A Prospective, Multicenter Study to Evaluate Functional Outcome After Knee Replacement

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Protocol Signature Page

This is to acknowledge that I have received the above-identified protocol, that I have read and understood its content, and that I agree to conduct the clinical trial in accordance with the procedures outlined therein.

Investigator Approval:

_____

Signature Date

_____

Print Name

1. INTRODUCTION, BACKGROUND & OBJECTIVE

Osteoarthritis or other degenerative changes or injury can cause damage to the structures in the knee, causing pain, discomfort, and lessening the quality of life. Knee replacement, or knee arthroplasty, is a common surgical procedure performed to relieve the pain and disability resulting from osteoarthritis. In general, the surgery consists of replacing the diseased or damaged joint surfaces of the knee with metal and plastic components shaped to allow continued motion of the knee.

Today, over 600,000 patients undergo total knee replacement each year in the United States, a number that is projected to increase greatly over the next 20 years (Kurtz 2007). Total knee replacement has been performed since 1964 and has been shown to be an effective, long-lasting procedure with good survivorship of the implants for patients with osteoarthritis. Despite the excellent survivorship, there are still a significant percentage of patients that remain dissatisfied with their results. Studies reveal that 14- 39% of patients report some level of dissatisfaction with their knees post-surgery (Noble 2006; Bourne 2010; Suda 2010).

This study is designed to compare outcome data for patients undergoing surgery with the iTotal® Cruciate Retaining (CR) Knee Replacement System (KRS) versus those who are undergoing surgery with Off-the-Shelf (OTS) systems.

To compare outcomes of these two study groups, this study will include the routine office questionnaires such as the 2011 Knee Society Knee Scoring System © (KSS) and the Knee Injury and Osteoarthritis Outcome Score (KOOS). However, literature suggests that these questionnaires fail to capture the change in functional activities post total knee replacement (Mizner 2010). It has been noted that patients "dramatically overestimate their functional ability early after surgery" (Mizner 2010). The Mizner study showed that there was an increased use in assistive devices and a decrease in functional testing scores post-surgery, while the patient reported outcome scores failed to show worsening. To capture these changes, this study will also conduct multiple functional tests on all patients pre- and post-surgery.

The functional tests used in this study are commonly used as an objective method to assess patients' functional status. The testing is designed to closely mimic daily activities that the patients are familiar with. In this study, the patient will have a pre-operative visit to serve as a baseline, and then will be retested at predefined post-operative intervals. The patient will perform the same group of functional tests pre- and post-operatively using methods that are summarized below in section 4 and in Appendix B.

2. DEVICE DESCRIPTION

The iTotal CR Knee Replacement System (hereafter referred to as the "iTotal CR") is a patient-specific tricompartmental faceted posterior cruciate ligament (PCL) retaining knee replacement system. The iTotal CR is a semi-constrained cemented knee implant which consists of a femoral, tibial and patellar component.

Using computed tomography (CT) and a combination of proprietary and off-the-shelf software a patient-specific implant is designed, that best meets the geometric and anatomic requirements of the specific patient. The femoral component is manufactured from cobalt chromium molybdenum

("CoCrMo") alloy. The tibial component includes a metal tray manufactured from CoCrMo alloy and polyethylene inserts. The polyethylene inserts may be manufactured from either UHMWPE or a highly cross-linked Vitamin E infused polyethylene (iPoly XE™). The patellar component is also manufactured from either UHMWPE or from a highly cross-linked Vitamin E infused polyethylene (iPoly XE).

Several key features of the iTotal CR are listed below:

- Disposable, patient-specific instrumentation
- Simple, reproducible surgical technique
- Potential for less post-operative pain and shorter post-operative recovery time

The control will be one of three off-the-shelf CR systems:

- DePuy Synthes: Attune
- Zimmer: Persona
- Stryker: Triathlon

For all procedures, the patella will be resurfaced using the patella implant available through the respective manufacturer.

3. STUDY DESIGN

This is a prospective, blinded, multi-center study that will be conducted in the US, UK, and Germany. The study will include a minimum of 450 and a maximum of 600 subjects across up to 20 sites with up to 225 min- 300 max subjects in the iTotal CR arm and 225 min- 300 max subjects in the off-the-shelf total knee arm. An additional 25% may be enrolled to account for subject discontinuation.

Subjects will be consecutively recruited in groups of 10, alternating between study arms until enrollment is completed. Once a series of 10 is recruited (subject signed consent and completed pre-op questionnaires), then the next series of 10 is to be recruited.

To ensure that enrollment in each arm remains relatively even, sites assigned odd site numbers will begin by enrolling off-the-shelf subjects and even numbered sites will begin by enrolling ConforMIS subjects. Subjects will be implanted with either an iTotal CR or an off-the-shelf cruciate retaining total knee replacement.

The person administering the functional tests will be blinded. The blind will be maintained for at least one year in order to maintain an objective assessment of each patient's function. Investigators and study staff will make every attempt to maintain the blind by limiting access to study data, x-rays, and other evaluations.

For all surgeries, the preferred surgical approach is to make an incision that is midline or slightly medial to midline, followed by a parapatellar arthrotomy, or a subvastus arthrotomy with prior written approval from Sponsor. The surgeon must use the same approach for all study subjects.

For surgical technique, the off-the-shelf goal is to obtain mechanical alignment.

4. ECONOMIC SUBSTUDY

This study will include a prospective economic analysis of US sites if contracted by the Sponsor. Please refer to Appendix C for complete description.

5. FUNCTIONAL TESTING

Each subject enrolled in the study will be asked to perform a series of functional tests under static and dynamic conditions that they routinely encounter during their daily lives. These tests include:

1. The Timed "Get-up and Go" Test (TUG) is a functional test that physical therapists have been using since the late 1980s to assess balance in elderly people (Mathias 1985; Podsiadlo 1991; Nordin 2006; Wall 2000). This is a quick test where no special equipment is needed to quantify functional mobility. The test will involve a standard chair, a walkway long enough for a subject to walk 3 meters and turn around, a stopwatch, and an administrator to observe and time the subject. The test administrator will instruct the subject to "go" and start the stopwatch. The subject will rise from the chair, walk 3 meters, turn around, walk back to the chair, and sit down again. Once the subject's buttocks touch the seat, the stopwatch will be stopped by the test administrator. The subject will be instructed to walk as quickly as they feel safe and comfortable. Assistive devices are allowed only if the subject does not feel safe or cannot do this test without the assistive devices. The test administrator will take note if an assistive device was used during the test. There will be 3 timed trials. The average will be used for data analysis.

2. The 8 Meter Walk is a functional test that measures locomotion. "Locomotion refers to the act of moving from one place to another place, reflecting ambulation ability including walking distance, velocity and quality of gait" (National Institutes of Health 2012). In this test, the distance of 4 meters will be marked by a cone. The subject will begin at one end of the walkway. The test administrator will instruct the subject to "go" and start the stopwatch. The subject will walk towards the cone, around the cone, and back to the starting location at the pace that they normally walk. Once the subject is back at the starting point, the stopwatch will be stopped by the test administrator. There will be 3 timed trials. The average will be used for data analysis.

3. The Timed Up and Down Stairs Test (TUDS) is a functional test that "demands more balance, coordination, strength and muscle control than walking demands" (Lepage 1998; Zaino 2004). This test will involve a stopwatch and a flight of stairs with rails. A usual set of stairs is 12 steps that are 18cm high with a depth of 28cm. The flight of stairs used during testing must have a minimum of 4 steps. The subject will stand at the bottom of the stairs. The test administrator will voice the command "go" and start the stopwatch. The subject will walk as quickly as they feel safe and comfortable to the top of the stairs, turn around, and come back down the stairs. Once the subject is safely back down with both feet back on the landing, the test administrator will stop the stopwatch. The subject may use the rail, but the preference is to do this test without the use of a rail. Assistive devices are allowed only if the subject does not feel safe or cannot do this test without the assistive devices. The test administrator will take note if the rail or an assistive device was used during the test. Again, the subject will be instructed to move as quickly as they

feel safe and are comfortable. There will be 3 timed trials. The average will be used for data analysis.

The Aggregated Locomotor Function (ALF) score is formed by summating the mean of the above three timed tests (McCarthy 2004). Suggested instructions are located in Appendix B.

6. STUDY DURATION

The study subjects will be required to complete follow-up visits at predetermined intervals for 10 years post-implantation. The in-office follow-up visits will occur at 90 days, 180 days, 1 year, 2 years, 5 years, and 10 years post-implantation. The remaining follow-up data collected at years 3, 4, 6, 7, 8, and 9 may be collected via phone call, mail, or email and does not require an in-office visit.

7. STUDY ENDPOINTS

7.1. **Primary Endpoints**

The primary functional endpoint will be measured by the Aggregated Locomotor Function (ALF) score (TUG, 8 Meter Walk, and TUDS activities) and/or its components at 1 Year post-implantation.

7.2. **Secondary Endpoints**

The study secondary endpoints are:

1. The 2011 Knee Society Knee Scoring System© (KSS) and/or its subscales at 1 Year post-implantation
2. The Knee Injury and Osteoarthritis Outcome Score (KOOS)
3. Incidence of major procedure–related and device-related complications, including revision rates
4. Post-operative limb alignment

8. INCLUSION AND EXCLUSION CRITERIA

Per CONSORT data reporting guidelines, all patients considered for this study will be tracked on a log documenting their eligibility, and enrollment status. For further details, please refer to Appendix D.

8.1. **Inclusion Criteria**

1. Clinical condition included in the approved Indications For Use for the iTotal CR
2. Osteoarthritis, as confirmed by the investigator's assessment of disease status at screening visit that warrants a TKR procedure. Disease status is determined by Clinical and Radiographic assessment
3. Willingness to participate in the clinical study, to give informed consent and to attend all follow-up visits
4. > 18 years of age

8.2. **Exclusion Criteria**

1. Subject will require a simultaneous bilateral procedure

2. Lower extremity surgery (orthopaedic or ligament injury) on either limb to the hip, ankle, feet occurring or expected to occur within 1 year of surgery on the evaluated knee
3. Severe (> 15º) fixed valgus or varus deformity
4. Severe (> 15º) extension deficit
5. Severe instability due to advanced loss of osteochondral structure
6. Loss of bone or musculature, osteoporosis, neuromuscular or vascular compromise in the area of the joint to be operated on to an extent that the procedure is unjustified
7. Insufficient bone stock on the femoral or tibial surfaces
8. Contralateral knee replacement occurring or expected to occur within 6 months of surgery on the evaluated knee
9. BMI > 40
10. Active malignancy (defined as a history of any invasive malignancy – except non-melanoma skin cancer), unless patient has been treated with curative intent and there have been no clinical signs or symptoms of the malignancy for at least 5 years
11. Poorly controlled diabetes (defined as HbA1c >7 or surgeon discretion)
12. Immunocompromised
13. Other physical disability affecting the hips, spine, or contralateral knee that limits function
14. Disabling chronic pain with narcotic dependence
15. Compromised PCL or collateral ligament
16. Prior history of failed implant surgery of the joint to be treated, including Unicompartmental Knee Arthroplasty (UKA), or Bicompartmental Knee Arthroplasty (BKA)
17. Prior history of failed High Tibial Osteotomy (HTO)
18. Participation in another clinical study which would confound results
19. Inability to complete the protocol in the opinion of the clinical staff due to safety or other reasons

9. SITE SELECTION

All sites will be selected by a Site Selection Committee based on a set of defined criteria. The Site Selection Committee will be led by Clinical Affairs. The site selection criteria includes but is not limited to:

- Interest in participating in the study as demonstrated by responsiveness
- Demonstrated technical and surgical skills with iTotal CR device - Investigator must have completed a cadaver training at minimum prior to enrolling their first subject
- Sufficient patient volume to expect timely subject enrollment
- Ability to adhere to the standards of Good Clinical Practice (GCP) and Good Documentation Practice (GDP)
- Clinical study experience and resources that demonstrate good compliance with study requirements and timely, complete documentation of subject follow-up
- Willingness to allow personnel from ConforMIS (or its designate) access to the hospital records, Investigator's study records, data and patient files as they pertain to the study

During the study, an oversight committee comprised of three individuals: the Lead Study Principle Investigator in the U.S., a second study investigator, and a statistician will review site

performance and data integrity. This committee will determine if the data collected is consistent with the cohort, and meets the minimum enrollment threshold for the study.

If a site has not enrolled a minimum of 20 subjects into the study, data may be excluded from analysis. Likewise, if data quality is inadequate or data is incomplete, the committee may exclude a site's data.

10. ENROLLMENT

Potential subjects will be identified by the Investigator or study staff based on patients' clinical and radiographic assessments during regular medical care. The Investigator or study staff will provide study information and the approved Informed Consent Form to all eligible subjects, (determined via Inclusion/Exclusion criteria), as well as answer any questions about the study.

Once the consent form is signed, the subjects will be assigned a unique subject identification number through the EDC system. Once they complete the first set of pre-operative questionnaires, they will be assigned to one of two treatment arms: A) Treatment with the iTotal CR or B) Treatment with an off-the-shelf knee replacement. The site will be instructed to consecutively enroll 10 subjects per treatment arm, alternating between each arm, until enrollment is completed.

The subject identification number will be comprised of a five digit number starting with a two digit site number assigned by ConforMIS at the Site Initiation followed by a three digit subject number, assigned chronologically for the entire study. For example, at site 01, the first subject enrolled will receive number 01-001, followed by 01-002, 01-003, etc.

The Investigator and/or study staff will assess the subject against the Inclusion and Exclusion criteria to determine eligibility. Eligibility includes clinical assessments, radiographic assessments, and a review of the subject's medical history. The radiographic assessments should include:

1. Knee x-ray: 3 views – AP, lateral, sunrise or Merchant
2. Three foot standing x-ray (full length, full weight-bearing film): AP view

If the subject is not eligible to participate in the study, the subject will not be enrolled and is considered a screen failure. All screen failures will be tracked by the site manually in a tracking spreadsheet and electronically in a clinical database. Subject identification numbers for screen failures will not be re-used.

The following Case Report Forms will be completed for all screen failures:

- SUBJECT INFORMATION/MEDICAL HISTORY
- INCUSION/EXCLUSION CRITERIA

If the subject is eligible to participate in the study, they will be assigned to a treatment arm and will be considered enrolled when they are implanted with a device.

11. SCHEDULE OF EVALUATIONS BY VISIT

A table displaying the Schedule of Evaluations is in Appendix A. Regardless of treatment arm assigned, subjects will complete each visit in the schedule of evaluations below.

11.1. Preoperative Visit (Up to 4 months prior to Surgery)

Many of the screening assessments required to ensure subject eligibility are also considered the pre-operative assessments. The results of the assessments will be captured on the following Screening/Pre-operative Case Report Forms:

- SUBJECT INFORMATION / MEDICAL HISTORY
- CONCOMITANT MEDICATIONS
- PAIN MEDICATIONS
- INCLUSION/EXCLUSION CRITERIA
- KNEE SOCIETY SCORE (Surgeon portion)

The subject will complete the following function tests and questionnaires to assess pain and function as part of their preoperative assessment:

- THE KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE (KOOS)
- KNEE SOCIETY SCORE (Subject portion)
- TIMED "GET UP AND GO"
- 8 METER WALK
- TIMED UP AND DOWN STAIRS

X-rays:

- 3 views – AP, lateral, sunrise or Merchant
- Three foot standing x-ray (full length, full weight-bearing film): AP view

11.2. Surgery Visit (Day 0)

The Investigator will surgically implant either the iTotal CR in compliance with the ConforMIS surgical training and Instructions for Use, or the off-the-shelf TKR per their surgical training and the manufacturer's Instructions for Use.

The site will complete the following Case Report Forms:

- SURGICAL SUMMARY
- DISCHARGE SUMMARY
- CONCOMITANT MEDICATIONS (optional)
- PAIN MEDICATIONS
- ADVERSE EVENTS (if any occur during surgery through discharge from hospital)

X-rays: None

11.3. 90 Days Follow-up Visit (± 14 days)

At the 90 days follow-up visit, the Investigator or study staff will perform a post-operative knee assessment and identify any adverse events that have occurred since the subject was discharged from the hospital. The site will also collect the Uniform Billing (UB) form from their billing department if contracted with the Sponsor to participate in the Economic Sub-study.

The site will complete the following Case Report Forms:

- FOLLOW UP
- KNEE SOCIETY SCORE (Surgeon portion)

- CONCOMITANT MEDICATIONS (optional)
- PAIN MEDICATIONS
- ADVERSE EVENTS (if any)
    - REVISION FORM (if necessary)

The subject will complete the following function tests and questionnaires to assess post-operative pain and function:

- THE KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE (KOOS)
- KNEE SOCIETY SCORE (Subject portion)
- TIMED "GET UP AND GO"
- 8 METER WALK
- TIMED UP AND DOWN STAIRS

X-rays:

- 3 views – AP, lateral, sunrise or Merchant*
- Three foot standing x-ray (full length, full weight-bearing film): AP view*

**(Depends on hospital standards. Protocol requires only one set of post-op x-rays at either 90 or 180 days)*

11.4. 180 Days Follow-up Visit (± 21 days)

At the 180 days follow-up visit, the Investigator or study staff will perform knee assessments and identify any adverse events that have occurred since the last visit.

The site will complete the following Case Report Forms:

- FOLLOW UP
- KNEE SOCIETY SCORE (Surgeon portion)
- CONCOMITANT MEDICATIONS (optional)
- PAIN MEDICATIONS
- ADVERSE EVENTS (if any)
    - REVISION FORM (if necessary)

The subject will complete the following function tests and questionnaires to assess post-operative pain and function:

- THE KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE (KOOS)
- KNEE SOCIETY SCORE (Subject portion)
- TIMED "GET UP AND GO"
- 8 METER WALK
- TIMED UP AND DOWN STAIRS

X-rays:

- 3 views – AP, lateral, sunrise or Merchant*
- Three foot standing x-ray (full length, full weight-bearing film): AP view*

**(depends on hospital standards. Protocol requires only one set of post-op x-rays at either 90 or 180 days)*

11.5. Year 1, 2, and 5 Follow-up Visits (± 2 months)

At the 1 year, 2 year, and 5 year follow-up visits, the Investigator or study staff will perform a knee assessment and identify any adverse events that have occurred since the subject's last visit.

The site will complete the following Case Report Forms:

- FOLLOW UP
- KNEE SOCIETY SCORE (Surgeon portion)
- CONCOMITANT MEDICATIONS (optional)
- PAIN MEDICATIONS
- ADVERSE EVENTS (if any)
    - REVISION FORM (if necessary)

The subject will complete the following function tests and questionnaires to assess post-operative pain and function:

- THE KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE (KOOS)
- KNEE SOCIETY SCORE (Subject portion)
- TIMED "GET UP AND GO"
- 8 METER WALK
- TIMED UP AND DOWN STAIRS

X-rays: None

11.6. Year 3, 4, 6, 7, 8, and 9 Follow-up Visits (± 3 months)

On the anniversary of the implant surgery for years 3, 4, 6, 7, 8, and 9, the Investigator or study staff will assess the subject for complications or adverse events, and specifically to determine if the iTotal CR or off-the-shelf total knee has been revised. It is not necessary for the subject go to the clinic for a visit, as the site can obtain the data via direct communication with them (such as via telephone or email).

The site will complete the following Case Report Form:

- FOLLOW UP
- ADVERSE EVENTS (if any)
    - REVISION FORM (if necessary)

X-rays: None

11.7. Year 10 Follow-up Visit (± 4 months)

On the 10 year anniversary of the implant surgery, the Investigator or study staff will assess the subject to determine if the iTotal CR or off-the-shelf total knee has been revised.

The site will complete the following Case Report Form:

- FOLLOW UP
- KNEE SOCIETY SCORE (Surgeon portion)
- CONCOMITANT MEDICATIONS (optional)
- PAIN MEDICATIONS
- ADVERSE EVENTS (if any)
- REVISION FORM (if necessary)

The subject will be asked to complete the following function tests and questionnaires to assess long term post-operative pain and function. Note that the subject should return to the clinic to complete these questionnaires.

- THE KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE (KOOS)
- KNEE SOCIETY SCORE (Subject portion)
- TIMED "GET UP AND GO"
- 8 METER WALK
- TIMED UP AND DOWN STAIRS

X-rays: None

11.8. Early Termination Visit

In the event that the study subject ends their participation in the study prior to the 10 year visit, the investigator or designated study staff will complete the following CRFs:

- SUBJECT DISPOSITION
- CONCOMITANT MEDICATIONS (optional)
- PAIN MEDICATIONS
- ADVERSE EVENTS (if any)
    - REVISION FORM (if necessary)

The Investigator or designated study staff will make every attempt to complete the following evaluations:

- THE KNEE INJURY AND OSTEOARTHRITIS OUTCOME SCORE (KOOS)
- KNEE SOCIETY SCORE (Subject and Surgeon portion)
- TIMED "GET UP AND GO"
- 8 METER WALK
- TIMED UP AND DOWN STAIRS

12. SAFETY REPORTING

All Adverse Events (AEs) that are at least possibly related to the knee replacement device or procedure will be recorded by the site from surgery on the Adverse Event CRF and should be reported to Sponsor within 5 working days of site becoming aware of the event. In addition, all Serious Adverse Events (SAEs) and Unanticipated Adverse Device Effects (UADEs) must be reported to ConforMIS or designee via telephone (781-345-9001) or email (clinical-affairs@conformis.com) as soon as possible once discovered by the site. SAEs should be reported to ConforMIS within 3 working days, and UADEs should be reported to ConforMIS within 2 working days. The Investigator and investigative site will also be responsible for required reporting to the site's Institutional Review Board / Independent Ethics Committee (IRB/IEC) for all AEs, SAEs, and UADEs.

In the communications to ConforMIS or the IRB, include the protocol number and subject ID either in the subject of the email or the beginning of the call. ConforMIS will confirm receipt of the AE/SAE. If possible, include the AE/SAE CRF and supporting documents to ConforMIS as soon as possible.

For the purposes of this protocol, for the first 90 days following surgery, all AEs categorized as Possible, Probable or Definite in relationship to the device or procedure should be

recorded. At day 91, only those AEs categorized as Possible, Probable, or Definite in relationship to the device, as deemed by the investigator, will be recorded. Those events that are Unlikely or Not Related to the device and procedure will not be collected. Please see definitions below.

All SAEs will be recorded regardless of relationship to the device or procedure.

ConforMIS will be responsible for safety reporting as required by applicable regulatory bodies.

Adverse Event: Any untoward or unfavorable medical occurrence associated with the use of a medical product in a human patient, including any abnormal sign, symptom, or disease. Report only those AEs with Possible or above, relationship.

Definite:	Clear-cut temporal association and no other possible cause.
Probable:	Clear-cut temporal association and a potential alternative etiology are not apparent.
Possible:	Temporal association is less clear and other etiologies are also possible.
Unlikely:	Temporal association and the nature of the event is such that the study device is not likely to have had any association with the observed event (cause and effect relationship improbable but not impossible)
Not Related:	There is no temporal association and/or evidence exists that the event is definitely related to another etiology

Serious Adverse Event: Any undesirable experience associated with the use of a medical product in a patient in which the patient outcome is: death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect or requires intervention to prevent permanent impairment or damage.

Unanticipated Adverse Device Effect (21 CFR 812.3): Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), instructions for use, informed consent or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

13. DATA MANAGEMENT

Each site will be responsible for accurate, complete, and timely collection/recording of data using the CRF (or EDC system) provided. Data will be stored in a validated and secure database for analysis. ConforMIS will periodically review all data, and specifically adverse event data to determine interim revision rates, frequency of serious adverse events and patient outcomes. If

missing data fields or incorrect data are identified, the site may be contacted to provide the missing/correct data.

ConforMIS or a designee will provide Case Report Forms (paper and/or electronic) to the study sites, along with access the to the EDC system.

14. MONITORING

ConforMIS or designee will monitor clinical sites using risk-based monitoring to review source data, study conduct, and compliance to the protocol. Each site will be monitored shortly after beginning enrollment to ensure early identification and resolution of any issues. After the initial monitoring visit, the site will be monitored at a frequency determined by ConforMIS or designee based on a variety of variables including but not limited to the risk of the site, rate of enrollment, the number of issues identified that require follow-up, changes in site personnel, etc.

15. STATISTICAL METHODS

All statistical processing will be performed using SAS® Version 9.3 or later unless otherwise stated.

For continuous variables, descriptive statistics will include n (number of subjects), mean, standard deviation (SD), median, minimum, and maximum. For categorical variables, the number and percentage of subjects in each category will be presented. Appropriate inferential statistics will be used for the primary and secondary efficacy variables.

Populations
The safety population will be comprised of all subjects for whom the procedure is initiated.

The Full Analysis Set (FAS) will be comprised of all subjects for whom the procedure is completed.

The Per-Protocol (PP) population will include all subjects in the FAS who complete the 1 Year visit without significant protocol violations. The PP population will not include subjects who meet any of the following criteria:

- Violated inclusion/exclusion criteria, without sponsor waiver;
- Did not attend the 1 Year visit
- Out of window at the 1 Year visit by +/- 2 months
- Have undergone a procedure to the contralateral knee which may impact the follow-up assessments

Additional criteria may be added to the list to accommodate for unforeseen events that occur during the conduct of the study that impact efficacy assessments. The PP population will be determined prior to data base lock.

Demographic and Baseline Characteristics
Demographic variables (e.g. age, gender, ethnicity, race) and baseline characteristics will be recorded in the CRF. For continuous variables, comparisons between treatment groups will be

conducted with an analysis of variance (ANOVA). A Cochran-Mantel-Haenszel (CMH) test will be used for testing categorical variables.

Efficacy Analysis

Primary Efficacy Analysis
The absolute change from baseline to 1 Year for each primary endpoint will be analyzed using an analysis of covariance (ANCOVA) with factor of treatment (iTotal CR, OTS) and the respective baseline score as a covariate. The least squares means will be presented along with the observed means.

Secondary Efficacy Analyses
Secondary endpoints will be analyzed as follows:

- The absolute change from baseline to 1 Year for each subscale of KSS will be analyzed using an analysis of covariance (ANCOVA) with factor of treatment (iTotal CR, OTS) and the respective baseline score as a covariate. The least squares means will be presented along with the observed means.
- The absolute change from baseline to 1 Year for each subscale of KOOS will be analyzed using an analysis of covariance (ANCOVA) with factor of treatment (iTotal CR, OTS) and the respective baseline score as a covariate. The least squares means will be presented along with the observed means.
- Post-operative limb alignment will be dichotomized as in and out of "safe zone" (+/- 3 degrees neutral mechanical axis alignment). The proportion of subjects in each study arm summarized and compared using a CMH test.

Safety Analysis
Procedure-related and device-related adverse events (AEs) occurring during the study will be recorded. For the safety population, AEs will be summarized by study arm, the number of subjects reporting AEs, severity, relationship to procedure, relationship to device, and seriousness.

In addition to overall AE summaries, AEs will be summarized for the following study periods:
- Day of procedure to 6 months post procedure
- Annual summaries (1 Year, 2 Year, etc.) from day of procedure

All serious adverse events (SAEs) will be summarized by study arm, severity, relationship to procedure, and relationship to device. SAEs will also be listed by subject.

All information pertaining to AEs noted during the study will be listed by subject.

The Fisher's Exact test will be used to compare the proportion of subjects in each study arm who have the following:
- procedure-related AEs
- device-related AEs
- revision procedures

Missing Efficacy Data Imputation

The last observation carried forward (LOCF) method will be used to impute missing efficacy data.

Sample Size Determination
A total sample size of a minimum of 450 and a maximum of 600 subjects will be prospectively enrolled in a consecutive fashion, to each arm of the study (approximately 225-300 in the iTotal CR arm and 225-300 in the OTS arm). To ensure that enrollment in each arm remains relatively even, sites assigned odd site numbers will begin by enrolling off-the-shelf subjects and even numbered sites will begin by enrolling ConforMIS subjects. Based on data from a previous study, it is expected that a minimum of 450 and a maximum of 600 total subjects will provide greater than 80% power for the primary functional endpoint.

16. SUBJECT PROTECTION

Data will be de-identified on forms and in the clinical database, and subjects will be identified only by a code or subject number. All information and data sent to ConforMIS or designee concerning patients or their participation in this study will be considered confidential, and confidentiality shall be observed by all parties involved at all times during the study. All data used in analysis and reports will be used without identifiable reference to the subject. All data will be secured against unauthorized access. The Investigator and investigative site will be responsible for compliance with all local privacy regulations.

17. ETHICAL CONSIDERATIONS

The protocol and Informed Consent Form must be approved by a central IRB or the IRB/IEC for the institution where the study is conducted. Each subject shall give informed consent in a form and manner that meets all IRB/IEC requirements. All subjects must be informed that the device is available commercially and that participation in the clinical study is not required for them to be treated with the device. Investigators shall agree to conduct the study in compliance with the provisions of the Declaration of Helsinki and with ICH/GCP Standards.

In compliance with the Food and Drug Administration Amendments Act of 2007 (FDAAA), this study will be listed in www.clinicaltrials.gov.

18. REPORTS

A final study report shall be prepared and provided to all investigative sites for submission to their IRB/IEC. The final study report will be made a permanent record in the ConforMIS document control system.

19. LITERATURE

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PROTOCOL HISTORY

Protocol Version	Protocol Date	Updated by:	Changes Made:
1.0 AA	13 November 2013	Shirley Mak-Parisi	Initial release
2.0 AA	06 April 2015	Shirley Mak-Parisi	Added protocol signature page Throughout protocol- iTotal CR KRS was shortened to iTotal CR Throughout protocol- updated the reference structure from footnotes to MLS format. Study design: added UK Added Economic sub study to protocol and appendix Functional testing: Updated tests to be listed in the order that they will be performed. Deleted the Berg and 6minute walk Added 8 meter walk Added ALF details Updated primary and secondary endpoints Enrollment, randomization: Updated the alternative way of randomizing a patient. Throughout protocol: Deleted 6 weeks Added 90 days and updated 6 months to 180 days Safety reported: added the sentence "for the first 90 days, ALL AEs should be recorded. At day 91" this is to capture all AEs in the first 90 days for a patient. Monitoring: added risk based monitoring Worksheets: Updated and renamed "instructions" Updated: "Patients" to "Subjects" throughout the protocol Removed all references to the Patient Satisfaction Survey, Berg Balance and Forgotten Joint Score Changed section 9 (schedule of evaluations by visit) to indicate that both types of radiographic evaluation

			can occur at either the 90 days or 180 days visit. Fixed Appendix A to indicate the change described above concerning radiographic evaluations, and indicated that the Follow-up CRF is to be completed at the 90 days visit, as well as an Adverse Events/Revision form if applicable. Stats section updated to reflect protocol updates
3.0 AB	14 October 2015	Tyler Halloran	Updated Marc Quartulli's job title. Under Study Design (section 3), surgical approach was updated to allow for other approaches. Changed the name of section 7.1 from "Primary Endpoint" to "Primary Endpoints". In section 7.1, Primary Endpoints, further detailed the components comprising the ALF score. Updated section 8, Site Selection, to section 9, in turn correcting an overall issue with the numbering throughout the remainder of the protocol. Updated AE language (section 12) so that only AEs that are at least possibly related to the device or procedure are captured in the first 90 days post-op. Updated Appendix A, combining Onsite and Remote Follow Up and altering the spacing/positioning. Updated Appendix B to clarify instructions. Added Appendix D, CONSORT Data Reporting Guidelines, and an explanation in Section 8, Inclusion/Exclusion Criteria, how sites will log all patients considered for the study. Updated the Table of Contents.

4.0 AC	30 April 2016	Shirley Mak-Parisi	Updated versioning to 4.0 AC in all headers and footers and protocol signature page. Under Study Design (section 3), surgical approach was defined and updated to allow for only medial parapatellar or subvastus approach. Under schedule of evaluation section, for concomitant medications, added the word "(optional)" for all time points except for screening. Under Appendix A, added an "*" to radiographic evaluation (long leg) row to indicate that this is to occur at the 90 Days or 180 Days visit. Updated Functional Testing Worksheet in Appendix B to make changes to CRF, including shading and a typo. Appendix C updated SAS version to match main protocol
5.0 AD	27 March 2017	Shirley Mak-Parisi	Updated the title from: "A Prospective, Randomized, Multicenter Study to Evaluate the ConforMIS iTotal (CR) Knee Replacement System versus Off-the-Shelf Replacement" to "A Prospective, Multicenter Study to Evaluate Functional Outcome After Knee Replacement" Throughout document, oxford comma used Updated ConforMIS address Added ConforMIS internal use ID Deleted randomization throughout the protocol Deleted the use of patient specific instrumentation. Updated the study design to reflect no randomization. Deleted double blinding. Only functional tester is blinded. Updated throughout protocol. Updated N

			Updated language for economic study. Only sites who are contracted with ConforMIS will take part. Updated timed "Get-up and Go" test definition to clarify the length of the walk. Updated 8 meter walk with the correct reference. National Institutes of Health instead of McCarthy. Updated the Timed Up and Down Stairs Test to include a minimum of 4 steps in a flight of stairs. Deleted the patient reported outcomes as a primary endpoint. Added KSS as a secondary endpoint. Updated statistical analyses with KSS information. Updated exclusion criteria to provide clarity. Deleted "Other lower extremity surgery within 1 year" to "Lower extremity surgery (orthopaedic or ligament injury) on either limb to the hip, ankle, feet occurring or expected to occur within 1 year of surgery on the evaluated knee" Updated exclusion criteria to provide clarity. Changed "Contralateral knee replacement surgery within the past 6 months" to "Contralateral knee replacement occurring or expected to occur within 6 months of surgery on the evaluated knee" Added instructions on how a site will consecutively enroll subjects. Administrative changes to provide clarity. Clarified Safety reporting. Added phone number and email along with instructions of what needs to be included in the communications to the sponsor and the IRB. Updated efficacy analysis

			Updated the sample size determination paragraph Updated Appendix A to reflect changes

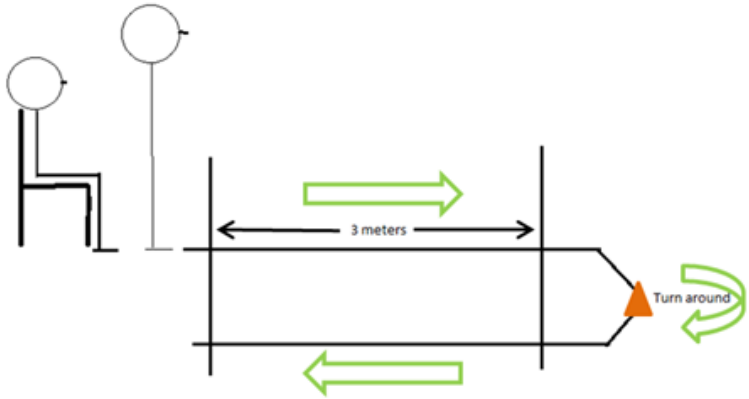
20. APPENDIX A – Schedule of Evaluations

Evaluation	Screening/ Pre-Op	Surgery	90 Days Follow-up	180 Days Follow-up	Year 1, 2, 5 Follow-up	Year 3, 4, 6, 7, 8, 9 Follow-up	Year 10 Follow-up
Visit window	**Up to 4 months prior to surgery**	**N/A**	**± 14 days**	**± 21 days**	**± 2 months**	**± 3 months**	**± 4 months**
Inclusion/Exclusion Criteria	**X**						
Subject Information & Medical History	**X**						
Pain Medications & Concomitant Medications‡	**X**	**X**	**X**	**X**	**X**		**X**
Knee Society Score (KSS)	**X**		**X**	**X**	**X**		**X**
Knee Injury & Osteoarthritis Outcome Score (KOOS)	**X**		**X**	**X**	**X**		**X**
Functional Testing	**X**		**X**	**X**	**X**		**X**
Radiographic Evaluation *	**X**		**X†**	**X†**			
Surgical & Discharge Summary		**X**					
Adverse Events & Serious Adverse Events		**X**	**X**	**X**	**X**	**X**	**X**
Follow Up			**X**	**X**	**X**	**X**	**X**
Subject Disposition							**X+**

‡ The collection of Concomitant Medications is optional after the Pre-operative visit
*Radiographic evaluation includes: Knee x-ray 3 views- AP, lateral, sunrise or Merchant; Long Leg x-ray (full length flim with full weight bearing)- AP view
†Post-operative radiograph can be performed at 90 or 180 days depending on hospital standard
+ Subject Disposition to be completed either at the 10 year visit or when the subject withdraws from the study

21. APPENDIX B – Functional Testing Instructions

Timed Get Up and Go Test



Equipment needed: Arm chair, tape measure, tape, stopwatch, and cone

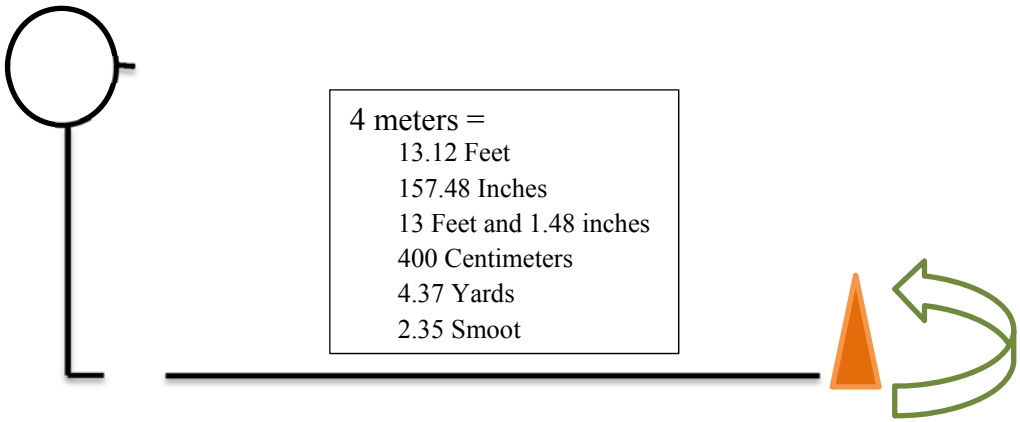
Test Set Up:

1. Place a chair in an area with adequate space for the patient to walk and turn around.
2. Measure 30.5 cm (12 inches; 1ft) in front of the chair and place a piece of tape there.
3. From the piece of tape, measure 3 meters (118 inches; 9ft & 10 in) and place another piece of tape at the end.
4. Place the cone on top the piece of tape at the 3 meter mark (ensure the middle of the cone is aligned with the center of the tape.

Test Instructions:

1. The subject should begin the test sitting comfortably in the chair with their feet on the ground. The subject is allowed to use the arm rests during the sit and stand movements. The subject is allowed to use assistive devices such as a cane or walker. If the subject uses the arm rests or an assistive device, please record this on the form.
2. Instruct the subject using the following command:
   - "On the word 'GO' you will stand up, walk to the cone, walk around the cone, and then walk back towards the chair to sit down. Walk as quickly as you feel safe."
3. Stopwatch instructions:
   - Start timing when you say "GO."
   - Stop timing when the subject is completely seated (same as starting position).
4. There will be 3 individually timed tests.

8 Meter Walk



Equipment needed: Stopwatch, cone, tape measure, and tape

Test Set Up:

1. Place a piece of tape as a starting point in an area with adequate space for the patient to walk and turn around.
2. Measure 4 meters from that point and place a second piece of tape at that location.

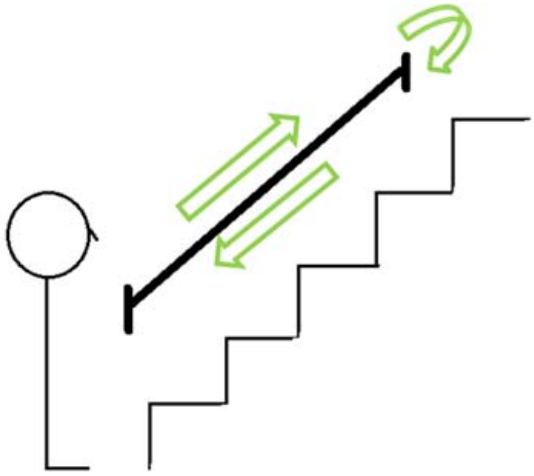
    4 meters =

    13.12 Feet
    157.48 Inches
    13 Feet and 1.48 inches
    400 Centimeters
    4.37 Yards
    2.35 Smoot
3. Place the cone on top the piece of the second piece of tape.

Test Instructions:

1. The subject should stand at the first piece of tape.
2. Instruct the subject using the following command:
    - "On the word 'GO' you will walk to the cone, walk around the cone, and then walk back towards first piece of tape. Walk as quickly as you feel safe."
3. Stop watch instructions:
    - Start timing when you say "GO."
    - Stop timing when the subject's second foot touches the first piece of tape.
4. There will be 3 individually timed tests.

Timed Up & Down Stairs Test



Equipment needed: Stopwatch, Flight of Stairs

Test Set Up:

1. Count the number of steps and record this on the form. Count the steps in one direction. For example, in the diagram above, there are 5 steps. The flight of stairs used in this test must have a minimum of 4 stairs.
2. If possible, please use the same flight of stairs for all subjects.

Test Instructions:

1. The subject should stand at the bottom of the flight of stairs.
2. Instruct the subject using the following command:
   - "I am going to ask you to stand at the bottom of the stairs so that your first step is up. My commands will be 'ready, set, GO'. Then you are going to walk as quickly as you feel safe and comfortable to the top of the stairs, turn around, and come back down. You may use the rail, but if you can go without the rail, please try to do so."
3. Stop watch instructions:
   - Start timing when you say "GO."
   - Stop timing when the subject's second foot touches the landing at the bottom of the stairs.
4. At the end of each test, ask the subject about their pain level during the test, their confidence, and their comfort in completing another trial.
5. If the subject answers "no" concerning their comfort in completing the stairs, then do not have them attempt the stairs again.
6. There will be 3 individually timed tests if the subject if the subject feels comfortable completing each test.

Time Point *(check one)*: ○ Pre-op ○ 90 Days ○ 180 Days ○ Year 1 ○ Year 2 ○ Year 5 ○ Year 10				
Trial	**Get Up & Go Time (mm:ss.ms)**	**Get Up & Go Rest Time (mm:ss.ms)**	**Arms Used?**	**Circle Pain Level After Each Trial**
1	__ __ : __ __ . __ __	__ __ : __ __ . __ __	Y N	0 1 2 3 4 5 6 7 8 9 10
2	__ __ : __ __ . __ __	__ __ : __ __ . __ __	Y N	0 1 2 3 4 5 6 7 8 9 10
3	__ __ : __ __ . __ __	__ __ : __ __ . __ __	Y N	0 1 2 3 4 5 6 7 8 9 10
Did the subject require a rest between the Chair and Walking activities?				Y N

Trial	**Walking Time (mm:ss.ms)**	**Walking Rest Time (mm:ss.ms)**	**Circle Pain Level After Each Trial**
1	__ __ : __ __ . __ __	__ __ : __ __ . __ __	0 1 2 3 4 5 6 7 8 9 10
2	__ __ : __ __ . __ __	__ __ : __ __ . __ __	0 1 2 3 4 5 6 7 8 9 10
3	__ __ : __ __ . __ __	__ __ : __ __ . __ __	0 1 2 3 4 5 6 7 8 9 10
Did the subject require a rest between the Walking and Stairs activities?			Y N

Trial	**Stairs Time (mm:ss.ms)**	**Stairs Rest Time (mm:ss.ms)**	**Rails Used?**	**Circle Pain Level After Each Trial**
1	__ __ : __ __ . __ __	__ __ : __ __ . __ __	Y N	0 1 2 3 4 5 6 7 8 9 10
How *confident* were you in your ability to complete the Stairs during that trial?			Very Somewhat Not Very Not At All	
Do you feel comfortable completing the Stairs a second time?				Y N
2	__ __ : __ __ . __ __	__ __ : __ __ . __ __	Y N	0 1 2 3 4 5 6 7 8 9 10
How *confident* were you in your ability to complete the Stairs during that trial?			Very Somewhat Not Very Not At All	
Do you feel comfortable completing the Stairs a third time?				Y N
3	__ __ : __ __ . __ __	__ __ : __ __ . __ __	Y N	0 1 2 3 4 5 6 7 8 9 10
How *confident* were you in your ability to complete the Stairs during that trial?			Very Somewhat Not Very Not At All	

Number of Steps (in staircase): _____

Observations: _____

22. APPENDIX C – U.S. Economic Sub-Study

A cost comparison between the groups will be performed. Each site will obtain the Uniform Billing (UB) forms from their billing department. These forms will have the following information for analysis:

- Length of stay
- Blood transfusions throughout the stay (number of units and type of transfusions)
- Patient discharge disposition
- Patient comorbidities
- Readmission to hospital and 30-day readmission rate
-

Additionally, in the case report forms, the following information will be collected for analysis:

- Number of trays used
- Instances of compromised tray sterility
- Procedure and device related adverse events

Primary outcome:
Economic Outcomes as measured by collected hospital data and Uniform Billing (UB) forms

Statistics:
All statistical processing will be performed using SAS® Version 9.3 or later unless otherwise stated.

No imputations will be made for missing observations. Continuous variables will be summarized with sample size, mean, standard deviation, median, minimum, maximum, and 95% confidence intervals, as appropriate. Categorical variables will be summarized with frequency counts, percentages, and 95% confidence intervals, as appropriate.

Demographic Evaluations & Cost Analysis
Demographic variables (age, gender, ethnicity, and race) will be recorded in the database and summarized using descriptive statistics. For continuous variables, comparisons between treatment groups will be conducted with an analysis of variance (ANOVA). A Chi-square test will be used for testing categorical variables.

23. APPENDIX D – CONSORT Data Reporting Guidelines

CONSORT
TRANSPARENT REPORTING of TRIALS

CONSORT 2010 Flow Diagram