Randomized controlled study comparing iASSIST Knee system versus conventional instrumentation

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AE	Adverse Event
AKSS	American Knee Society Score
CRF	Case report form
CT	Computed tomography
EQ-5D	EuroQol questionnaire for quality of life assessment
EC	Ethics committee
FAS	Full Analysis Set
FTA	Femorotibial angle
ITT	Intention to treat
OA	Osteoarthritis
OKS	Oxford knee Score
PI	Principal Investigator
(S)AE	(Serious) Adverse Event
(S)ADE	(Serious) Adverse Device Event
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
TKA	Total Knee Arthroplasty
USADE	Unanticipated Serious Adverse Device Event

SUMMARY

TITLE	Randomized controlled study comparing with *iASSIST Knee* system versus conventional instrumentation
DESIGN	Prospective, comparative, randomized, controlled, multi center
PURPOSE	Determine the effectiveness of the *iASSIST Knee* in terms of precise implant alignment by comparing *iASSIST Knee* component alignment with conventional instrumentation
OUTCOME MEASURES	Safety will be assessed by monitoring Adverse Events and Revisions. Clinical outcome will be assessed by monitoring Oxford Knee Score, American Knee Society Score (2011), EQ-5D and Radiographic Assessments.
POPULATION	A multi-center study with a total of 100 subjects (2 groups of 50 subjects) in the Japanese patient population at a maximum of 6 sites.
ELIGIBILITY	Patients will be included according to the locally approved labeling of device in accordance with indications and contraindications for use.
DURATION	Follow-up will take place at 6 months postoperatively. Assuming the enrolment will be completed in 18 months, the total study duration will be 27 months, including central CT assessments.

1. INTRODUCTION

1.1 BACKGROUND

Total Knee Arthroplasty (TKA) is a well-established surgical intervention for patients who suffer from pain and dysfunction due to joint deformation consecutive to degenerative disease such as osteoarthritis and rheumatoid arthritis. Although TKA has been showing excellent clinical results, some early complications have been reported. One identified cause was implant mal-positioning. In order to overcome such alignment issues, implant manufacturers opted to improve the reproducibility of precise osteotomy and other companies have developed computer based technologies such as navigation systems. Navigation systems improved accuracy of implant alignment; however the initial costs and running costs are high. Furthermore, hospitals require sufficient storage space due to the size of certain equipment.

Zimmer Biomet® has developed the *iASSIST Knee* portable intelligent system in order to overcome the cost issues as well as storage space availability while maintaining the advantages of navigation systems. In addition, the accelerometer and gyroscope based *iASSIST Knee* system does not require many steps of pre-operative and intra-operative registration processes.

1.2 DEVICE DESIGN AND DESCRIPTION

The *iASSIST Knee* System is a computer assisted stereotaxic surgical instrument system to assist the surgeon in the positioning of orthopedic implant system components intra-operatively. It involves surgical instruments and position sensors to determine alignment axes in relation to anatomical landmarks and to precisely position alignment instruments and implant components relative to these axes.

iASSIST Knee involves microelectronics instrumented cutting blocks that provide intra-operative verification at each surgical step (bone cuts, overall alignment), thereby reducing mechanical errors. *iASSIST Knee* features simple and intuitive instrumentation based on conventional total knee arthroplasty instrumentation. By eliminating the setup hassles associated with navigation and robotics, *iASSIST Knee* should take less than 2-3 minutes on average to setup, providing a significant cost-effectiveness benefit to patients and surgeons.

The device has been registered in numerous countries across the world for use in routine TKA.

1.3 RATIONALE AND PURPOSE FOR CURRENT STUDY

The purpose of this study is to compare the accuracy of knee component alignment between patients operated with *iASSIST Knee* (Investigational group) versus patients operated without *iASSIST Knee* (Control group) using the same implant system (*Persona*).

2. STUDY DESIGN

The study is a prospective, non-blinded, randomized multi-center study, comparing the use of *iASSIST Knee* versus conventional instrumentation in the hands of experienced surgeons. A total of 100 subjects will be recruited prospectively and randomized according to a 1:1 scheme.

2.1 STUDY GROUPS/TREATMENTS

There will be 2 study groups with each 50 subjects. Patients will be assigned to the investigational or the control group using 1:1 randomization. In the investigational group, patients will be treated with *Persona* and the orientation sensor based device, *iASSIST Knee*. Patients in the control group will have *Persona* TKA with conventional instrumentation.

Group 1 "Investigational": Patients receiving a *Persona* TKA using *iASSIST Knee*.
Group 2 "Control": Patients receiving a *Persona* TKA using conventional instrumentation.

2.2 NUMBER OF SITES AND SUBJECTS

A total of 100 subjects will be enrolled and randomly assigned to either the investigational or the control group. This study will be conducted at a maximum 6 Japanese sites.

2.3 PRIMARY AND SECONDARY ENDPOINTS

Primary Endpoint

The primary study endpoint is the alignment accuracy of the knee femoral and tibial components at 6 months for the investigational group compared to the control group.

Secondary Endpoints

- Health Status assessed with the EQ-5D form [5]
- Operating Room efficiency
    - OR time
    - Number of instrument trays used
- Complication rate: incidence of adverse events as well as the proportion of patients who experience at least one complication related to *iASSIST Knee* or conventional instrumentation

2.4 ASSESSMENT PROCEDURE

The study assessment period will be 24 months, 18 months recruitment and 6 months follow-up. The follow-up for all patients will be at the following time points: baseline (preoperative), surgery and 6 months.

A. Preoperative:
    a. Informed consent
    b. Randomization
    c. Enrollment form
    d. Historical record
    e. OKS
    f. AKSS
    g. EQ-5D

B. Operative
    a. Operative Form
        i. OR time
        ii. Number of instrument trays used
        iii. Patella resurfacing (Yes/No)
        iv. Implanted component information
        v. Surgical approach

C. 6 months
    a. Limb CT scanning
    b. Complications (if applicable)
    c. OKS

d. AKSS

e. EQ-5D

2.5 ASSESSMENT PARAMETERS AND METHODS

Preoperative Data

After the patient has been consented he/she will be assigned randomly to either the investigational or the control group. Historical information will be collected, a detailed medical history will be obtained and a physical examination will be performed (including height and weight). Current medications and smoking history, if applicable, will also be recorded. A baseline OKS, AKSS and EQ-5D will be collected.

Clinical Assessments

OKS and AKSS will be used to assess the difference between the investigational and the control group. This assessment will be completed preoperatively and at 6 months post-operatively.

Patient Questionnaires

EQ-5D[5] will be taken preoperatively and at 6 months post-operatively.

EQ-5D: Descriptive system of health-related quality of life states consisting of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression).

Radiographic Assessments

The scan will be performed preferably using the Perth CT protocol (Chauhan et al., 2004). Patient is placed in the supine position with legs rotated into the AP position. The legs should be in maximum tolerable extension. Immobilization sponges may be used as necessary. Allow table movement to cover from ASIS to distal talus. It is preferable that the patient is positioned feet first into the CT gantry. Perform an AP and a lateral scout to cover from ASIS to the mid talus. Scanning parameters will differ according to the CT scanner used and optimal parameters must be standardized based on its own working conditions. Ensure the scan is a low dose scan. Aim to have an effective dose of 2-3 mSv. Helical scan should cover from just above acetabulum to just below ankle joint. FOV should cover both legs. Image reconstruction 2 mm thickness at 1.6 mm interval is desirable. Bone and soft tissue reformats.

Each clinical site sends the scanned image to the independent reviewer with DICOM format after removal of personal information from the image.

2.6 ASSESSMENT TIMELINES/SCHEDULE

Each follow-up visit time point will be determined based on the date of surgery. Each follow-up visit has a specific allowed time window:

- Preoperative (within 3 months prior to surgery)
- Admission period
- 6 months post-operatively (+/- 4 weeks)

The assessment and data collection schedule is outlined in the table below.

Assessment	Preop	Operative	6 Months
Informed Consent	*		
Randomization	*		
Historical Record	*		
Operative Record		*	
OKS, AKSS	*		*
EQ-5D	*		*
Limb CT scanning			*
Independent CT Review			*
Complications		As needed	As needed

3. SELECTION AND WITHDRAWAL OF PATIENTS

3.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, a patient must meet all of the following criteria.

- Knee (either unilateral or bilateral) osteoarthritis (varus deformity only)
- Male or female
- At least 20 years of age
- Patients willing to return for follow-up evaluations.

Study Specific Requirements for Principal Investigator/Site

- Principal Investigator (PI) must have experience of at least 5 TKAs of *iASSIST Knee* with *Persona* and *Persona* conventional instrument system before any study specific activities.
- Site has sufficient resources to take limb CT scanning at 6 months follow-up visit.

3.2 EXCLUSION CRITERIA

A potential patient who meets any of the following criteria will be excluded from participation in this study.

Absolute contraindications include:

- Knee degenerative diseases other than knee osteoarthritis (such as necrosis/rheumatoid arthritis)
- Too severe OA deformation (FTA: > 190 degrees/< 175 degrees)
- Active infection (or within 6 weeks after infection)
- Sepsis
- Osteomyelitis
- Any type of implant is inserted in the affected side of lower extremity
- Hip and/or foot disease on the affected side

Additional contraindications include:

- Uncooperative patient or patient with neurologic disorders who are incapable of following directions
- Diagnosed osteoporosis or osteomalacia
- Metabolic disorders which may impair bone formation
- Distant foci of infections which may spread to the implant site
- Rapid joint destruction, marked bone loss or bone resorption apparent on roentgenogram
- Vascular insufficiency, muscular atrophy or neuromuscular disease.

3.3 PATIENT WITHDRAWAL

It is recognized that the patient's participation in this study is entirely voluntary, and that he/she may refuse to participate and may withdraw from participation at any time without jeopardy to any future medical care. It is also recognized that the PI, at his/her discretion, may withdraw a subject from this study based upon his/her professional judgment. In event of subject withdrawal, applicable local procedures should be followed.

If a patient is withdrawn or rescinds their consent, a "Lost to Follow-up" CRF should be completed detailing the reason for the patient withdrawal. The PI should also notify the Ethics Committee (EC) if applicable. If a patient is withdrawn from the study, he/she should be notified of his/her removal by the PI or according to the condition set by the EC.

It is required that patients return within the defined follow-up period to complete all study assessment forms and CT scanning. Patients that miss or will not return for follow-up are not considered "protocol deviations" or "lost to follow-up."

Specific criteria for withdrawal (if applicable)

If patients meet any of the following criteria, a "Subject Withdrawal" CRF should be completed, and below data documented on the form:

1. Patient rescinds consent in writing: Date of occurrence
2. Patient death: Reason and date of death should be documented.
3. Implant removal: Date of revision, all component part numbers removed, and reason for revision
4. Revision of metal components (Femur or Tibia)*: Date of revision, all component part numbers removed, and reason for revision

**Bearing revisions in which only the polyethylene is replaced will not be withdrawn from the study.*

Replacement of individual patients after withdrawal

Patients will not be replaced, unless they do not have surgery or intraoperatively it has been recognized the patient is not eligible for a treatment with *Persona*.

Follow-up of patients withdrawn from treatment

Patient withdrawn from the study will obtain standard medical treatment as foreseen at the investigational site.

4. PROTOCOL DEVIATION MANAGEMENT AND REPORTING

Any deviation from the protocol should be documented on the "Protocol Deviation" CRF.

5. ADVERSE EVENT MANAGEMENT AND REPORTING

Any adverse event should be documented on the "Adverse Event" CRF. A record of all adverse events, including details of the nature, onset, duration, severity, relationship to the device, relationship to the operative procedure and outcome, will be made on the relevant section(s) of the patient's CRF. The patient will be questioned about any adverse event(s) at each subsequent follow-up assessment visit.

Any serious adverse events (SAE/SADE/USADE) must be reported to head of site and must be notified to other sites participating in this study in accordance with EC and Ethical Guidance for clinical study including human subject.

Adverse Event (AE):

An adverse event is any untoward medical occurrence in a patient receiving an investigational medical device that does not necessarily have to have a causal relationship with the device under investigation. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or condition temporally associated with the use of a medical device whether or not considered related to the medical device.

Serious Adverse Event (SAE):

A serious adverse event is an adverse event that

a) led to death,

b) led to a serious deterioration in the health of the patient that

c) led to fetal distress, fetal death or a congenital abnormality or birth defect.

1) resulted in a life-threatening illness or injury,

2) resulted in a permanent impairment of a body structure or a body function,

3) resulted in medical or surgical intervention to prevent permanent impairment to body structure or body function, or

4) required in-patient hospitalization or prolongation of existing hospitalization.

A planned hospitalization for a pre-existing condition, or a procedure required by this protocol, without serious deterioration in health, is not considered a SAE.

Adverse Device Effect (ADE):

An ADE is any untoward and unintended response to an investigational medical device.

Serious Adverse Device Effect (SADE):

A SADE is any untoward and unintended response investigational medical device that has resulted in any of the consequences characteristic of a SAE or that might have led to any of these consequences if suitable action had not been taken or intervention had not been made or if circumstances had been less opportune.

Unanticipated serious adverse device effect (USADE)

SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report (see section 10).

6. IMPLANT RETRIEVAL AND ANALYSIS OF REMOVED IMPLANTS

Should any implant failures occur, contact the Study Manager or any other Zimmer Biomet personnel to coordinate the implant retrieval process.

7. STATISTICAL ANALYSIS PLAN

The primary analysis for the study will compare the proportion of alignment accuracy of the knee femoral or tibial components ranging +/- 3 degrees from neutral based on the 6 month postoperative CT scan for *iASSIST Knee* vs. Control (conventional instrumentation).

The primary analysis will test the null hypothesis that the proportion of tibial or femoral component alignment within +/- 3 degrees of neutral for the Investigational group (*iASSIST Knee*) is equal to that of the patients operated without *iASSIST Knee*. The alternative hypothesis is that the proportion of tibial or femoral component alignment within +/- 3 degrees of neutral for the *iASSIST Knee* group is not equal to that of the patients operated without *iASSIST Knee*.

Null Hypothesis: Ho: $\pi A - \pi B = 0$
Alternative Hypothesis: HA: $\pi A - \pi B \neq 0$

where πA represents the proportion of tibial or femoral alignment within +/- 2 degrees from neutral in investigational group on the 6 month postoperative CT scanning and πB represents the proportion of tibial or femoral alignment within +/- 2 degrees from neutral in control group on the 6 month postoperative CT scanning.

If we reject the null hypothesis, we can conclude that *iASSIST Knee* are more accurate than conventional instrumentation in TKA surgery for either the tibial or femoral component alignment.

Alignment accuracy is defined as the deviation of an angle obtained from the CT scans versus a predefined angle that is accepted for an aligned knee component (refer to the Table 1). Intraoperative validation angles will also be used as targets in the *iASSIST Knee* group. A deviation of +/- 3° is considered to be within the accepted range of an aligned knee component, as reported in the literature[7, 8]. Massé *et al.* have demonstrated 4.8% iASSIST and 30.4% conventional outliers of ± 2° from neutral for the femur varus-valgus angle, 9.5% iASSIST and 60.9% conventional outliers of ± 2° from neutral for the femur flexion-extension, 4.8% iASSIST and 30.4% conventional outliers of ± 2° from neutral for the tibial varus-valgus angle and 28.6%

iASSIST and 73.9% conventional outliers of ± 2° from neutral for the tibia slope[9]. The improvement of the accuracy achieved by the use of the iASSIST Knee validation feature will be evaluated as part of the study for both femur and tibia cuts in both planes. The first tibial proximal and the first femoral distal cuts will be performed and validated. If the validation values are outside of +/-2 degrees from target, the surgeon will adjust the cut as per the iASSIST surgical technique recommendations, re-cut and re-validate.

Table 1. Predefined Target Component Angles

Plane	Component	*Persona* component Angles
Frontal	Femoral	90
	Tibial	90
Sagittal	Femoral	defined by preoperatively
	Tibial	defined by preoperatively

SAMPLE SIZE

This sample size calculation was conducted anticipating the use of a Fisher's exact test.

Alpha level: 5% (two-sided)

Power: 80%

Assuming we anticipate that 95% of the investigational group has an angle deviation within +/- 2° and that for the control group, 70% have an angle deviation within +/- 2°, the calculation for sample size when comparing proportions is 31 patients. 50 patients per group comfortably exceeds 20% attrition. Therefore, this provides for a total of 100 patients for both arms.

7.1 DETAILED DESCRIPTION OF RANDOMIZATION

In this study, patients will be randomized in one of the two treatment arms: *Persona* TKA with *iASSIST Knee* system (Investigational group) or *Persona* TKA with conventional instrumentation (Control group). The randomization scheme is based on equal numbers per group. The randomization will occur via a random number generator (computer) using blocked randomization procedure. The PI or his/her team does not have influence on the randomization scheme. Sealed opaque envelopes, which will be prepared based on predetermined randomization assignment, will be provided to each study site before study initiation.

7.2 HANDLING OF MISSING AND INCOMPLETE DATA

Data will be considered "missing" for the primary endpoint if this outcome cannot be determined or is unavailable for a subject. Every effort will be made to collect the data necessary to evaluate the primary endpoint. Patients who have been lost to follow-up and do not have Tibial alignment at 6 months will not be included in the primary study analysis.

Sensitivity analyses will be performed to assess the impact of missing data on the primary study analysis. These analyses may include a best-case and worst-case imputation as well as a tipping point analysis.

7.3 DATA ANALYSES

Data will be analyzed using SAS 9.0 or higher. The Type I error rate for the primary study analysis will be 0.05. Comparisons for secondary, exploratory, and safety analyses will be two-sided comparisons using $\alpha = 0.05$, with no adjustment for multiple comparisons.

Primary Analysis: The primary analysis will be presented as both intention-to-treat (ITT) and Full Analysis set (FAS). In the ITT analysis for the primary endpoint, missing data will be treated as described in Section 7.2. A two-tailed Fisher's Exact Chi-Square test at $\alpha = 0.05$ will be used to assess the study hypotheses and determine whether there is a statistically significant difference between investigational and control groups with regard to the proportion of patients with femoral or tibial component alignment within +/- 3 degrees from predefined angles (Table 1).

Secondary Analysis: Analyses for secondary endpoints will be FAS, and will only use those cases with complete data for the endpoint being analysed.

Continuous data (e.g. age, BMI, VAS pain) will be reported using mean, standard deviation, median, and range. Comparisons of Investigational vs Control with regard to continuous baseline and secondary outcomes will be performed using standard statistical tests and will be chosen as appropriate for the scale and distribution of the measures being analyzed. For example, a t-test, Wilcoxon test, or one-way ANOVA (as appropriate) may be performed to assess differences.

Categorical data (e.g. gender) will be reported using frequency and percentage. Comparisons of Investigational vs Control with regard to categorical baseline, secondary and safety outcomes will be performed using standard statistical tests and will be chosen as appropriate for the scale and distribution of the measures being analyzed. For example, categorical outcomes may be compared for investigational and

control groups using the Fisher's Exact test (for 2x2 tables) or the Likelihood Ratio chi-square test (for tables larger than 2x2).

Knee prosthesis survivorship will be assessed using a Kaplan-Meier analysis. Comparison of survivorship for Investigational vs Control will be done using the Log-Rank test.

7.4 STUDY REPORT

The primary analysis will be performed after all patients reach the 6 months follow up time point. Data will be analysed using the methods described in Section 7.3.

8. DATA COLLECTION, HANDLING AND RETENTION

8.1 SOURCE DOCUMENTATION REQUIREMENTS

Source documents will be made available to the Sponsor for verification according to local law.

8.2 CASE REPORT FORMS

Data for this clinical study will be collected and documented on CRFs provided in an electronic form or paper form. Authorized study site personnel will complete CRFs only. CRFs must be reviewed by the PI or his/her designees.

8.3 STUDY DOCUMENT RETENTION

Study documents should be retained for 5 years after the study is completed.

9. DATA REPORTING

Within 6 months of the study close the Sponsor will present a final study report to summarize all data collected throughout the study duration, complications throughout the course of the data collection, and general findings.

The report will contain the results of all primary and secondary endpoints. Also, patient follow-up will be analyzed throughout the data collection according to the following definition and equations:

Lost To Follow-Up:
1. Death
2. Implant removal: Date of revision, all component part numbers removed, reason for revision, and any relation to study device.
3. Revision of metal* components (Femur or Tibia): Date of revision, all component part numbers removed, and reason for revision Consent Rescinded.

**Bearing revisions in which only the polyethylene is replaced will not be withdrawn from the study.*

$$\text{Percentage Follow-up} = \frac{\text{\# Patients with Follow-Up}}{\text{(Theoretically due – Lost To Follow-Up)}} \times 100$$

$$\text{Percentage Accounted for} = \frac{\text{(\# with Follow-Up + Lost To Follow-Up)}}{\text{Theoretically due}} \times 100$$

10. RISK ANALYSIS

The site and PI is responsible for following all directions and labeling associated with the product device and its use in TKA. It is expected that all use of the product will be according to the label with full knowledge of all Warnings, Precautions, and Possible AEs associated with the device.

In accordance with the risk management file of the Sponsor the following risk may occur:

- Higher wear rates may be caused by cement or metal particles or other debris that can cause abrasion of articulating surfaces. A high level of wear can shorten the service life of the prosthesis and lead to early revision for the replacement of worn prosthetic components.
- In all cases of joint replacement, asymptomatic localized progressive bone resorption (osteolysis) may be noted around prosthetic components as a result of foreign body reactions triggered by particles. These particles are generated by the interaction between the various components, as well as between the components and bone, mainly through mechanisms of wear, adhesion and fatigue. Other particles may also be produced by the wearing of another body. Osteolysis may lead to successive complications requiring the removal and replacement of prosthetic components.

- Calcification or periarticular ossification, peroneal nerve palsy and hematoma can result from improper handling of implants and associated instrumentation. The risk of embolism, pain and postoperative infections associated with any surgical procedure also applies to the implementation of this prosthesis.
- Although rare, cases of metal intolerance following joint replacement have been observed. Implantation of foreign material in tissues may result in histological reactions involving the formation of macrophages and fibroblasts.
- Dislocation or subluxation of prosthetic components due to improper positioning and/or migration of components can occur. Muscle and fibrous tissue laxity can also contribute to these conditions.
- Prosthetic components can loosen or migrate following trauma.

11. MONITORING PLAN

The Sponsor will monitor the data collection to ensure that the investigation is being conducted consistent with the protocol. The following describes the monitoring activities, which may take place during the course of the study.

11.1 FREQUENCY

Pre-Investigational Visit/Conference:

Prior to initiation of the study, the study manager will provide the PI with all the necessary information to enable him to carry out his responsibilities. This prepares the site with an in-depth training on the protocol, CRFs, and data collection process for the length of the study. The study manager will also train the site on using the Sponsor's electronic CRF upon choice of CRF system.

Monitoring of the Data

Monitoring of the data will occur at least annually.

11.2 SAMPLING PLAN

All data will be monitored for completeness and accuracy on at least an annual basis.

11.3 MONITORING TASKS

The Sponsor will continually monitor the progress of the clinical study. These activities include:

- Tracking of patient enrollment,
- Review of all electronic patient data forms received for completeness,
- Tracking of patient visits to ensure follow-ups are being completed at appropriate intervals,
- Review of all AEs,
- Maintaining open communication with all investigational sites in order to ensure the quality of the clinical study, and
- In-house audits as needed.

Upon completion of any type of monitoring, the site is responsible for resolving all discrepancies found in a timely manner. These will be sent to the site with an audit report by the study manager. All discrepancies found within the online database will be queried and sent directly to the site. Delays in resolving queries are to be avoided at all costs; this provides the study with the most accurate data, prevents delay in reporting procedures & publication.

11.4 STUDY CLOSE-OUT

When a site has completed their data collection, a visit may be necessary by a Sponsor's monitor to ensure all data has been obtained. Data will be reviewed for completeness, and monitored to ensure that all discrepancies have been resolved.

12. LABELING

The devices and products will be used in accordance with their instructions for use and/or approved labeling. The package insert for the device(s) in this study is included in the Investigator Binder.

13. ETHICAL AND REGULATORY REQUIREMENTS

13.1 CODE OF CONDUCT

The PI will ensure that the clinical study is conducted in accordance with

1. Study Protocol and
2. Ethical Guidance for clinical study including human subject (MHLW, Dec. 22, 2014).

13.2 INSTITUTIONAL REVIEW BOARDS/ETHICS COMMITTEE

The PI must obtain appropriate EC approval before the study can be initiated.

13.3 INFORMED CONSENT

Patients (or the patient's legally authorized representative) will be provided with an informed consent and patient information sheet, and given ample opportunity to review the consent and ask questions. The signed informed consent will be obtained before any study procedures begin. If the patient agrees to participate in the study, the patient/representative must sign the informed consent form. The witness and the PI must also sign the informed consent form. A copy of the informed consent form should be given to the patient/representative. All patients who meet all of the entry criteria will be considered for inclusion in this study. Any subject meeting any of the exclusion criteria will be excluded from the study.
The informed consent form must be approved by the site's EC prior to the study initiation.

Patients will be informed of new information learned during the study, which may affect the patient's decision to continue participation in the study.

An Informed Consent Log should be completed to document the existence of the signed informed consent form. The log will contain: Subject ID, date informed consent form signed, and the version signed.

13.4 SUBJECT CONFIDENTIALITY

The CRFs do not include any patient identifying information. Therefore, once the data is entered in the online database a patient can no longer be identified.

By assigning patients a unique ID number, their identity is protected in the online database. The database is restricted, allowing a doctor to only view and enter data from his/her own patients. User authentication is required to view the data. The data is transmitted to a centralized database through a secured (SSL) channel on the Internet. Data in transit is in 128-bit encryption. The access to the centralized database is limited to those who are responsible for maintaining the database.

14. PUBLICATION PLAN

Both the Sponsor and PI will make reasonable efforts to publish the results of this study. Upon completion of all CT measurements and statistical analyses, a manuscript is to be written in English to meet peer-reviewed journal requirements. The manuscript will be submitted to one of below or other suitable journals.

- KSSTA (Knee Surgery, Sports Traumatology, Arthroscopy)
- CORR (Clinical Orthopaedics and Related Research)
- JOA (Journal of Arthroplasty)
- Acta Orthopaedica
- The Knee

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16. APPENDICES

Appendix 1 Instructions for Use