Sponsor Name and Address:	Smith & Nephew, Inc., 1450 E. Brooks Road, Memphis, TN 38116, United States
Investigational Product(s)	The JOURNEY II CR Total Knee System
Protocol Author(s):	Jing Xie, Clinical Senior Vice President Lili Li, Associate Clinical Study Manager Olayinka, Babajide, Statistician

1 SIGNATURES
1.1 Principal Investigator Signature Page

This page will be returned to Smith & Nephew Inc. and a copy retained at the investigational site.

☐ I have read the attached protocol entitled "A Prospective Multi-Centre Study in Patients Undergoing Total Knee Replacement with JOURNEY II CR Total Knee System", version <2.0>, dated <02/Jun/2021>, and agree to abide by all provisions set forth herein.

I agree to comply with the Investigator's Obligations stipulated in Section 22.3 of the protocol,

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the described clinical investigation without the prior written consent of Smith & Nephew Inc.

Name, Address, Professional Position	Signature and Date / DocuSign Stamp

1.2 Coordinating Investigator Approval

☐ I have read the attached protocol entitled "A Prospective Multi-Centre Study in Patients Undergoing Total Knee Replacement with JOURNEY II CR Total Knee System", version <2.0>, dated <02/Jun/2021>, and agree to abide by all provisions set forth therein.

Name, Address, Professional Position	Signature and Date / DocuSign Stamp

1.3 Sponsor Approval

Name and Title	Signature and Date / DocuSign Stamp
Head of Global Clinical Operations Racheal, Winter	
Publications Strategy & Operations, Director Kamali, Amir	
Head of Global Data Analytics Alan, Rossington	
Medical Affairs Representative Orlandini, Luca Claudio	

2 SYNOPSIS

Title of Study:	A Prospective Multi-Centre Study in Patients Undergoing Total Knee Replacement with JOURNEY II CR Total Knee System
Study Design:	<table><tr><th>Study Design</th><th>Implant</th></tr><tr><td>Prospective non-randomized comparative (across sites)</td><td>JOURNEY II CR TKA (resurfaced patella and un-resurfaced patella)</td></tr></table> Sites have the options of conventional, navigation or robotics TKA and also the patella resurface technique (inlay/onlay). Regardless of which approach/technique, the approach/technique in single site should be used consistently for all study subjects if all possible.
Study Type:	Prospective, Non-randomized
Study Product:	The JOURNEY II CR Total Knee System consists of femoral component made from oxidized zirconium (OXINIUM)
Study Purpose:	Post-market evidence generation for JOURNEY II CR Total Knee System
Study Objective(s):	1.Evaluate performance of JOURNEY II TKA in APAC patient populations 2.Evaluate impact of patella resurfacing on the outcomes of JOURNEY II TKA
Sample Size:	Total：Up to 480 knees (JOURNEY II CR TKA) with or without Patella Resurfaced • Resurfaced Patella: up to 240 knees • Un-resurfaced Patella: up to 240 knees (Decision on whether to resurface patella or not will be made by investigator based on patient's conditions.)
Number of Study Sites:	up to 15 sites
Targeted Global Regions:	India/China Mainland/China (Hongkong)/Singapore/Thailand/Japan
Inclusion Criteria:	• Subjects with degenerative Osteoarthritis. • Subject is planning to have TKA using JOURNEY II CR. • Subject is able and willing to provide voluntary consent to study participation. • Subject is 18-80 years old (inclusive) * (* For Japan, the minimum inclusion age is 20 years old.)

Exclusion Criteria:	• Subjects with rheumatoid arthritis/inflammatory arthritis, posttraumatic arthritis. • Previous surgeries including HTO, UKA or TKA on the subject knee. • Subject is pregnant or breast feeding or those at a child-bearing age planning to become pregnant during the follow up. • Subject does not meet the indication or is contraindicated for JOURNEY II CR's IFU.
Study Duration:	Total – 4.5 years (1.5 years enrolment + 3 years follow-up)
Primary Endpoint	•OKS at 2 years
Secondary endpoint:	•FJS •OKS •KSS •Patient Expectation •Patient Satisfaction •Radiographic Assessment
Safety Data	•All adverse events (AEs) including intra-operative adverse events and complications •Device related re-intervention •Device Deficiencies
Data Collection Platform	Medidata EDC System for data collection and centralized evaluation Centralized Radiographic Analysis
Study Data Collection	**Pre-op - Baseline characteristics:** •Age, BMI, gender •Diagnosis •Comorbidities •Radiographic assessment •KSS, OKS, Patient Expectation **Surgery/Discharge:Perioperative:** •Surgery info – Data, Side, Implant details, patella resurfacing, Use of enabling technologies (e.g. Robotics/Navigation), OR time, Blood loss •Discharge info – Date, Discharge Destination **Postoperative:** •KSS, OKS, FJS, Patient Satisfaction •Radiographic assessment • All adverse events (AEs) including intra-operative adverse events and complications •Device related re-intervention •Device Deficiencies
Data Analysis	•Outcomes and complications data will be analysed centrally blinded. •Radiographs* will be collected at each site and quantitative analysis will be conducted centrally. * The data confidentiality rules will be followed in different countries.

STUDY SCHEDULE

Schedule of Events[1]	Pre-Operative -28 to 0 days	Operation Day 1	Immediate Post - op to 6 weeks Post-Op (Day 1 to 6 weeks+14 days)	6 months Post-Op (± 14 days)	1 year Post-Op (± 30 days)	2 years Post-Op (± 60 days)	3 years Post-Op (± 60 days)
Informed Consent	x						
Inclusion/Exclusion	x						
Demographics/Medical History	x						
Operative Data Collection		x					
Discharge Data Collection			x				
OKS[2]	x			x	x	x	x
FJS[2]				x	x	x	x
KSS[2]	x			x	x	x	x
Patient Expectation	x						
Patient Satisfaction [2]				x	x	x	x
Quantitative Radiographic Assessment	x[3]		x[4]	x[5]	x[5]	x[5]	
Safety Assessment (AEs, DDs)		x	x	x	x	x	x
End of Study/Exit		x[6]	x[6]	x[6]	x[6]	x[6]	x

1. All the data will be collected based on knee, except inform consent, inclusion/exclusion and demographic/medical history.
2. Patient reported outcome can be assessed and collected remotely for follow-up period.
3. The radiographic images prior to 3 months can be accepted for pre-operative screening data due to hospital's SoC.
4. Radiographic assessment can be conducted at discharge if it's the SoC of the site.
5. Radiographic images can be retrieved from other hospital/facility under specific image acquisition protocol and send back to site for assessment.
6. Exit form to be completed at the point of withdrawal if the study is not completed.

3 CONTENTS
3.1 Table of Contents

3.2 List of Abbreviations and Definitions

Abbreviation	Definition
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
AVN	Avascular Necrosis
BCS	Bi-cruciate Stabilized
CRF	Case Report Form(s)
CR	Cruiciate Retaining
CRO	Contract Research Organization
CV	Curriculum Vitae
DA	Degenerative Arthriti
DD	Device Deficiency(ies)
DFMEA	Design Failure Mode Effects Analysis
FAS	Full Analysis Set Population
FDA	Food and Drug Administration
FU	Follow-Up
GCP	Good Clinical Practice
HTO	High Tibial Osteotomy
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFU	Instructions for Use
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention to Treat population
KSS	Knee Society Score
LOCF	Last Observation Carried Forward
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
NSAID	Nonsteroidal Anti-inflammatory Drug

OA	Osteoarthritis
OKS	Oxford Knee Score
PI	Principal Investigator
PMA	Pre-Market Authorization
PP	Per-protocol Population
PTA	Post Traumatic Arthritis
RA	Rheumatoid arthritis
RCT	Randomized Controlled Trial
ROM	Range of Motion
S+N	Smith&Nephew.Inc
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAF	Safety population
SAP	Statistical Analysis Plan
SoC	Standard of care
THA	Total Hip Arthroplasty
TKA	Total Knee Arthroplasty
USADE	Unanticipated Serious Adverse Device Effect(s)
WOMAC	Western Ontario and McMaster Universities Arthritis

4 INTRODUCTION

4.1 Background

Arthritis is a clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. Two common etiologies of arthritis are degeneration of the joint, osteoarthritis (OA), and inappropriate inflammatory response, rheumatoid arthritis (RA). OA is characterized by loss of cartilage, remodeling of adjacent bone, and inflammation in the affected joint [1, 2]. RA is a progressive inflammatory disease that eventually causes systemic joint damage and disability [3]. Post-traumatic arthritis is a form of osteoarthritis following an injury to a joint. Inappropriate joint biomechanics due to deformities is the main risk factor for OA [4]. The joint biomechanics are directly affected by the malalignment of the lower extremities due to anatomical deformities [5]. Varus deformity is an excessive inward angulation of the lower leg and results in a bowlegged appearance. It may cause an overloading and cartilage wear in the medial knee compartment, which could support a degeneration of the knee joint leading to OA [5].

Initial treatment of arthritis may include physical therapy, nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and corticosteroids which can be taken orally or by injection.

Avascular necrosis (AVN) has several etiologies but fundamentally results from a decrease in blood flow to the affected bone, leading to cellular death [7]. Studies have reported a 3.4% and 9.4% incidence of spontaneous osteonecrosis in persons older than 50 and 65 years of age, respectively [8]. Initial treatment of AVN may include medication, stretching, not walking on the affected leg.

Complex epiphyseal fractures around the knee joint involve the distal femur or proximal end of the tibia. The management of these fractures especially in elderly patients is challenging [9].

When the damage to the joint is advanced or available conservative treatment options are exhausted, knee arthroplasty is considered the most effective treatment for patients with any of these indications.

Total knee arthroplasty (TKA) is a highly successful and frequently performed surgical treatment to reduce disability caused by end-stage osteoarthritis and other conditions affecting articular cartilage [10, 11]. It has been widely used in the treatment of knee osteoarthritis. Among them, patellofemoral joint and patellar treatment have long been the focus of scholars.

Currently, there are three methods to treat patella during TKA: conventional replacement, selective replacement and never replacement [12].Scholars who advocate non-replacement of patella believe that patients' own patella can provide better

patella movement track which can improve the function of knee joint and avoid prosthesis related complications [13,14].After patella replacement, the incidence of complications such as patella fracture, osteonecrosis, and knee extensor device rupture will significantly increase, and there will be prosthesis loosening, rupture and other complications caused by the prosthesis itself. The incidence of patellofemoral article-related complications can be effectively reduced by performing patelloplasty in TKA to remove peripatellar osteophytosis, repair the articular surface of patella and perform peripatellar electroablation [15]. However, scholars who advocate patella replacement believe that patella replacement can greatly improve the motor function of the knee joint by reducing the pain of the knee and enhancing the quadriceps muscle strength. Moreover, compared with the prosthesis, although the patella of the patient can better fit to the trochlear surface of the human body and will have better movement track of the patella, the patellofemoral joint surface and mechanical properties of the femoral prosthesis will change after TKA, and the original bonding advantages will no longer exist [16,17,18]. Some scholars reported [14] that in the first TKA operation, the patients with good chondral surface of patella were found to have chondral surface destruction during the second operation. Therefore, a patellar component matching the femoral component should be used to prevent damage to the patellar cartilage. Now patella replacement has become an operative method that can greatly improve patient satisfaction during TKA [19]. However, due to the occurrence of patellar fracture, prosthesis wear and loose, patellar impact-syndrome and other complications after patellar replacement, some scholars are more inclined to choose patellar replacement. Many scholars also recommend the selective replacement of patella based on patella thickness, preoperative pre-knee pain, patellar cartilage damage, rheumatoid arthritis, and operator's surgical experience [15]. The utilization rate of patella replacement in TKA varies from country to country.

The purpose of this study is to investigate the treatment standards and concepts of patella treatment in various research centres and the impact of relevant treatments on postoperative outcomes of patients on JOURNEY II CR Total Knee System.

4.2 Literature Summary

A thorough analysis of the clinical literature was performed for JOURNEY II CR Total Knee Systems.

4.2.1 JOURNEY II CR Total Knee System

The clinical literature analysis was performed and one clinical publication was identified. involved JOURNEY II CR system which focused on primary TKA.

Demographic information

The demographic information was summarized as shown in Table 4-1.

Table 4-1. Demographic information for JOURNEY II CR knee system from included study

Author, Year	JOURNEY II Components	Male (%)	Joints (FU)	Avg FU, yrs (range)	Avg Age, yrs (range)
Chow 2017[20]	OxZr CR Femoral CR Insert	43.9%	114	0.5	66.4

One study which involved JOURNEY II CR system was identified. A number of 114 joints were followed for 6 months in order to compare sensor-assisted TKA outcomes with manual TKA outcomes. No information of diagnosis for TKA was reported. In this study, standard tibial inserts of the knee system were used. Although material of the femoral component was not mentioned, JOURNEY II CoCr femoral component was not available during the implantation data of this study (May 2015 through March 2016). Therefore, the material of femoral component that implanted in this study was assumed to be OxZr.

Clinical outcomes

Table 4-2 below shows clinical outcomes for JOURNEY II CR system from included study.

Table 4-2. Clinical outcome information for JOURNEY II CR knee system from included study

Author, Year	OKS		KSS (pain)		KSS (function)		KSS (total)		ROM	
	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op	Pre-op	Post-op
Chow 2017[20] (sensor-assisted TKA)	-	(+17)	-	36	-	27	-	63	105.4°	-
Chow 2017[20] (manual TKA)	-	(+13)	-	29	-	23	-	52	109.3°	-

Chow et al compared sensor-assisted TKA outcomes with manual TKA outcomes, both with JOURNEY II CR system implanted. Results at 6 months follow-up showed that patient-reported clinical outcomes were slightly higher in the sensor-assisted TKA group than in the manual TKA group.

Survivorship and Adverse events

The study by Chow et al. that involved JOURNEY II CR system did not report any survival or revision information. Reported postoperative complications included pain control issues, bleeding issues, nausea, kidney function issues, cardiac issues, reactive leukocytosis, dyskinesia, and transient hypotension. None of the postoperative complications were related to knee

instability or unanticipated limits in range of motion.

All found adverse events, where relevant, are covered under DFMEAs of JOURNEY II CR system.

The literature review demonstrated that the JOURNEY II CR Knee System provides acceptable clinical performance with few complications reported. The reviewed literature did not identify additional risks beyond those previously identified in the DFMEA.

4.3 Study Purpose

This is a post-market study, and the purpose is for evidence generation for JOURNEY II CR Total Knee System

4.4 Safety Consideration

The contraindications, potential adverse events, precautions and warnings of JOURNEY II CR can be found in Instructions for Use (IFU).

5 OBJECTIVE(S)

The objectives of the study are listed as below,

1. Evaluate performance of JOURNEY II TKA in APAC patient populations

2. Evaluate impact of patella resurfacing on the outcomes of JOURNEY II TKA

6 INVESTIGATIONAL PRODUCT(S)

6.1 Identification

6.1.1 Investigational Product

The JOURNEY II CR belongs to JOURNEY II Total Knee Systems, and manufactured by Smith & Nephew, Inc. It is intended to be used in total knee arthroplasty surgery.

The design philosophy behind development of the JOURNEY II CR Total Knee System is to provide the ability for greater flexion (155°) to those patients who have the anatomical capability to allow a greater flexion range. The JOURNEY II CR components are designed to work with a functional posterior cruciate ligament (PCL).

The JOURNEY II CR Total Knee System components include:

- •JOURNEY II CR Femoral Components which are available in right and left designs in Oxinium material in sizes 1-10 or CoCr material in sizes 1-9.

- •JOURNEY II CR Articular Inserts which are available in sizes 1-2, 3-4, 5-6, and 7-8 in right and left designs, and offered in 9-18 mm thicknesses and manufactured from cross-linked polyethylene (XLPE) material.
- •JOURNEY II Deep Dished Inserts, cruciate substituting (deep dished) articular inserts, which are available in sizes 1-2, 3-4, 5-6, and 7-8 in right and left designs with 9-21mm thicknesses and manufactured from cross-linked polyethylene (XLPE) material.

JOURNEY II Knee components are supplied sterile for single use only. Components do not incorporate medicinal substances, tissues, or blood products, nor is it present in the manufacturing process.

JOURNEY II CR total knee system was first approved by FDA in 2012.

The JOURNEY II CR Total Knee System consists of femoral component made from oxidized zirconium (OXINIUM) will be used for this study.

Figure 6-1. JOURNEY II CR Total Knee System (OXINIUM)

6.2 Product Use

Please refer to IFU of the JOURNEY II CR Total Knee System for full instructions.

6.3 Packaging and Labelling

Packaging and labeling will be prepared to meet regulatory requirements. Package integrity and labelling should be verified prior to use of the product and confirmed in the eCRF.

6.3.1 Labelling

JOURNEY II CR Total Knee System (Oxinium) is commercial product for sites in India, China mainland, China (Hong Kong), Singapore, Thailand and Japan. Packaging and labelling will be prepared per the standard commercial packaging and local regulatory requirements.

6.4 Product Accountability Procedures

This study is a post-market study but OXINIUM Femoral component is supplied by the Sponsor in China sites and accountability procedure should be followed in China sites.

China investigational sites will maintain an inventory of the IP/Ancillary Products and Study Supplies.

The Sponsor or its designee will provide a log(s) to facilitate IP/Ancillary Products and Study Supplies inventory control. All IP/Ancillary Products and Study Supplies accountability logs must be retained in the Investigator Site File (ISF). These records must be available for inspection by the Sponsor, its designees, or by regulatory agencies at any time.

The Study Monitor will ensure that the procedures and records are in place for the appropriate reconciliation of all IP/Ancillary Products and Study Supplies. As part of monitoring, the Study Monitor will check that site personnel are following the proper procedures for accountability and completing all necessary documentation.

Only the product components provide by sponsor need to follow the accountability procedure, for the components purchased by investigational site, no product accountability procedure will be applied.

6.5 Surgical Technique

All study related procedures with the JOURNEY II CR Total Knee System must be performed according to the surgical technique and IFU of the specific Smith+Nephew Implant System.

Surgeons selected to participate in this study will be familiar with the JOURNEY II CR Total Knee System and have written evidence of training and expertise in the study procedure. Pre-study cases shall be performed until the surgeon feels comfortable with the system in order to prevent any learning curve during the study. The number of pre-study cases depends on the level of the individual experience of the surgeon.

6.6 Medical Procedure

All surgical related procedures with the JOURNEY II CR Total Knee System must be performed according to the surgical technique and IFU of the specific Smith+Nephew Implant System.

7 SUBJECT ENROLLMENT AND WITHDRAWAL

7.1 Subject Population

A total of up to 480 knees' information will be collected in up to 15 sites in India, China mainland, Hong Kong, Singapore, Thailand and Japan There will be up to 240 knees for resurfaced patella group and up to 240 knees for un-resurfaced patella group.

Group	# of sites	Resurfaced Patella	Un-resurfaced Patella

Up to 480 knees (JOURNEY II CR TKA)	Up to 15	Up to 240 knees	Up to 240 knees

7.2 Inclusion Criteria

Subjects will be considered qualified for enrollment if they meet the following criteria:

1. Subjects with degenerative Osteoarthritis.
2. Subject is planning to have TKA using JOURNEY II CR.
3. Subject is able and willing to provide voluntary consent to study participation.
4. Subject is 18-80 years old (inclusive).*

* For Japan, the minimum inclusion age is 20 years old.

7.3 Exclusion Criteria

Any one (1) of the following criteria will disqualify a potential subject from participation in the study:

1. Subjects with rheumatoid arthritis/inflammatory arthritis, posttraumatic arthritis
2. Previous surgeries including HTO, UKA or TKA on the subject knee
3. Subject is pregnant or breast feeding or those at a child-bearing age planning to become pregnant during the follow up.
4. Subject does not meet the indication or is contraindicated for JOURNEY II CR's IFU.

7.4 Screening

Participating study sites are required to document all screened subjects considered for inclusion in this study. If a subject is excluded from the study, the reasons for exclusion will be documented in the subject's source documents and noted on the Screening and Enrollment Log.

7.5 Informed Consent

Before conducting any study procedures or examinations, the purpose and nature of the study should be explained to the subject in their native language.

The subject, or their legally authorized representative, will then **read**, **sign**, and **personally date** the IRB/IEC-approved informed consent document(s) (see below for difficulties with reading and writing). Additionally, the individual who obtains

consent from the subject will sign and date the informed consent document. A copy of the signed informed consent document will be provided to the subject, a copy will be placed in the subject's medical record, with the original filed in the ISF.

If the subject is unable to read, the informed consent document and associated study information may be read aloud to the subject in the presence of an impartial witness. If possible, the subject shall sign and personally date the Informed Consent Form (ICF). Where this is not possible, due to difficulties in writing, the subject shall provide verbal consent to participate in the study. The witness shall then personally sign and date the informed consent form, attesting that the information was accurately explained and that the informed consent was freely given.

7.6 Enrolment

Subjects for whom the consent process has been completed and have been treated with the study product are considered enrolled.

Subjects that provided informed consent but do not receive the study treatment for any reason will be considered as screen failure.

7.7 Lost to Follow-up

A subject will be considered lost to follow-up if he/she does not appear for the scheduled study visit for 2 consecutive visits, and study personnel are unable to contact the subject.

Some actively enrolled subjects will not return for follow-up exams on time. Study personnel must make a reasonable effort to contact the subject and document the following contact attempts before declaring a subject to be lost to follow-up: the subject has been contacted according to the site's policies, but no fewer than two documented phone contacts and one certified letter without response. Copies of all attempts to reach the subjects by mail or email and/or the attempts to contact the subject via other means should be documented, and that documentation should be kept with the subject's source documents.

7.8 Withdrawal

7.8.1 Withdrawal from Treatment

Subjects may be withdrawn early from study treatment for the following reasons:

- At the discretion of the Investigator due to:
    - A change in treatment is clinically warranted
    - An adverse event
    - Any other significant reason identified by the Investigator

7.8.2 Withdrawal from Study

The Investigator may withdraw subjects from the study for many reasons, including but not limited to the following:

- Subject noncompliance (e.g., did not follow instructions)
- Subject lost to follow-up
- The Investigator or the Sponsor stops the study for any reason and decides to withdraw subject(s) from the study
- Concurrent illness
- Adverse Events/Adverse Device Effects
- Any other significant reason identified by the Investigator

For each case, information will be obtained in the source document and the Case Report Form (CRF), detailing circumstances leading to the withdrawal.

Subjects who drop out or are withdrawn will not be re-entered into the study at a later date.

If at any point during the study, the prosthesis needs to be revised for any reason the following will apply: Subjects shall continue to have follow-up visits in order to monitor the subject's health status. Potential data following the revision surgery will not be included as study data but presented separately as safety data.

For minor revisions, where not the whole knee implant system is replaced (e.g. replacement of inserts) the subject shall continue with the study specific schedule and data will be presented.

7.8.3 Subject's Withdrawal of Consent to Participate in Study

Study participation is voluntary, and subjects may withdraw at any point during the study without giving their reason for doing so. Where subjects withdraw consent, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's privacy. The reason for withdrawal will be recorded in the CRF and source documents.

7.8.4 Use of Data Following Withdrawal

In cases where the subject withdraws consent, the data collected up to the point of withdrawal may be used, but no additional data for that subject may be collected.

8 STUDY DESIGN

8.1 Study Design

This study is a prospective, non-randomized multi-centre study to evaluate the performance of JOURNEY II CR Total Knee System in APAC patient populations, also to evaluate impact of patella resurfacing on the outcomes of JOURNEY II TKA. Totally up to 15 sites will participate within India, China mainland, Hongkong, Singapore, Thailand and Japan. Totally up to 480 knees information will be collected. The details can be seen in below Table 8-1.

The decision on whether to resurface patella or not will be made by investigator based on patient's conditions.

Table 8-1: Overview of Study Design

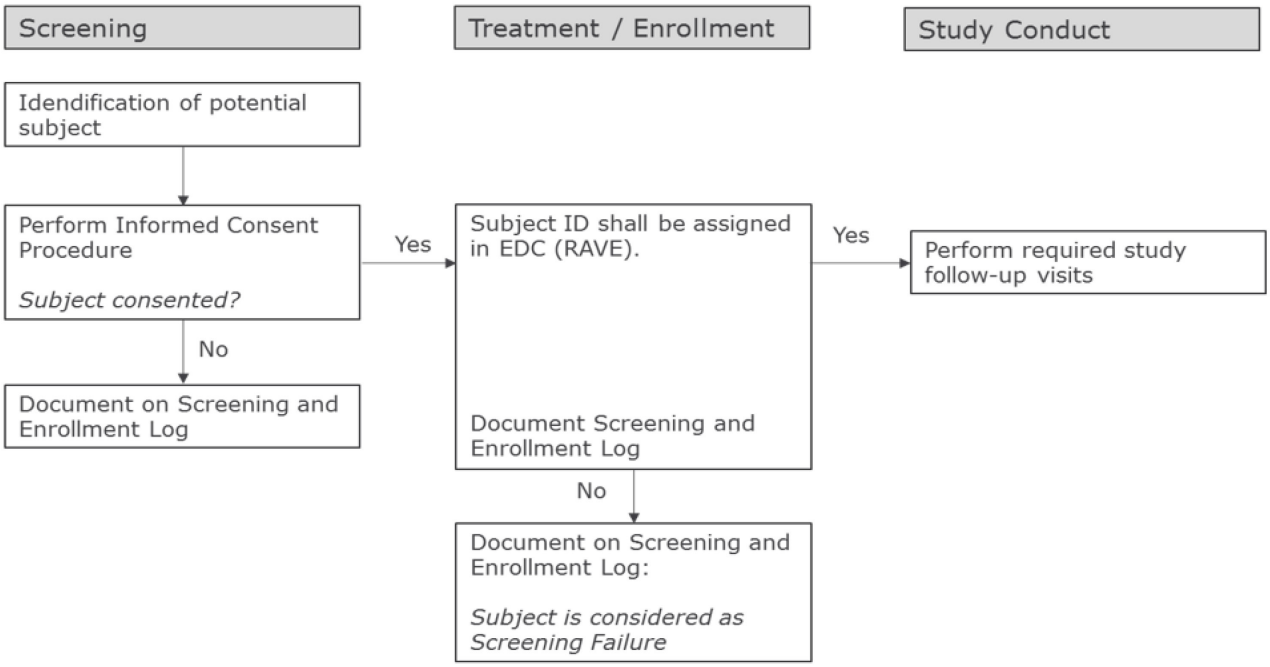
Study Design	Implant	Total Sample Size	Number of sites	Resurfaced Patella	Un-resurfaced Patella
Prospective non-randomized comparative (across sites)	JOURNEY II CR TKA	Up to 480 knees	Up to 15	Up to 240 knees	Up to 240 knees

Figure 8-1: Study Recruitment Timeline

The study is expected to enroll all subjects within a 18 month timeframe. Subjects will be followed-up for a time period of 36 months after surgery. Figure 8-1 details the Study Recruitment timeline. For the study flowchart, please see below Figure 8-2.

This study is being conducted in parallel to another study (which is under same umbrella) titled: "A Prospective Multi-Centre Study in Patients undergoing Total Knee Replacement with Journey II BCS and CR Total Knee System" (Protocol ID: Journey II CR + BCS.2020.12). The study data may be combined for analysis. Further details are described in Statistical Design and the Statistical Analysis Plan (SAP).

Figure 8-2: Study Flowchart



8.2 Allocation and Blinding

8.2.1 Treatment Allocation

There's no randomization for this study.

8.2.2 Blinding

To minimize the impact of bias associated with treatment assignment during the study, since the surgeon cannot be blinded to the identity of the surgical product, it is planned to appoint independent evaluators for the study, who will be blinded and responsible for completing study related outcome & complication upon central analysis.

8.3 Data Management

This study utilizes a validated, electronic data capture system. Access to the electronic data capture system is controlled through Smith and Nephew procedures.

8.3.1 Data Review and Quality Assurance

Data will be transcribed from the data source to an electronic Case Report Form (eCRF). All data requested on the eCRFs are considered required. Data points not collected and/or recorded will be considered deviations unless otherwise specified.

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The Principal Investigator must provide his/her electronic signature on the appropriate eCRFs to be documented in compliance with local regulations. Changes to data previously submitted to the sponsor will require a new signature by the Investigator to acknowledge/approve the changes.

Visual and computer data review will be performed in line with Smith and Nephew procedures to identify possible data discrepancies. Manual and automatic queries will be created within the electronic data capture system, and will be issued by Smith and Nephew to the site for appropriate response. Site staff are responsible for resolving all queries in the electronic data capture system.

8.3.2 Retention Period

All eCRFs will be archived once the study is completed and will kept for a period of no less than five years after the later of the following dates: the date of which the study is terminated or completed or; the date that the records are no longer required supporting marketing applications.

8.4 Study Endpoints

8.4.1 Primary Endpoint

The primary endpoint for the study is defined as the OKS at 2 years.

8.4.2 Secondary Endpoint

The following secondary endpoints have been defined for this study as below,

- OKS
- FJS
- KSS
- Patient Expectation
- Patient Satisfaction
- Radiographic Assessment

8.5 Methods Used to Minimize Bias and Maximize Validity

8.5.1 Multiple sites

In order to eliminate selection bias, investigators will continuously screen eligible subjects. After fulfillment of all eligibility criteria (including informed consent), subjects will be enrolled at multiple sites, utilizing up to 15 sites in total for the study. Subject enrollment will continue until the completion of recruitment of up to 480 subjects. File records and enrollment registration forms for screening work must be retained and submitted to the Sponsor as needed.

8.5.2 Prospective Consecutive Enrolment

Subjects meeting all inclusion/exclusion criteria will be allocated to receive JOURNEY II CR TKA with resurfaced patella or un-resurfaced patella in a 1:1 allocation ratio. The decision on whether to resurface patella or not will be made by investigator based on patient's conditions.

8.5.3 Subject Attrition

Subject attrition for the sample size has been accounted for in the sample size estimation.

8.5.4 Pre-specification of Statistical Analysis

The key outcome measure has been pre-specified as well as the type of statistical analysis to be performed in order to evaluate this outcome. The details of the analysis will further be pre-specified in the Statistical Analysis Plan (SAP) so to minimize any threats to validity and yield clinically relevant estimates of effects and precision.

9 STUDY PROCEDURES

9.1 Visits and Examinations

9.1.1 Summary

For a summary of the required procedures by visit, refer to the Study Schematic Table 9-1: Study Procedures by Visit.

Table 9-1: Study Procedures by Visit

Schedule of Events[1]	Pre-Operative -28 to 0 days	Operation (Day 1)	Immediate Post-op to 6 weeks Post-Op (Day 1 to 6 weeks+14 days)	6 months Post-Op (± 14 days)	1 year Post-Op (± 30 days)	2 years Post-Op (± 60 days)	3 years Post-Op (± 60 days)
Informed Consent	x						
Inclusion/Exclusion	x						
Demographics/Medical History	x						
Operative Data Collection		x					
Discharge Data Collection			x				
OKS[2]	x			x	x	x	x
FJS[2]				x	x	x	x
KSS[2]	x			x	x	x	x
Patient Expectation	x						
Patient Satisfaction [2]				x	x	x	x
Quantitative Radiographic Assessment	x[3]		x[4]	x[5]	x[5]	x[5]	
Safety Assessment (AEs, DDs)		x	x	x	x	x	x

End of Study/Exit		x[6]	x[6]	x[6]	x[6]	x[6]	x

1. All the data will be collected based on knee, except inform consent, inclusion/exclusion and demographic/medical history.
2. Patient reported outcome can be assessed and collected remotely for follow-up period.
3. The radiographic images prior to 3 months can be accepted for pre-operative screening data due to hospital's SoC.
4. Radiographic assessment can be conducted at discharge if it's the SoC of the site.
5. Radiographic images can be retrieved from other hospital/facility under specific image acquisition protocol and send back to site for assessment.
6. Exit form to be completed at the point of withdrawal if the study is not completed.

9.1.2 Screening/Pre-operative Visit (-28 to 0 days)

1.	Obtain written informed consent from the subject as detailed in Section 7.5 **----- Do not proceed until consent has been obtained -----**
2.	Obtain demographic information and medical history.
3.	Screen the subject for protocol inclusion/exclusion criteria.
4.	The eCRF will assign the subject a study number. The subject identification log shall be completed accordingly.
5.	Instruct the subject on treatment procedures.
6.	Collect radiographic assessment information.
7.	Collect the Patient Expectation.
8.	Collect the KSS score objective measures (joint alignment, instability, motions & symptoms).
9.	Have the subject complete the KSS score subject questions.
10.	Have the subject complete the OKS patient-reported outcome measure.
11.	Subjects will be instructed to return for the Operation Visit on a scheduled date.

9.1.3 Operation Visit (Day 1)

1.	Check if there is any change in eligibility of the subject since the pre-operative visit. If the subject is no longer eligible, document as screening failure.
2.	The subject will be assigned to treatment group by investigator.
3.	Query subject regarding any changes in general health and the use of concomitant medications/therapies.
4.	Perform surgery and collect intra-operative data on the appropriate eCRF.
5.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 adverse events and device deficiencies.
6.	Instruct the subject on proper postoperative care/procedures.
7.	Instruct the subject returning to the site for the next follow up visit on immediate post-op to 6 weeks.

9.1.4 Immediate Post-op to 6 weeks (Day 1 to 6 Weeks+14 days)

1.	Query subject regarding any changes in general health and the use of concomitant medications/therapies.
2.	Collect discharge information and complete discharge eCRF.
3.	Collect the radiographic assessment if it's the SoC of the hospital.

4.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 adverse events and device deficiencies.
5.	Instruct the subject on follow-up procedures, including returning to the site for the next follow-up visit in 6 months (185 ± 14 days) after the surgery date.

9.1.5 6 months (6 months ± 14 days) after surgery

1.	Query subject regarding any changes in general health and the use of concomitant medications/therapies.
2.	Collect the KSS score objective measures (joint alignment, instability, motions & symptoms).
3.	Have the subject complete the KSS score subject questions.
4.	Have the subject complete the OKS patient-reported outcome measure
5.	Collect the Patient Satisfaction information.
6.	Have the subject complete the FJS patient-reported outcome measure.
7.	Collect the radiographic assessment information.
8.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 adverse events and device deficiencies.
9.	Instruct the subject on follow-up procedures, including returning to the site for the next follow-up visit in 1 year (365 ± 30 days) after the surgery date.

9.1.6 1 year (1 year ± 30 days) after surgery

1.	Query subject regarding any changes in general health and the use of concomitant medications/therapies.
2.	Collect the KSS score objective measures (joint alignment, instability, motions & symptoms).
3.	Have the subject complete the KSS score subject questions.
4.	Have the subject complete the OKS patient-reported outcome measure
5.	Collect the Patient Satisfaction information.
6.	Have the subject complete the FJS patient-reported outcome measure.
7.	Collect the radiographic assessment information.
8.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 adverse events and device deficiencies.
9.	Instruct the subject on follow-up procedures, including returning to the site for the next follow-up visit in 2 years (730 ± 60 days) after the surgery date.

9.1.7 2 years (2 years ± 60 days) after surgery

1.	Query subject regarding any changes in general health and the use of concomitant medications/therapies.
2.	Collect the KSS score objective measures (joint alignment, instability, motions & symptoms).
3.	Have the subject complete the KSS score subject questions.
4.	Have the subject complete the OKS patient-reported outcome measure
5.	Collect the Patient Satisfaction information.
6.	Have the subject complete the FJS patient-reported outcome measure.
7.	Collect the radiographic assessment information.
8.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 adverse events and device deficiencies.
9.	Instruct the subject on follow-up procedures, including returning to the site for the next follow-up visit in 3 years (1095 ± 60 days) after the surgery date.

9.1.8 Exit visit 3 years (3 years ± 60 days) after surgery

1.	Query subject regarding any changes in general health and the use of concomitant medications/therapies.
2.	Have the subject complete the OKS patient-reported outcome measure
3.	Collect the Patient Satisfaction information.
4.	Have the subject complete the FJS patient-reported outcome measure.
5.	Collect the KSS score objective measures (joint alignment, instability, motions & symptoms).
6.	Have the subject complete the KSS score subject questions.
7.	If any adverse device effects or device deficiencies are observed or reported, they must be recorded as instructed in Section 12 adverse events and device deficiencies.
8.	Complete Exit Visit eCRF.

9.1.9 Unscheduled Visits

All information obtained during an unscheduled visit should be recorded in the source documents and on the appropriate CRF.

9.1.10 Concomitant Medications and Therapies

Concomitant medications and concomitant therapies (e.g., physical therapy, pain medication) are recorded at any time from enrollment into the study through the subject's last study visit.

Concomitant Medications

Excluded Concomitant Medications

There are no restrictions on concomitant medications for this study.

Recording Concomitant Medications in CRF

Medications related to the study treatment and medications used to treat an adverse event will be recorded in the eCRF. Reference the eCRF Completion Guidelines for how medications are recorded.

Concomitant Therapies

Therapies Prohibited During the Study

There are no restrictions on concomitant therapies for this study.

Recording Concomitant Therapies in the CRF

Therapies related to the study treatment and therapies used to treat an adverse event will be recorded in the eCRF. Reference the eCRF Completion Guidelines for how therapies are recorded.

9.1.11 Discontinued Subjects

Discontinued subjects are those who voluntarily discontinue participation, who are withdrawn for reasons of safety or use of prohibited concomitant medication/therapies, who are lost to follow-up, refer to section 7.8 for further details. Where possible, a full Exit Visit should be completed for all subjects who discontinue the study early. Where consent is withdrawn, the date and any reason given for discontinuation should be captured, at a minimum (see Section 7.8.3).

Finally, if appropriate, the Investigator will also advise the subject of subsequent therapy and/or procedures necessary for their medical condition.

9.1.12 Subject Pregnancy

Pregnant or breast-feeding women or women at a child-bearing age planning to become pregnant during the follow up are excluded from the study. Also, if a woman becomes pregnant during the study, S+N must be contacted immediately once the investigator is made aware of the pregnancy. All study procedures that are contraindicated during pregnancy and/or lactation (e.g., x-rays) will not be required. A decision will be made regarding the continuation in the study of the pregnant woman. Pregnancy is not an adverse event; however, complications related to the pregnancy may be reportable as determined on a case-by-case basis. Pregnancy-related information will be collected until the end of the pregnancy.

9.2 Study Methods and Measurements

9.2.1 Standard Radiographic Evaluation

Standard radiographic evaluation on antero-posterior (A/P) and lateral views shall be performed at the determined time point before and after surgery in order to identify any radiographic observations such as radiolucent lines around the implant components. The presence of radiolucent lines, osteolysis & implant migration shall be recorded in the eCRF.

9.2.2 Oxford Knee Score (OKS)

The Oxford Knee Score (OKS) is a Patient Reported Outcome questionnaire that was developed to specifically assess the patient's perspective of outcome following Total Knee Arthroplasty. The OKS is a patient self-completion PRO containing 12 equally weighted questions on activities of daily living. The OKS has been developed and validated specifically to assess perceived function and pain answered on a Likert scale after TKA. Responses to each question ranges from 0-4 with a range of a possible overall score from 0-48. A score of 0 is the worst possible outcome while a score of 48 is the best possible outcome. The benefit to this questionnaire is that it is short, practical, reliable, valid and sensitive to clinically important changes over time.

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses for the OKS will then be recorded in the eCRF.

9.2.3 Forgotten Joint Score (FJS)

The FJS comprises measures for the assessment of joint-specific patient reported outcomes. This questionnaire focuses on the study subject’s awareness of the partially or fully replaced knee joint in everyday life. Joint awareness can be simply defined as any unintended perception of a joint [49]. Subjects are asked to rate their awareness of their knee arthroplasty in 12 questions with a five-point Likert response format: “Never”, “almost never”, “seldom”, “sometimes” and “mostly”. The item scores are summed and linearly transformed in a 0 to 100 scale with a high value reflecting the ability of the subject to forget about the replaced knee joint during the activities of daily living.

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses for the FJS will then be recorded in the eCRF.

9.2.4 Knee Society Score (KSS)

The KSS is a validated tool that combines an objective physician-derived component with a subjective subject-derived component. The Objective Knee Score is rated by the clinician and assesses a range of clinical outcomes: UKA alignment, stability, ROM and symptoms. The Subject Satisfaction Score assesses the satisfaction with 5 daily activities (sitting, lying in bed, getting out of bed, light household duties, and leisure activities). The Subject Expectation Score evaluates the subject's expectations prior to surgery. The post-operative questions differ from the pre-operative questions and ask if the subject's pre-operative expectations have been met. As the pre- and post-operative scores are based on different questions, they cannot be directly compared. The Functional Knee Score is derived from assessments of walking and standing, standard activities, advanced activities, and discretionary activities.

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses for KSS will then be recorded in the eCRF.

9.3 Health Economics/Quality of Life

Not Applicable.

10 STATISTICAL DESIGN

A Statistical Analysis Plan (SAP) will be written and finalized prior to database lock. The following is a brief description of the analyses to be described in this plan.

10.1 General

S+N's Global Biostatistics group will conduct the statistical analysis for this study. Unless otherwise stated, all significance tests and hypothesis testing will be two-sided, performed at the 5% significance level. Resulting p-values will be quoted and 95% two-sided confidence intervals will be generated where appropriate. Where data summaries are specified, categorical and ordinal variables will be summarized with frequencies and percentages. Continuous variables will be summarized with the following summary statistics: the number of observations, mean, median, standard deviation, minimum and maximum values.

Different statististical test will be performed based on the different data type. For continuous variables, if normality can not be assumed, a commensurate non-parametric test would be used. All analyses will be performed using SAS version 9.3 (or a later version).

10.2 Analysis Populations

The following are the analysis populations:

- Safety Population (SAF): This is defined as all subjects who were enrolled and treated with the study devices.
- Intent-to-Treat Population (ITT): The ITT population is defined as subjects from SAF, who have at least one post-operative assessment on any of the effectiveness endpoints.
- Per-Protocol Population (PP): The PP population is a subset of subjects in the ITT population, who do not have major protocol deviations and who satisfied all enrolment eligibility criteria. All major protocol deviations will be formally classified on a case-by-case basis prior to the final study database lock.

10.3 Baseline Data

All observations available prior to the operative date will be defined as baseline (or preoperative) data. All demographic and pre-operative characteristics data will be summarized at baseline. All demographic and baseline characteristics will be summarized using the SAF, ITT and PP analysis populations.

10.4 Efficacy Analysis

10.4.1 Analysis of Primary Endpoints

The primary endpoint of this study is the OKS at 2 years. If we assume the mean of OKS at 2 years for the subjects with implant JOURNEY II TKA with and without Patella Resurfaced as $\mu 1$ and $\mu 2$. The hypothesis test will be as following:

H0: $\mu 1 = \mu 2$ vs
H1: $\mu 1 \neq \mu 2$

The mean difference ($\mu 1$-$\mu 2$) and 95% CI will be estimated. If zero is included in 95% CI of mean difference, then null hypothesis will be accepted, which means patella resurfacing has no impact on the outcomes of JOURNEY II TKA.

Otherwise if zero is not included in 95% CI of mean difference, then alternative hypothesis (H1) will be accepted, which means patella resurfacing has significant impact on the outcomes of JOURNEY II TKA. If the lower limit of 95% CI is greater than 0, which means that the subject implant with Patella Resurfaced has higher OKS at 2 years. If the upper limit of 95% CI is less than 0, which means that the subject implant with Patella Resurfaced has lower OKS at 2 years.
In addition, the mean and 95% CI of OKS at 2 years for subjects implant with and without Patella Resurfaced will be estimated separately.
The primary endpoint will be summarized using the Per-Protocol (PP) population as the primary analysis population and then subsequently with the ITT population for sensitivity analysis.

10.4.2 Analysis of Secondary Endpoints

Knee Society Score (KSS), Oxford Knee Score (OKS) and Forgotten Joint Score (FJS)

The KSS score, OKS score and FJS score will be summarized at the pre-operative and postoperative visits and stratified by surgical method (resurfaced/un-resurfaced) using continuous summary characteristics. For each of these scores, repeated measures Analysis of Covariance (ANCOVA) models will be used to model the change from preoperative to postoperative and surgical method (resurfaced/ un-resurfaced patella). As a minimum, each model will contain a time points (pre-operative and postoperative), the investigational site and surgical method as fixed terms, subject as a random term. Pre-operative prognostic and demographic variables such as age, BMI, sex and other related factors will be introduced as covariates. These covariates will be added to the model using a stepwise approach and a covariate is retained in the final model if and only if its associated p-value ≤ 0.1. Model based means (adjusted means or Least Square Means), mean difference and corresponding standard errors associated with different time points, different surgical methods will be presented. If the p-value associated with the different time points and/or surgical methods in the model is significant (i.e. $p < 0.05$), then the 95% CIs corresponding to the model-based differences will additionally be presented.

Standard Radiographic Assessment

The presence of radiographic observations: implant loosening, implant migration, and osteolysis and other pertinent radiographic findings will be summarized as counts (n) and percentages (%) by visit. These would additionally be stratified by surgical method (resurfaced/un-resurfaced). Fisher Exact or Chi-Square test will be performed.

Radiolucent lines (mm) by zone and visit will be summarized using descriptive statistics for continuous variables. These would additionally be stratified by surgical method (resurfaced/un-resurfaced).

Patient expectation and patient satisfaction

The patient expectation and patient satisfaction will be summarized as counts (n) and percentages (%) by visit. These would additionally be stratified by surgical method (resurfaced/un-resurfaced). Fisher Exact or Chi-Square test will be performed.

All secondary endpoints will be analyzed and summarized using the ITT and PP population.

10.5 Safety Analyses

All safety data will be summarized separately for different surgical methods (resurfaced/un-resurfaced) as follows:

- Incidence of device-related re-interventions that occur on-study will be summarized as number (n) and percentages by different surgical methods and Fisher's exact test will be performed.
- Knee implant revision rate will be summarized as proportions with 95% CIs estimated using exact binomial methods for two surgical method separately. Proportion test will be performed to compare the revision rate from two surgical methods.

All safety analysis will be performed using the SAF analysis population.

10.6 Interim Analyses

An interim analysis is planned after completion of the 2 years visit. More specific details on the interim analyses will be included in the SAP.

11 SAMPLE SIZE JUSTIFICATION

The sample size is established primarily using a precision of estimates-based approach for resurfaced and unsurfaced Patella cohorts separately. As a secondary concern formal statistical hypothesis testing to assess differences between the cohorts will be a possibility.

Based on an underlying assumption of standard deviation of 7.4 in OKS reported in literature (Bohm et al 2012)., a minimum of 192 knees are required, per cohort, to ensure that there is an 80% probability that a 95% confidence interval constructed around the OKS score can be calculated to within ±1.2 units for each cohort of resurfaced and unresurfaced knees. To allow for up to 20% attrition during the data collection activity, this will be inflated to enrol a minimum of 240 knees per cohort.

12 ADVERSE EVENTS AND DEVICE DEFICIENCIES
12.1 Definitions

Table 12.1-1: Categories of Adverse Event

	Not Device-Related	Device- or Procedure- related	
Non-Serious	Adverse Event (AE)	Adverse Device Effect (ADE)	
Serious	Serious Adverse Event (SAE)	Serious Adverse Device Effect (SADE) (See 12.1.3)	
		Anticipated	Unanticipated
		Anticipated Serious Adverse Device Effect (ASADE)	Unanticipated Serious Adverse Device Effect (USADE)

12.1.1 Adverse Event

An Adverse Event (AE) is 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 and whether anticipated or unanticipated.

Note 1: This definition includes events related to the investigational medical device or the comparator.

Note 2: This definition includes events related to the procedures involved.

Note 3: For users or other persons, this definition is restricted to events related to the use of investigational medical devices.

AE is used both to refer to AE which do not meet the definitions of Adverse Device Effects or Serious Adverse Events and as an umbrella term referring to adverse events of all classifications.

An AE can be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease. For reporting purposes, emphasis is placed first and foremost on whether or not the event constitutes an untoward medical occurrence.

12.1.2 Adverse Device Effect

An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device.

Note 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation or operation, or any malfunction of the investigational medical device.

Note 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.

Note 3: This includes "comparator" if the comparator is a medical device.

Not Related - An AE is considered to be not related to the use of an IP or the procedure when the effect is DEFINITELY UNRELATED to have any relationship to the use of the IP or the procedure;

Related – An AE is considered to be related to the use of an IP or the procedure when there is a POSSIBLE, or DEFINITE relationship between the AE and the use of the IP or the procedure.

An ADE is further categorized depending on whether the criteria in section 12.1.3 and 12.1.4 are met.

12.1.3 Related Serious Adverse Events and Serious Adverse Device Effects

An AE or ADE is considered a **Serious** Adverse Event (SAE) or **Serious** Adverse Device Effects (SADE) if, it led to any of the following:

a) death,
b) serious deterioration in the health of the subject, users or other persons as defined by one or more of the following:
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function including chronic diseases, or
    3) in-patient or prolonged hospitalization, or
    4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,
c) fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

Note 1: Planned hospitalization for a pre-existing condition, or a procedure required by the study protocol, without serious deterioration in health, is not considered a serious adverse event.

12.1.4 Anticipated/Unanticipated Serious Adverse Device Effect

An Unanticipated Serious Adverse Device Effect (USADE) is a serious ADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk assessment.

Note 1: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk assessment.

12.1.5 Severity

The severity of every AE will be assessed by the PI or medically qualified site staff to whom the responsibility has been delegated and documented on the delegation of authority log. AE should be classified as mild, moderate, or severe, regardless of whether or not the AE are considered to be serious or non-serious. The classification should be based on the following definitions:

Mild - An event is mild if the subject is aware of, but can easily tolerate the sign or symptom;

Moderate - An event is moderate if the sign or symptom results in discomfort significant enough to cause interference with the subject's usual activities;

Severe - An event is severe if the sign or symptom is incapacitating and results in the subject's inability to work or engage in their usual activities.

12.1.6 Device Deficiency

A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. DD includes malfunctions, use errors and inadequate labeling.
Note 1: DD includes malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.
Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.
Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence
(a) if either suitable action had not been taken,
(b) if intervention had not been made, or
(c) if circumstances had been less fortunate,
are considered Device Deficiencies with potential to cause SADE and shall be reported as specified in section 12.3.

12.2 AE Coding Dictionary

Coding for this study will be done per International Medical Device Regulators Forum (IMDRF) AE Terminology Annex E – Clinical signs, symptoms, and conditions.

12.3 Reporting procedures

AE of any kind and DD will be recorded in the applicable CRF and source notes to include the date of occurrence, treatment and the details resolution. The Investigator will evaluate all AE for relationship to the device and procedure, seriousness, and severity (if applicable). DD will be evaluated for potential to cause SADE. The following timescales should be followed for the AE/DD information to be submitted/entered into the CRF and reported to the Sponsor or designee (see figure 12.2-1):

ADE and DD – without unreasonable delay

SAE, SADE and DD with potential to cause SADE – immediately (i.e. within 24 hours of the investigator being informed about the event)

All other events – according to usual timescales

In addition to inputting SAE and SADE information within 24 hours of being aware of the event, the investigator should email Clinical.safety@Smith-nephew.com to alert the safety representative of the events existence and to clarify details if necessary.

For ADE and DD, date of occurrence, and details of the product/procedure related to the event will be included and where applicable, pictures taken of the device. The deficient product should be retained for return to S+N unless it is contaminated (e.g., used dressings must not be retained). Updates to submitted information will be recorded in the CRF according to the timescales above.

All adverse events will be reviewed by a medically qualified person appointed by the Sponsor to determine which, if any, meet criteria for expedited reporting to the regulatory authorities.

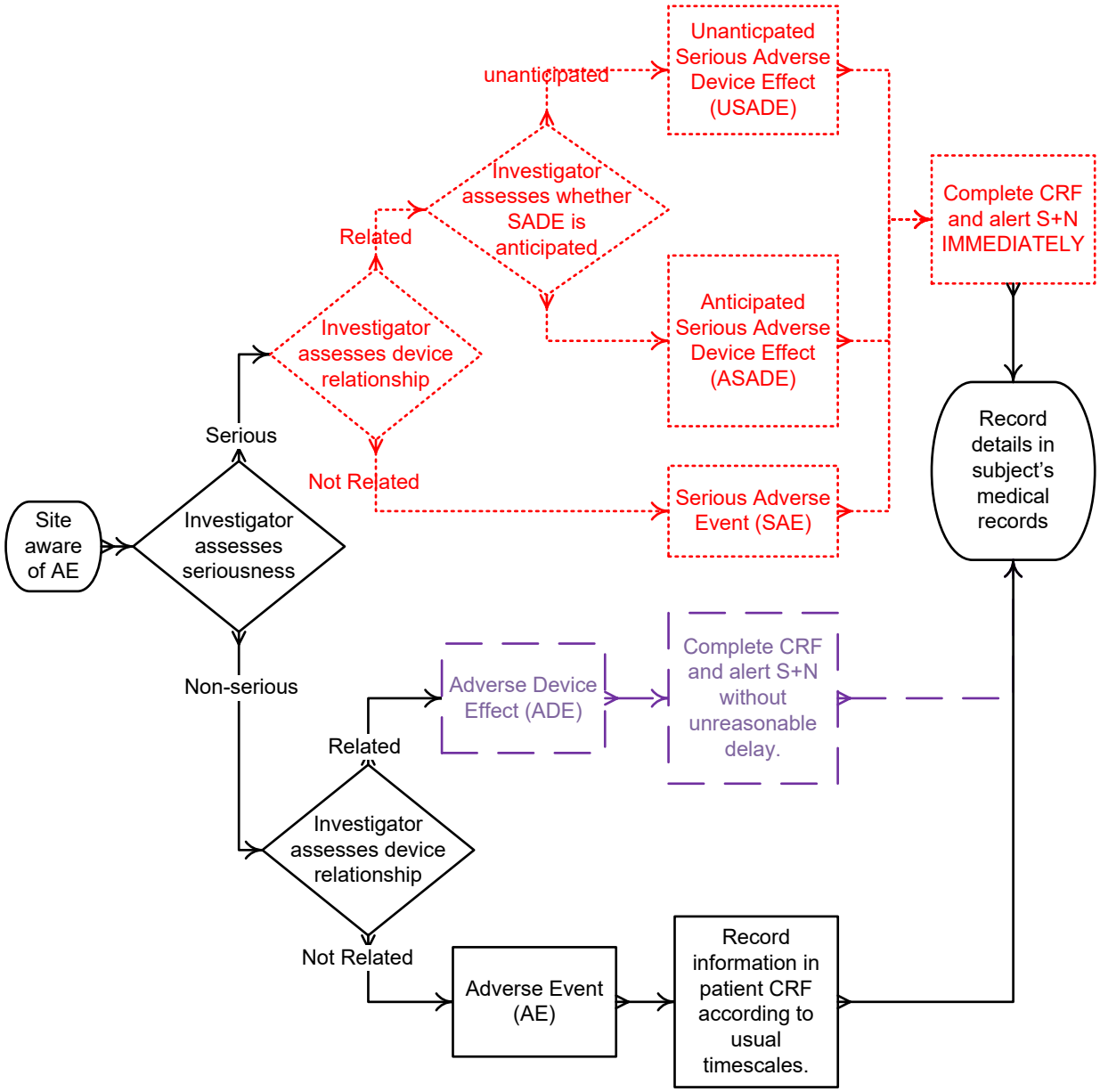
Safety reporting to the IRB/IEC and regulatory authority will be completed as per local IRB and regulatory authority reporting requirements and will be outlined in the study Safety Monitoring Plan (SMP).

If there are no mandatory timelines for reporting unanticipated SADE's and DD's that could have led to an SADE, these will be reported to IEC/IRB and regulatory authorities within 10 working days

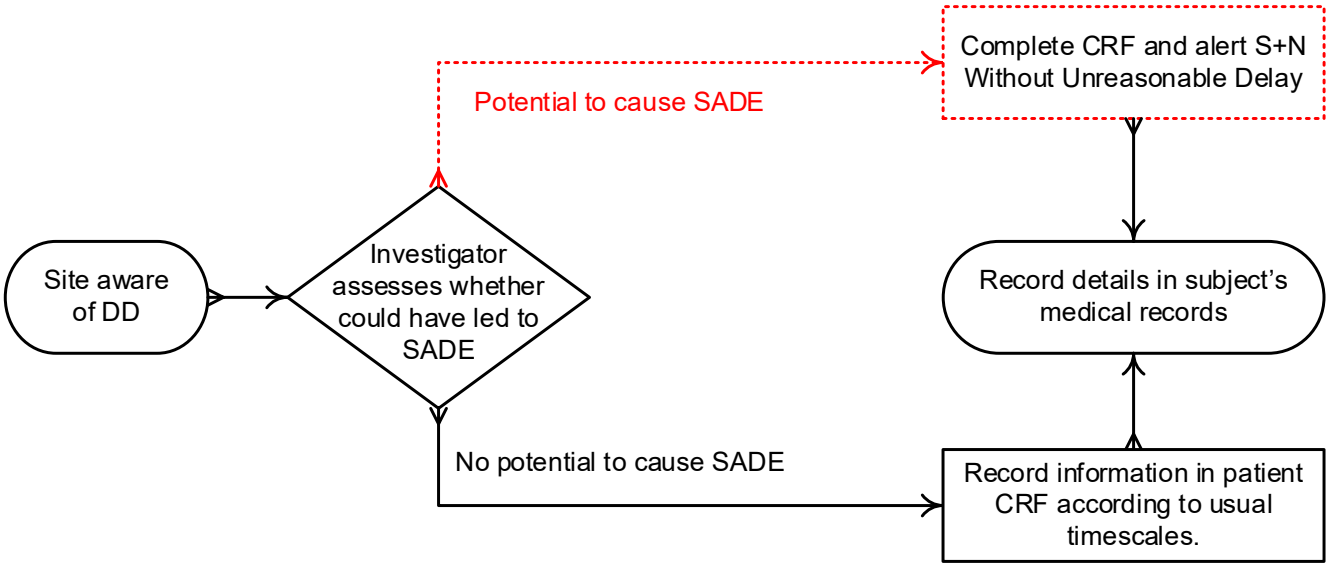
All other events will be reported on a periodic/annual basis.

Depending on the nature of the adverse event, S+N may request copies of the subject's medical records, Imaging, Operative notes, as well as results of any relevant laboratory tests performed or other documentation related to the AE. If the subject was hospitalized, a copy of the discharge summary may be requested by S+N and should be forwarded as soon as it becomes available. In certain cases, S+N also may request a letter from the Investigator that summarizes the events related to the case. Refer to the ISF Sponsor Contact Information Sheet to report SAE, unanticipated SADE, anticipated SADE, and DD.

Figure 12.3-1: Evaluation and Reporting of AE



13 FIGURE 13-1: EVALUATION AND REPORTING OF DD



13.1 Unblinding of Investigational Product

Not applicable.

13.2 Follow-up of Subjects with Adverse Events

For subjects who are experiencing ongoing unresolved AE at the time of their study completion or early discontinuation from the study, it is recommended that the Investigator schedule an appropriate follow-up visit to determine the outcome of the event.

Any additional data must be documented and available to the Sponsor who will determine whether the data need to be documented in the CRF/Clinical Study Report.

13.2.1 Ongoing Adverse Events at Study Discontinuation

Adverse events which are **related** to a study procedure or S+N IP and are ongoing at the end of subject's participation: The event should be followed until it is either resolved or until the event has become chronic and is not expected to further improve based on Investigator's review of the event.

Adverse events which are **not related** to a study procedure or S+N IP and are ongoing at the end of subject's participation should be followed for 30 days after discontinuation or if the AE is resolved, whichever is sooner.

At the time of data analysis (e.g., interim or final), an evaluation of ongoing events should take place and be listed as ongoing in the safety table.

14 INVESTIGATOR OBLIGATIONS

The Principal Investigator will comply with the commitments outlined in the Statement of Investigator, provided by the Sponsor, and with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Appendix- Principal Investigator Obligations.

In addition, the PI will ensure that the Financial Disclosure Statements will be completed by the PI and the Sub-Investigator upon entry into the study and as any changes that affect their financial disclosure status occur during the course of the study and up to one year after study completion.

15 SPONSOR AND MONITOR RESPONSIBILITIES

The Sponsor will designate a monitor to conduct the appropriate site visits at the appropriate intervals. The clinical investigation will be monitored to ensure that: the rights and wellbeing of the subjects are protected; the reported data are accurate, complete, and verifiable from the source documents; and the study is conducted in compliance with the currently approved protocol and amendment(s), if applicable, with GCP regulations, and with applicable regulatory requirements.

Detailed monitoring requirements will be documented in the Clinical Monitoring Plan for this study.

15.1 Contract Research Organization

The Sponsor may engage a Contract Research Organization (CRO) to assist in conducting this study.

15.2 Site Qualification Visit

A site qualification visit may be performed by the Sponsor prior to the execution of a clinical agreement to ensure that all Investigators have the appropriate training, staff, facilities, and resources to adequately conduct the study.

15.3 Site Initiation Visit

A site initiation visit to provide training on the specifics of the study, site obligations and expectations of study conduct will be performed by the Sponsor or qualified person designated by the Sponsor following the execution of the CTA and documented IRB/IEC approval.

15.4 Interim Monitoring Visit

Regular interim monitoring visits will be performed by the Sponsor or qualified person designated by the Sponsor.

15.5 Sponsor Audits and Regulatory Inspection

Quality Assurance auditors, whether an employee of the Sponsor or its designee, may evaluate study conduct at the study sites. These parties must have access to any and all study reports and source documentation.

15.6 Close-Out Visit

A study close-out visit will be performed by the Sponsor or designee to retrieve and account for all remaining clinical data and to resolve outstanding queries. During study close-out, the monitor will review investigator files to ensure required documents and records are on file, confirm the disposition of any other ancillary items used for the study, and review regulatory requirements regarding records retention and IRB/IEC reporting requirements. When no subjects have been included, a remote close-out visit may be conducted.

16 PROTOCOL DEVIATIONS

An Investigator must not make any changes or deviate from this protocol, except to protect the life and physical well-being of a subject in an emergency. Protocol deviations reported by the Investigator or discovered during monitoring visits will be compiled in a Protocol / GCP Deviation Log (TMP-CD-31-02 Protocol/GCP Deviation Log). Significant and/or recurrent protocol/GCP deviations will be documented on a protocol deviation form (TMP-CD-31-01 Protocol/GCP Deviation) including identified root cause and, as necessary, appropriate corrective and preventive actions will be put in place and signed off by the study personnel.

17 PROTOCOL AMENDMENTS

Amendments should be made only in necessary cases once the study has started. Protocol amendments must be approved by the protocol signatories prior to submission to the IRB/IEC. Protocol amendments need to be approved by the IRB/IEC, according to the applicable requirements prior to implementation at the site.

18 CONFIDENTIALITY OF THE STUDY

The confidentiality of this study and associated documents is governed by the terms of the Clinical Trial Agreement (CTA).

19 STATEMENTS OF COMPLIANCE

This clinical study will be performed in compliance with the ethical principles of the Declaration of Helsinki and ISO 14155: Clinical investigation of medical devices – Good Clinical Practice as far as relevant for the study type.

This clinical study will not commence until the required approval/favorable opinion from the IRB/IEC or regulatory authority has been obtained. Any additional requirements imposed by the IRB/IEC or regulatory authority will be followed.

Public/Products Liability Insurance has been purchased by Smith & Nephew plc. Worldwide and incorporates coverage for personal injury in respect of clinical studies.

20 END OF STUDY

The end of this study is defined by the last follow-up visit that occurs in the whole study population.

Should circumstances arise which require the termination of the entire study prior to its planned completion (e.g., safety concerns) or circumstances arise which mean the end of the participation of an individual site (e.g., departure of Investigator, non-compliance), then this will be undertaken according to the SOPs of the Sponsor. The requirement for subject follow up in these instances will be considered as part of these processes.

The sponsor may decide to discontinue a specific study site under the following conditions:

- Non-compliance to GCP or study protocol
- Failure to enroll in subjects
- Unsafe or unethical practices

21 PUBLICATION POLICY

21.1 Publication of Study Data

The preparation and submission for publication of manuscripts containing the study results shall be in accordance with a process determined by the Clinical Trial Agreements between the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws.

21.2 Data Sharing

Smith+Nephew is committed to upholding the highest ethical and legal standards involved in conducting clinical trials. Smith+Nephew, therefore, supports the data sharing requirements of The International Committee of Medical Journal Editors (ICMJE) published on the 6th June 2017. In accordance, Smith+Nephew will consider requests to share individual (de-identified) participant data that underlie the results of any interventional clinical trial, as presented from the 1st July 2018 within an ICMJE associated journal. Requests made by researchers who provide a methodologically sound proposal will be considered. Requests may include data that underlie results presented in text, tables, figures, and appendices, together with data dictionaries. Availability of these data will begin nine months and end 36 months after article publication. Data supplied may only be used by the researcher(s) named in the approved research proposal for the purposes of achieving the aims of the analyses specified therein. All proposals should be directed to datasharing.gcs@smith-nephew.com. To gain access, data requestors will need to sign a data access agreement.

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23 APPENDICES

23.1 Protocol Amendment

23.1.1 General Purpose

The purpose to have the 1st protocol amendment from version 1.0 into version 2.0 is to further update the section 12 about safety reporting process to compliance with the SOP requirements and update the section 6.2 about product accountability procedures for China specific requirement.

23.1.2 Rationale

The rationale to 1st update the protocol is due to SOP-CD-05 requirement that both AE and DD should be reported, thus update the section 12 to compliance with protocol SOP template TMP-CD-05-01. And as China need to free provide the Oxinium femoral component, the device accountability will be needed for China sites.

23.1.3 Effect on Study Status

Not applicable. This amendment is to be in effect and implemented prior to subject enrollment.

23.1.4 Details

1st Update from Version 1.0 to Version 2.0

Section	Current Text Version 1.0 (10DEC2020)	Revised Text Version 2.0 (02Jun2021)
Header	Version: 1.0, 10DEC2020	Version: 2.0, 02Jun2021
Section 2-Synopsis-Safety Data	• Adverse events (AEs) related to subsequent surgical interventions on subject knee due to any reasons • AEs identified from qualitative radiographic assessment	• All adverse events (AEs) including intra-operative adverse events and complications • Device related re-intervention • Device Deficiencies
Section 2-Synopsis-Study data collection-Postoperative	• Adverse events (AEs) related to subsequent surgical interventions on subject knee due to any reasons • AEs identified from qualitative radiographic assessment	• All adverse events (AEs) including intra-operative adverse events and complications • Device related re-intervention • Device Deficiencies
Section 2-Synopsis - Study Schedule	Adverse Events related to subsequent surgical interventions on subject knee due to any reasons & identified from qualitative radiographic assessment	Safety Assessment (AEs, DDs)

Section 6.4	6.4 Product Accountability Procedures No product accountability procedures will be applied for the JOURNEY II Knee Implant Systems as these are commercially available products.	This study is a post-market study but OXINIUM Femoral component is supplied by the Sponsor in China sites and accountability procedure should be followed in China sites. China investigational sites will maintain an inventory of the IP/Ancillary Products and Study Supplies. The Sponsor or its designee will provide a log(s) to facilitate IP/Ancillary Products and Study Supplies inventory control. All IP/Ancillary Products and Study Supplies accountability logs must be retained in the Investigator Site File (ISF). These records must be available for inspection by the Sponsor, its designees, or by regulatory agencies at any time. The Study Monitor will ensure that the procedures and records are in place for the appropriate reconciliation of all IP/Ancillary Products and Study Supplies. As part of monitoring, the Study Monitor will check that site personnel are following the proper procedures for accountability and completing all necessary documentation. Only the product components provide by sponsor need to follow the accountability procedure, for the components purchased by investigational site, no product accountability procedure will be applied.
Section 9.1-Table 9.1	Adverse Events related to subsequent surgical interventions on subject knee due to any reasons & identified from qualitative radiographic assessment	Safety Assessment (AEs, DDs)
Section 9.1.3- Part 5	Collect any adverse events related to subsequent surgical interventions on subject knee due to any reasons & identified from qualitative radiographic assessment.	Collect any adverse events or DDs
Section 9.1.4- Part 4	Collect any adverse events related to subsequent surgical interventions on subject knee due to any reasons & identified from qualitative radiographic assessment.	Collect any adverse events or DDs
Section 9.1.5- Part 8	Collect any adverse events related to subsequent surgical interventions on subject knee due to any reasons &	Collect any adverse events or DDs

	identified from qualitative radiographic assessment.	
Section 9.1.6- Part 8	Collect any adverse events related to subsequent surgical interventions on subject knee due to any reasons & identified from qualitative radiographic assessment.	Collect any adverse events or DDs
Section 9.1.7- Part 8	Collect any adverse events related to subsequent surgical interventions on subject knee due to any reasons & identified from qualitative radiographic assessment.	Collect any adverse events or DDs
Section 9.1.8- Part 7	Collect any adverse events related to subsequent surgical interventions on subject knee due to any reasons & identified from qualitative radiographic assessment.	Collect any adverse events or DDs
Section 12.1.6	N/A	A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. DD includes malfunctions, use errors and inadequate labeling. Note 1: DD includes malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling. Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator. Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence (a) if either suitable action had not been taken, (b) if intervention had not been made, or (c) if circumstances had been less fortunate, are considered Device Deficiencies with potential to cause SADE and shall be reported as specified in section 12.3.
Section 12.2	NA	Coding for this study will be done per International Medical Device Regulators Forum (IMDRF) AE Terminology Annex E – Clinical signs, symptoms, and conditions.

Section 12.3	Adverse events (AEs) related to subsequent surgical interventions on subject knee due to any reasons & identified from qualitative radiographic assessment will be recorded in the applicable CRF and source notes to include the date of occurrence, treatment and the details resolution. The Investigator will evaluate these AE for relationship to the device and procedure, seriousness, and severity (if applicable). The following timescales should be followed for the AE information to be submitted/entered into the CRF and reported to the Sponsor or designee (see Figure 12-1): • SAE – immediately (i.e. within 24 hours of the investigator being informed about the event) • All other events – according to usual timescales	AE of any kind and DD will be recorded in the applicable CRF and source notes to include the date of occurrence, treatment and the details resolution. The Investigator will evaluate all AE for relationship to the device and procedure, seriousness, and severity (if applicable). DD will be evaluated for potential to cause SADE. The following timescales should be followed for the AE/DD information to be submitted/entered into the CRF and reported to the Sponsor or designee (see figure 12.2-1): ADE and DD – without unreasonable delay SAE, SADE and DD with potential to cause SADE – immediately (i.e. within 24 hours of the investigator being informed about the event) All other events – according to usual timescales

23.2 Instructions for Use

Please refer to the IFU of JOURNEY II CR Total Knee Systems.

23.3 Principal Investigator Obligations

Since this is a multiple-country study, overall ISO14155 will be followed, and for each country, the study should be compliance with local regulations and laws.

23.3.1 ISO14155:2011

1. General:
   a. The role of the PI is to implement and manage the day-to-day conduct of the clinical investigation as well as ensure data integrity and the rights, safety, and well-being of the subjects involved in the clinical investigation.
2. Qualification of the PI. The PI shall:

a. be qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this International Standard; evidence of such qualifications of the PI and key members of the investigation site team shall be provided to the Sponsor through up-to-date Curriculum Vitae (CV) or other relevant documentation,
b. be experienced in the field of application and trained in the use of the investigational device under consideration,
c. disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results, and
d. be knowledgeable with the method of obtaining informed consent.

3. Qualification of investigation site. The PI shall be able to demonstrate that the proposed investigation site:
   a. has the required number of eligible subjects needed within the agreed recruitment period, and
   b. has one or more qualified investigators, a qualified investigation site team and adequate facilities for the foreseen duration of the clinical investigation.
4. Communication with the IEC. The PI shall:
   a. provide the Sponsor with copies of any clinical-investigation-related communications between the PI and the IEC,
   b. comply with the requirements described in 4.5 of ISO 14155:2011.
      i. Submit to the IEC the following information, any amendments and any additional documentation required by the IEC: the Protocol; IB or equivalent; informed consent form and any other written information provided to subjects; procedures for recruiting subjects and advertising materials, if any; a copy of the CV of the PI(s) for with the IEC has oversight.
      ii. Provide documentation of the IECs approval/favorable opinion, identifying the documents and amendments on which the opinion was based, to the Sponsor, prior to commencing the clinical investigation.
      iii. Submit the following to the IEC if required by national regulations, the protocol or IEC, whichever is more stringent:

         1. SAEs
         2. Requests for deviations, and reports of deviations, if the deviation affects subject's rights, safety, and well-being, or the scientific integrity of the clinical investigation. Document and report to the Sponsor and IEC a report of deviations made to protect the rights, safety, and well-being of human subjects under emergency circumstances.
         3. Progress reports, including safety summary and deviations
         4. Amendments to any documents already approved by the IEC.
         5. If applicable, notifications of suspension or premature termination
         6. If applicable, justification and request for resuming the clinical investigation after suspension.
         7. Clinical investigation report or summary.

      iv. As a minimum, during the clinical investigation, the following information shall be obtained in writing from the IEC prior to implementation:

         1. Approval/favorable opinion of amendments
         2. Approval of the request for deviations that can affect the subject's rights, safety, and well-being or scientific integrity of the clinical investigation
         3. Approval for resumption of a suspended clinical investigation if applicable.

   c. obtain the written and dated approval/favorable opinion of the IEC for the clinical investigation before recruiting subjects and implementing all subsequent amendments, if required,

d. promptly report any deviations from the protocol that affect the rights, safety or well-being of the subject or the scientific integrity of the clinical investigation, including those which occur under emergency circumstances, if required by the IEC, protocol or national regulations. In particular circumstances, the communication with the IEC can be performed by the Sponsor, partly or in full, in which case the Sponsor shall keep the Principal Investigator informed.

5. Informed consent process. The PI shall:
   a. General:
      i. Informed consent shall be obtained in writing from the subject and the process shall be documented before any procedure specific to the clinical investigation is applied to the subject; except when special circumstances for emergency treatments apply (see below)
   b. Process of obtaining informed consent. The general process for obtaining informed consent shall be documented in the protocol and shall comply with the following. These requirements also apply with respect to informed consent obtained from a subject's legally authorized representative:
      i. Ensure that the PI or his/her authorized designee conducts the informed consent process
      ii. Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
      iii. Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
      iv. Not waive or appear to waive the subject's legal rights
      v. Use native non-technical language that is understandable to the subject
      vi. Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation
      vii. Include personally dated signatures and the PI or an authorized designee responsible for conducting the informed consent process
      viii. Show how informed consent will be obtained in special circumstances (see below) where the subject is unable to provide him or herself, and
      ix. Ensure important new information is provided to new and existing subjects throughout the clinical investigation.
   c. Special circumstances for informed consent (the following provisions are subject to national regulations):
      i. Subject needing legally authorized representatives: informed consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation (e.g., infant, child, or juvenile, seriously ill or unconscious subject, mentally ill person, mentally handicapped person). In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.
      ii. Subject unable to read or write: informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent for attesting that the information was accurately explained and that the informed consent was freely given.
      iii. Emergency treatments:

         1. For clinical investigations involving emergency treatments, when prior informed consent of the subject is not possible because of the subject's medical condition, the informed consent of the subject's legally authorized representative, if present, shall be requested.

2. When it is not possible to obtain prior informed consent from the subject, and the subject's legally authorized representative, is not available, the subject may still be enrolled if a specific process has been described in the protocol.
3. Arrangements shall be made to inform the subject or legally authorized representative, as soon as possible, about the subject's inclusion in the clinical investigation and about all aspects of the clinical investigation.
4. The subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows.

d. The Principal Investigator may not enroll a subject without obtaining informed consent of the subject or his/her legally authorized representative only when the following conditions are fulfilled: the prospective subject fulfils the emergency conditions and is obviously in a life-threatening situation; no sufficient clinical benefits are anticipated from the currently available treatment; there is a fair possibility that the life-threatening risk to the prospective subject can be avoided if the investigational device is used; anticipated risks are outweighed by the potential benefits of applying the investigational device ; the legally authorized representative cannot be promptly reached and informed.
e. Information provided to the subject. All information pertinent to the clinical investigation, including at least the following, shall be provided in writing and in native, non-technical language that is understandable to the subject (or the subject's legally authorized representative):
   i. Description and purpose
   ii. Potential benefits
   iii. Risks and inconveniences or the subject and, when applicable, for any embryo, fetus or nursing infant
   iv. Alternative procedures
   v. Confidentiality
   vi. Compensation
   vii. Anticipated expenses, if any, to be borne by the subject for participating in the clinical investigation
   viii. Information on the role of Sponsor's representative in the clinical investigation
   ix. Contact persons
   x. Statement declaring that new findings or the reasons for any amendment to the protocol that affect the subject's continued participation shall be made available to the subject.
   xi. Statement indicating that, upon the subject's approval, the subject's personal physician will be informed of the subject's participation in the clinical investigation
   xii. Termination procedures
f. Informed consent signature shall contain the following:
   i. The voluntary agreement to participate in the clinical investigation and follow the investigator's instructions
   ii. A statement declaring that refusal of participation incurs no penalty for the subject
   iii. A statement declaring that discontinuation at any time incurs no penalty for the subject
   iv. A statement with regard to the possible consequences of withdrawal
   v. An acknowledgment of the information provided and confirmation that all the subject's questions were answered
   vi. A statement confirming that the subject or his/her legally authorized representative agrees to the use of the subject's relevant personal data for the purpose of the clinical investigation
   vii. A statement confirming that the subject or his/her legally authorized representative agrees that Sponsor's representatives, regulatory authorities and IEC representatives will be granted direct access to the subject's medical records.

g. New information: if new information becomes available that can significantly affect a subject's future health and medical care, that information shall be provided to the subject(s) affected in written form. If relevant, all affected subjects shall be asked to confirm their continuing consent in writing.
h. ensure compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent, and
i. ensure and document appropriate training if an authorized designee is appointed to conduct the informed consent process.

6. Compliance with the protocol. The Principal Investigator shall:
   a. indicate his/her acceptance of the protocol in writing,
   b. conduct the clinical investigation in compliance with the protocol,
   c. create and maintain source documents throughout the clinical investigation and make them available as requested during monitoring visits or audits,
   d. ensure that the investigational device is used solely by authorized users as specified in 6.2, and in accordance with the protocol and instructions for use,
   e. propose to the Sponsor any appropriate modification(s) of the protocol or investigational device or of the use of the investigational device,
   f. refrain from implementing any modifications to the protocol without agreement from the Sponsor, IEC and regulatory authorities, if required,
   g. document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation,
   h. ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
   i. ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,
   j. ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports,
   k. maintain the device accountability records,
   l. allow and support the Sponsor to perform monitoring and auditing activities,
   m. be accessible to the monitor and respond to questions during monitoring visits,
   n. allow and support regulatory authorities and the IEC when performing auditing activities,
   o. ensure that all clinical-investigation-related records are retained as required taking measures to prevent accidental or premature destruction, and
   p. review and sign the clinical investigation report, as applicable.
7. Medical care of subjects. The Principal Investigator shall
   a. provide adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of adverse events,
   b. inform the subject of the nature and possible cause of any adverse events experienced,
   c. provide the subject with the necessary instructions on proper use, handling, storage, and return of the investigational device, when it is used or operated by the subject,
   d. inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required,
   e. provide the subject with well-defined procedures for possible emergency situations related to the clinical investigation, and make the necessary arrangements for emergency treatment, including decoding procedures for blinded/masked clinical investigations, as needed,
   f. ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation,

g. if appropriate, subjects enrolled in the clinical investigation shall be provided with some means of showing their participation in the clinical investigation, together with identification and compliance information for concomitant treatment measures (contact address and telephone numbers shall be provided),
h. inform, with the subject's approval or when required by national regulations, the subject's personal physician about the subject's participation in the clinical investigation, and
i. make all reasonable efforts to ascertain the reason(s) for a subject's premature withdrawal from the clinical investigation while fully respecting the subject's rights.

8. Safety reporting. The Principal Investigator shall*:
   a. record every adverse event and observed device deficiency, together with an assessment,
   b. report to the Sponsor, without unjustified delay, all serious adverse events and device deficiencies that could have led to a serious adverse device effect; this information shall be promptly followed by detailed written reports, as specified in the protocol,
   c. report to the IEC serious adverse events and device deficiencies that could have led to a serious adverse device effect, if required by the national regulations or protocol or by the IEC,
   d. report to regulatory authorities, serious adverse events and device deficiencies that could have led to a serious adverse device effect, as required by the national regulations, and
   e. supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

*To the extent outlined in section 12.