic impregnated** bone cement **is not cleared for use in primary joint replacement in the United States** and will constitute a protocol violation if it is used. See Figure 11-1 for guidance.		

Figure 11-1 : Flowchart depicting regional considerations for permitted bone cement selection



12 INVESTIGATOR RESPONSIBILITIES AND GOOD CLINICAL PRACTICES

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

- Ensuring that a clinical investigation is conducted according to the Declaration of Helsinki, applicable local regulations, the signed Clinical Trial Agreement, and the Clinical Investigation plan;
- Protecting the rights, safety, and welfare of Subjects under the Investigator's care; and
- Ensuring the integrity of the data.

Prior to the initiation of this clinical investigation, the Principal Investigator at each site globally will approve this Clinical Investigation Plan (CIP) by signing the signature page. This signature confirms that the clinical investigation will be performed in compliance with the CIP.

12.1 IRB/ Ethics Committee Approval

All Principal Investigators must submit to their institution's IRB/EC for initial review a copy of the clinical investigational plan (CIP) and a sample Informed Consent Document (ICD) provided by the Sponsor. Many institutions request modification of the ICD to satisfy specific institutional requirements. The use of a modified or unique Informed Consent Document is permitted provided that the document is reviewed and approved by the Sponsor. Additionally, all translated consent forms require IRB/EC approval.

All Principal Investigators must submit the Clinical Investigation for continuing review and any other additional required submissions to their IRB/EC according to their IRB/EC's policies and procedures.

Initial approval/favorable opinion and all continuing review approvals must be documented; originals of correspondence and approvals are to be filed by the Investigator and copies forwarded to the Sponsor.

12.2 Informed Consent

The Principal Investigator is responsible maintaining source documents evidencing informed consent was obtained on study Subjects prior to their participation in the study.

If an Investigator performs any study-specific data collection without obtaining informed consent, the Investigator will report such use to the Sponsor and the reviewing IRB/EC within 5 working days.
For further details and a description of the Informed Consent process, please refer to Section 8.2.2, Subject Informed Consent.

12.3 Protected Health Information

The Principal Investigator is responsible to inform study Subjects their personal data will be collected, processed, and confidentially maintained in accordance with local data privacy regulation and law.

United States: The Principal Investigator is responsible for taking the necessary steps to collect, process, and maintain confidentiality of the study Subject's personal data in accordance with data protection legislation including the Health Insurance Portability and Accountability Act of 1996

(HIPAA). Subjects will be asked to sign an Authorization for Release of Personal Health Information (PHI) for the purpose of this investigation. This authorization may be combined with the ICD depending on local IRB preference.

European Union: The Principal Investigator is responsible for taking the necessary steps to collect, process, and maintain confidentiality of the study Subject's personal data in accordance with provisions of the national transposition of the EU Data Protection Directive 95/46/EC or local equivalent legislation, for Investigational sites outside of the US. Data protection consent will be obtained from the Subjects as part of the informed consent process.

Results from the Clinical Investigation may be published. However, Subject confidentiality will be maintained at all times and it will not be possible to identify individual Subjects from any data presented.

12.4 Subject Discontinuation from the Clinical Investigation

Any Subject is entitled to discontinue/withdraw from this clinical investigation for any reason without obligation and/or prejudice to further treatment. In addition, the Investigator may decide for reasons of medical prudence, to withdraw a subject.

The Investigator will clearly document the date and reason(s) for the Subject's discontinuation from this clinical investigation in the eCRF and submit to DePuy Synthes Joint Reconstruction.

Please refer to Section 8.4 Process for Discontinuation of Subject Participation for further details.

12.5 Source Documentation and Data Retention

Each Investigator will maintain a complete, current and accurate case history (Source Documentation records) on each Subject according to the usual procedure at the Site. Case histories medical records, including progress notes, hospital charts, nurses' notes, etc.
Additional documents to be retained include:

- Signed original Informed Consent Form,
- Executed Authorization for Release of Personal Health Information (may be combined with Informed Consent Form based on local IRB requirements) – not required outside USA.
- Completed Source Worksheets(if used),
- Results of relevant diagnostic and laboratory tests,
- Intraoperative and post-operative complications and treatment, and
- Any other relevant information or documentation pertaining to the condition of the Subject.

The Investigator should retain copies of all documents pertaining to this clinical investigation (for at least 5 years in the United Kingdom and for at least 3 years in the United States after this clinical investigation is completed, or according to institutional policy if longer. In addition, if the Investigator moves/retires, etc., s/he should provide DePuy Synthes Joint Reconstruction with the name and address of the person who will be responsible for the Subjects' clinical investigation related records.

The investigator agrees that the Sponsor's employees or designees will have the right to audit and review pertinent medical records relating to this clinical trial.

12.6 Record of Device Inventory

Not applicable as this is a post-market study on an FDA cleared/CE marked product.

12.7 Case Report Form Completion and Data Submission

Data will be captured within an electronic data capture system.
Electronic Case Report Forms (eCRFs) will be used to collect and submit all Subject data once a Subject is enrolled in the study. **Investigative study sites are asked to enter Subject data into the eCRFs preferably within 4 weeks from the time the Subject was seen for their scheduled study visit.**

Role-specific training on eCRF completion are included via Learning modules and are required to be completed by the Investigator(s) and study support staff prior to initiating Subject enrollment.

The eLearning will be assigned by the Clinical Operations representative and training signoff documented within the EDC system.

The personal data recorded on all documents, including copy documents, and within the EDC system, will be regarded as confidential. The Investigator will be responsible for the timing, completeness and accuracy of the details entered within the electronic data capture system. All data entered in the database must have source documents in the Subject's medical records.

There are no patient-reported outcome measures used in this study.

The protocol required data may be entered directly into the respective eCRF within the electronic data capture system by the Investigator or designee. The respective eCRFs must be fully completed for each Subject. The Investigator's electronic signature will be obtained within the EDC system once all study data has been entered, cleaned, and coded (and at interim analysis if applicable). Signoff can occur on a per form or per casebook level. Any changes to the data will break the Investigator's signature and signoff will need to be obtained again on the relevant data.

Paper Source Worksheets may be provided and may be used (optional) to supplement data points that are not typically collected in the medical record.. These data will then be required to be transferred directly to the eCRF within the electronic data capture system for submission to the Sponsor. If paper Source Worksheets are used, they must be stored in the Subject's research record, as these will be considered source documents, please refer to Section 12.5. Any errors on paper forms should be crossed out with a single stroke, initialed and dated. Typing correction fluid must not be used.

The Investigator must record the Subject's participation in this clinical investigation in the Subject's clinic notes. In addition, the Investigator must keep a separate list of all Subjects entered into this clinical investigation showing each Subject's name, date of birth and assigned Subject number (for identification purposes). A Patient Information log will be provided in the Investigator Site File for this purpose and remain at the site.

The Investigator should retain copies of all documents pertaining to this clinical investigation (including source documentation, the informed consent document and any other documents to

identify the Subjects) for at least 5 years after this clinical investigation is completed. In addition, if the Investigator moves/retires, etc., he should provide DePuy Synthes Joint Reconstruction with the name and address of the person who will be responsible for the Subjects' clinical investigation related records.

Data queries will be generated by the system at the time of data entry, if applicable. Resolution of the queries will be the responsibility of the Investigator and investigation team members. Following completion of all data queries on each eCRF, the Investigator will be responsible for reviewing and confirming agreement to the data within the system.

The platform software 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 data entry, validation of the study level components (i.e., data entry screens, associated edit checks and work flow) 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.

12.8 Protocol Adherence

The Investigator (s) agree to conduct the study in accordance with this protocol. Prior to beginning the study, the Investigator (s) must sign the protocol signature page.

An Investigator must not make any changes in a study without first receiving approval from the Sponsor and IRB/EC, except when necessary to eliminate apparent immediate hazards to a Subject.

With the exception of emergency situations, no deviations to this CIP will be permitted. In the event of an emergency situation, the Principal Investigator must notify their DePuy Synthes clinical operations contact immediately. A full written report of the situation must be forwarded to the IRB/EC who approved the original CIP and DePuy Synthes Joint Reconstruction within 10 working days of the event.

12.9 CIP Amendments

If it becomes necessary to amend the Clinical Investigation then the nature of the amendment will be agreed between the Sponsor and the Principal Investigator(s) and this will be recorded with a justification for the amendment. The appropriate IRB/EC, will be informed of any amendments.

12.10 Investigator Reporting Responsibilities

In fulfillment of study related requirements, the Investigator is responsible for preparing and submitting complete, accurate, and timely reports as described below.

Table 12-1: Investigator Reporting Responsibilities

Report	Description	Action
Withdrawal of IRB/EC approval	The Investigator will promptly notify the Sponsor of a withdrawal of approval by the reviewing IRB/EC or of the Investigator's part in an investigation within 2 weeks.	Preferably within 2 weeks
Progress Report	If required by your IRB/EC, the Investigator is responsible for submitting progress reports on the investigation to the reviewing IRB/EC.	As required per your IRB/EC
Reports of deviations from the investigational plan	The Investigator will notify the Sponsor of any deviation from the Investigational Plan as soon as able. The Investigator will notify the IRB/EC of any deviation from the Investigational Plan per the IRB/EC requirements.	Per IRB/EC requirements; at least annually
Other	The Investigator will, upon request of a reviewing IRB/EC or Sponsor, provide accurate, complete, and current information about any aspect of the investigation.	As requested

The Principal Investigator may delegate a qualified associate(s) to complete one or more of the above functions. However, the Principal Investigator retains the overall responsibility for Subject safety, proper conduct of the study including obtaining Subject Informed Consent, compliance with this study plan, and the collection of all required data.

12.11 Investigator Site File

Each Investigator and all personnel from the investigational site must maintain accurate, complete, and current information about all aspects of this Clinical Investigation. This includes documentation relating to the Investigator's participation, Subject information and correspondence: electronic, written, and verbal, relating to any aspect of the clinical investigation.

The records are maintained in the Investigator Site File consisting of, but not limited to, correspondence with other participating Investigators, the reviewing IRB/ EC, and the Sponsor.

Upon receipt of copies of changes or revision updates to the Clinical Investigation Plan (otherwise known as the Study Protocol) from the Sponsor, the Investigator will add the updated document and Revision Log to the Investigator File. The outdated version will be filed.

12.12 Regulatory Requirements

This clinical investigation is a post-marketing surveillance study to obtain additional data. The devices are FDA cleared/approved and CE marked products cleared for sale by the appropriate regulatory authority in the country(ies) in which this clinical investigation is to be conducted.

12.13 Investigator Study Termination

The Investigator may prematurely terminate the clinical investigation at any time. Should this be necessary, the procedures will be arranged on an individual clinical investigation basis after review and consultation by both parties. In terminating the clinical investigation, the Sponsor and the Investigator will assure that adequate consideration is given to the protection of the Subject's interests, all documentation is archived per Section 12.5 and the appropriate bodies such as the IRB/EC are informed as appropriate.

13 SPONSOR OBLIGATIONS

13.1 IRB/EC Approval

The Sponsor requires this Clinical Investigation Plan to be submitted to the IRB/EC for initial review and approval before implementation at each site. Additionally, all protocol amendments must be submitted to the IRB/EC for review and approval before implementation.

Each site is required to submit a copy of the IRB/EC initial approval. Additionally, US sites are required to submit a copy of the IRB renewal(s), typically annually, to the Sponsor for filing in the study's Trial Master File. The site is to maintain the original documentation of the initial approval and annual renewals in the site's Investigator Site File.

13.2 Investigator Training, Pre-Investigational Visit

Prior to enrolling Subjects in this study, the Investigator and/or appropriate site personnel will be trained on the study protocol to include:

- the general aspects of study administration,
- all procedures in the protocol, and
- the procedure for e-data acquisition and transmission.

The Sponsor will be offering hands on training to supplement professional education of the surgeon on the implant and surgical instruments, as needed.

13.3 Study Monitoring

Sponsor oversight will be maintained per Sponsor policies and procedures. On site monitoring will be done at the discretion of the Sponsor. Should a monitoring visit be required, the Sponsor will work with the site to determine the date(s).

During the visit, the Sponsor and authorized Sponsor representatives shall be given access to all study records, to include study Subject medical records.

All study Subjects are required to sign the Informed Consent Document allowing access to and release of their personal health information.

13.4 Labeling

Refer to Exhibit D for Product Labeling.

13.5 Sponsor Study Termination

The Sponsor may prematurely terminate or suspend the clinical investigation 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, device related problems, alignment with business strategy or administrative issues.

In the event of the study being terminated, any enrolled Subjects that have not yet had the surgical procedure would be treated as per their surgeon's standard practice using implants and instruments of the surgeon's choice. All enrolled Subjects who have received an ATTUNE implant within the study would continue to be cared for by their surgeon according to his/her standard of care. No further study-related procedures or data collection would occur.

13.6 Sponsor Reporting Responsibilities

The Sponsor is responsible for preparing and submitting complete, accurate and timely reports per Section 9.6.3.

13.7 Financial Agreement

Funding of the clinical investigation will be detailed in 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).

13.8 Publication Policy and Public Disclosure

The Sponsor is committed to publication of this study. A multi-center publication will be completed prior to allowing individual sites to publish their own data. Authorship decisions will be aligned with the International Committee of Medical Journal Editors[F]. All manuscripts including data from this study will be reviewed and approved by the Sponsor, and each author, prior to any submission. All authors must disclose financial or personal affiliations that could be considered conflicts of interest.

The sponsor will register this study on www.clinicaltrials.gov per FDAAA regulations.

13.9 Insurance

The Sponsor will secure and maintain in full force and effect, throughout the duration of the Clinical Investigation, clinical trial insurance in line with national regulations. The type of insurance for each participating site is detailed within the respective Clinical Trial Agreement or equivalent which will be executed before the start of Subject recruitment at that site.

[F] http://www.icmje.org/

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15 CLINICAL INVESTIGATIONAL PLAN EXHIBITS

Exhibit	Description of Exhibit
A	Sample Case Report Forms
B	Surgical Technique
C	Implant Product Codes
D	Instructions for Use (IFU)
E	Adverse Events: Tips & Pearls • Listing of Non-reportable Adverse Events • Preferred Terms for Select TKA Related Adverse Events • Flowchart for AE reporting
F	Radiographic Protocol