Smith+Nephew

Clinical Protocol

A Prospective, Multi-center, Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) and total knee arthroplasty (TKA) procedures

Sponsor and funding source:	Smith & Nephew Inc, 1450 E. Brooks Road, Memphis, Tennessee 38116, USA
Local Representative	Smith & Nephew Operations B.V, Bloemlaan 2, 2132 NP Hoofddorp, The Netherlands
Investigational Product(s)	REAL INTELLIGENCE™ CORI™ (referred as "CORI Robotics" throughout this document)
Single Identification Number of Clinical Investigation	N/A
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Summary of Revision History	V5.0, 08/Nov/2022 V4.0, 18/Jun/2020 V3.0, 08/Jun/2020 V2.0, 29/Apr/2020 V1.0, 24/Feb/2020

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-center, Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) and total knee arthroplasty (TKA) procedures", version 6.0, dated 15/Jan/2024, and agree to abide by all provisions set forth herein.

I agree to comply with the Investigator's Obligations stipulated in Section 22.7 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**

1.2Coordinating Investigator Approval

☒ I have read the attached protocol entitled "A Prospective, Multi-center, Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) and total knee arthroplasty (TKA) procedures", version 6.0, dated 15/Jan/2024, and agree to abide by all provisions set forth therein.

Name, Address, Professional Position	**Signature and Date / DocuSign Stamp**
Prof. Edward T Davis The Royal Orthopaedic Hospital NHS Foundation Trust, Bristol Road South, Birmingham, West Midlands, UK, B31 2AP Consultant Arthroplasty Surgeon and Clinical Service Lead for Arthroplasty	DocuSigned by:  Signer Name: Edward Davis Signing Reason: I approve this document Signing Time: 09-Mar-2024 | 19:17:26 GMT 7851C4166EEE49A2B4DA05B0009685E7

1.3Sponsor Approval

Name and Title	Signature and Date / DocuSign Stamp
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Sam Timson Sr. Clinical Compliance & Training Specialist (Clinical Compliance and Training/Clinical Quality Assurance)	DocuSigned by: Sam Timson Signer Name: Sam Timson Signing Reason: I approve this document Signing Time: 11-Mar-2024 | 08:25:29 GMT 638643A36EEA420D82707565773EC196

2.SYNOPSIS

Title of Study:	A Prospective, Multi-center, Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) and total knee arthroplasty (TKA) procedures
Sponsor and Funding Source:	Smith & Nephew Inc, 1450 E. Brooks Road, Memphis, Tennessee 38116, USA
Study Design:	• Prospective • Multi-center – up to 8 sites • Cohort study • 2 arms • 80 subjects (40 x UKA, 40 x TKA) • 1 year follow-up
Study Type:	Post-market study Interventional, non-randomised, non-blinded
Study Product:	REAL INTELLIGENCE™ CORI™ (CORI Robotics) is a computer-assisted orthopedic surgical navigation and burring system. CORI Robotics is designed to aid surgeons in planning and executing a procedure involving bone preparation for unicondylar knee arthroplasty (UKA) and total knee arthroplasty (TKA) procedures. CORI Robotics is comprised of a console control unit, optical tracking camera, primary and secondary input displays (tablet and optional display monitor), and foot pedal. The CORI Robotics software consists of a patient and user management module, a surgical planner, and an intra-operative cutting module.
Comparison Group(s)*: (*if applicable)	N/A
Study Purpose:	This is a prospective study to demonstrate the safety and effectiveness of the CORI Robotics to meet the post-market clinical follow-up requirement in Europe and the US.
Primary Objective:	To evaluate the use of CORI Robotics in UKA and TKA procedures in achieving post-operative leg alignment.
Secondary Objective(s):	To assess the safety and performance of the CORI Robotics up to 12 months after surgery.

Other Objective(s):	To determine the Robotics System time and cutting time of the robotic drill of UKA and TKA procedures with the CORI Robotics.
Sample Size:	80 CORI Robotics procedures: • 40 unicondylar knee arthroplasty (UKA) • 40 total knee arthroplasty (TKA) The statistical justification is provided separately for UKA and TKA and is based on data collected from the NAVIO™ Surgical System. N=40 subjects per arm, based on post-operative alignment (±3 degrees) with expected 92.1% NAVIO™ Surgical System vs. 73.4% from a historical control.
Number of Study Sites:	Up to 8 sites
Targeted Global Regions:	Europe, UK, India, and the US
Inclusion Criteria:	1) The subject's treating clinician has decided that REAL INTELLIGENCE™ CORI™ and a compatible Smith+Nephew Knee Implant System is the best treatment for the subject's UKA or TKA and the subject has agreed to the treatment. 2) Subject requires a cemented UKA or TKA as a primary indication that meets either criterion A or B. A. Subject requires a cemented UKA as a primary indication due to any of the following conditions: 1. Non-inflammatory degenerative joint disease, including osteoarthritis 2. Avascular necrosis 3. Requires correction of functional deformity 4. Requires treatment of fractures that were unmanageable using other techniques B. Subject requires a cemented TKA as a primary indication due to any of the following condition: 1. Degenerative joint disease, including osteoarthritis 2. Rheumatoid arthritis 3. Avascular necrosis 4. Requires correction of functional deformity 5. Requires treatment of fractures that were unmanageable using other techniques 3) Subject is of legal age to consent and considered skeletally mature (≥ 18 years of age at the time of surgery) 4) Subject agrees to consent to and to follow the study visit schedule (as defined in the study protocol and informed consent form), by signing the Ethical Committee (EC) or Institutional Review Board (IRB) approved informed consent form. 5) Subject plans to be available through one (1) year postoperative follow-up.

	6) Routine radiographic assessment is possible. 7) Subject able to follow instructions and deemed capable of completing all study questionnaires.
Exclusion Criteria:	1) Subject receives a CORI Robotics UKA or TKA on the index joint as a revision for a previously failed surgery, or need for complex implants, or any other implant than a standard UKA or TKA (e.g. stems, augments, or custom made devices). 2) Subject has been diagnosed with post-traumatic arthritis 3) Subject receives bilateral UKA or TKA. 4) Subject does not understand the language used in the Informed Consent Form. 5) Subject does not meet the indication or is contraindicated for UKA or TKA according to specific Smith+Nephew knee system's Instructions For Use (IFU). 6) Subject has active infection or sepsis (treated or untreated). 7) Subject is morbidly obese with a body mass index (BMI) greater than 40. 8) Subject is pregnant or breast feeding at the time of surgery. 9) Subject, in the opinion of the Investigator, has advanced osteoarthritis or joint disease at the time of surgery and was better suited for an alternate procedure. 10) Subject has a condition(s) that may interfere with the TKA or UKA survival or outcome (i.e., Paget's or Charcot's disease, vascular insufficiency, muscular atrophy, uncontrolled diabetes, moderate to severe renal insufficiency or neuromuscular disease, or an active, local infection). 11) Subject in the opinion of the Investigator has an emotional or neurological condition that would pre-empt their ability or willingness to participate in the study including mental illness, mental retardation, drug or alcohol abuse. 12) Subject, in the opinion of the Investigator, has a neuromuscular disorder that prohibited control of the index joint 13) Subject is a prisoner or meets the definition of a Vulnerable Subject per ISO 14155 Section 3.55.
Study Duration:	Estimated total study timeline: 36 months (Enrolment period: 24 months, Follow-up period: 12 months)
Primary endpoint:	The evaluation of the proportion of subjects achieving post-operative leg alignment at 6 weeks post-surgery. Achieved leg alignment is defined as ± 3° from the subject's specific target.
Secondary endpoint(s):	• Component Alignment 6 weeks post-surgery • Radiographic assessment (Presence of radiolucent lines, osteolysis & implant migration) 12 months post-surgery

	• 2011 Knee Society Score (KSS) at baseline, 6 weeks, 6 and 12 month post-surgery • Oxford Knee Score (OKS) at baseline, 6 weeks, 6 and 12 month post-surgery • Forgotten Joint Score (FJS) at 6 weeks, 6 and 12 month post-surgery • Five-level EuroQol five-dimensional (EQ-5D-5L) VAS and index scores at baseline, 6 weeks, 6 and 12 month post-surgery
Other exploratory endpoint(s):	• Leg alignment pre- and post-cementation • Robotics System time as extracted from the Subject's CORI Robotics Case Report generated by the CORI Robotics Software. • Cutting time of the robotic drill s extracted from the Subject's CORI Robotics Case Report, generated by the CORI Robotics Software.
Safety Data	• All adverse events (AEs) and complications occurring from the time of subject enrollment until study termination or study completion including intra-operative adverse events and complications. • Device related re-intervention • Device Deficiencies • Knee implant revision rate All AEs will be categorized in terms of seriousness and relatedness to the study device or to the surgical procedure (Adverse Events, Serious Adverse Events, Adverse Device Effects, Serious Adverse Device effects). All Serious Adverse Device Effects will be further categorized as Anticipated or Unanticipated. The definitions for each of these categories are based on ISO 14155. (Including hardware and instrumentation), complications, and revisions.

STUDY SCHEDULE

Visit Type	Time point
Pre-Operative	-90 to 0 days
Operative Data & Discharge	Day 0 (+ up to 9 days)
6-Week Follow-Up	Day 42 ± 14

6-Month Follow-Up*	Day 185 ± 14
12-Month Follow-Up	Day 365 ± 30

* The 6 month visit may be conducted remotely

3.CONTENTS

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3.4 List of Abbreviations/Acronyms and Definitions

Abbreviation/Acronym	Definition
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
ACL	Anterior Cruciate Ligament
A/P	Antero-posterior
AVN	Avascular Necrosis
CAS	Computer-assisted navigation systems
CE	Conformité Européene
CI	Confidence Interval
CORI Robotics	REAL INTELLIGENCE™ CORI™
eCRF	Electronic Case Report Form(s)
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency(ies)
FAS	Full Analysis Set Population
FDA	Food and Drug Administration
FJS	Forgotten Joint Score
FU	Follow-Up
GCP	Good Clinical Practice
GDPR	EU Global Data Protection Regulation
HIPAA	Health Information Portability Accountability Act
HRQoL	Health Related Quality of Life
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

L	Lateral
LCL	Lateral Collateral Ligament
LOCF	Last Observation Carried Forward
MCL	Medial Collateral Ligament
NA or N/A	Not Applicable
N (or n)	Total Sample Size (or subgroup sample size)
NAVIO	NAVIO™ Surgical System
NMPA	National Medical Products Administration
OA	Osteoarthritis
OKS	Oxford Knee Score
OR	Operating room
PCL	Posterior Cruciate Ligament
PI	Principal Investigator
PMA	Pre-Market Authorization
PP	Per-protocol Population
PSI	Patient specific instrumentation
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
S+N	insert sponsor as per front page
SADE	Serious Adverse Device Effect(s)
SAE	Serious Adverse Event(s)
SAF	Safety population
SAP	Statistical Analysis Plan
TKA	Total Knee Arthroplasty
UKA	Unicondylar Knee Arthroplasty
UL	Upper Limit
USADE	Unanticipated Serious Adverse Device Effect(s)

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].

As of 2010, there were approximately 250 million people globally with osteoarthritis of the knee joint (3.6% of the global population) [6]. The prevalence was higher in females than in males [6]. 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]. Technical outcomes for TKA are excellent, with favorable postoperative health-related quality of life [12]. Also, survivorship of primary knee replacements is excellent with reported survivorship of 82.3% at 25 years [13]. TKA has traditionally been indicated in the elderly population with relatively sedentary lifestyles, but more active, younger patients (<55) are receiving TKA due to the desire for a pain-free, active lifestyle with the demand projected to continue to increase for this group. A recent systematic review has shown that functional outcomes are similar in this population compared to elderly patients with no increase in the burden of revision [14].

Unicondylar knee arthroplasty (UKA) is another conservative surgical treatment for patients with OA or AVN that only affects a single compartment of the knee [15, 16]. In 2018, 11% of all knee arthroplasties in the United Kingdom were compartmental knee arthroplasties (UKA) [17].

In the United States, it is estimated that 600,000 primary TKAs and 45,000 primary UKAs are performed each year, and the amount of procedures is expected to annually increase by 10% [18, 19]. The escalating prevalence of end-stage OA places an increased burden on healthcare providers, especially on less experienced surgeons and facilities that perform low numbers of arthroplasties [20, 21]. Lower volume hospitals (<25 procedures/year) report higher revision rates and more complications by 5 to 8 years compared to high volume hospitals (>200 procedures/years) [21, 22]. Therefore, technology or techniques that could improve outcomes and reduce the risk of revision are becoming increasingly important.

Surgical factors that must be considered in knee arthroplasty include lower leg alignment, soft tissue balancing, maintenance of the joint line, and component size and fixation [23]. Malalignment of components in any anatomical plane can cause major complications including aseptic loosening, instability, poor function, polyethylene wear, and pain [23-25]. Additionally, implant malposition and malalignment of the joint can result in failure of the prosthesis [26]. When not aligned within a narrow tolerance of ≤3° of the mechanical axis, poor functional outcomes, decreased implant survivorship, increased wear, and early failure from component loosening may occur [27].

Evidence has shown that neutral mechanical alignment provides optimal outcomes in knee arthroplasty, which is achieved with conventional alignment guides in approximately 75% of TKA cases [28].

For partial knee procedures, approximately 30-60% of UKAs have been reported to be malaligned using conventional manual instruments [29]. The importance of alignment can be demonstrated by observing higher revision rates of UKA attributed to malposition or malalignment of partial knees [29, 30] while roughly 25% of TKAs have been revised for instability or malalignment [31].

As an alternative to mechanical alignment, kinematic alignment technique for knee arthroplasty aims to restore the individual knee anatomy and ligament tension, to restore native knee kinematics [32]. Kinematic alignment restores the obliquity and level of the joint line anatomically so the femoral component is slightly more valgus (1° to 2°) and the tibial component is slightly more varus (1° to 2°) than mechanically aligned components.

A significant innovation in knee arthroplasty has been the introduction of computer navigation and robotic-assisted surgery. One such technology is the CORI Robotics. This system is a semi-autonomous image-free system. During the surgery, the surgeon maps the condylar landmarks and determines alignment indices to define the volume and orientation of bone to be removed. The tools to remove the bone and place the implants are controlled and manipulated by the surgeon with the guidance of a 3-dimensional digital map of the surgical surface.

Comparisons of robotic systems to conventional instruments have demonstrated that robotic platforms produce fewer positioning errors in both UKA and TKA [33-35]. When used in medial or lateral UKA procedures, robotics reported short learning curves, increased accuracy in

posterior tibial slope, and coronal tibial alignment in comparison to other alignment methods [36-38].

A summary of known and potential risks and benefits to humans of CORI Robotics can be found in the Instructions for Use (IFU).

4.2 Literature Summary

A thorough analysis of the literature was performed, and publications were identified that contained clinical outcomes, accuracy measurements, or safety information pertaining to the Robotic Knee Surgical Systems.

Use of the Robotic Knee Surgical Systems was reported in 7 publications with 1 being a prospective study and the remaining 6 being retrospective studies shown in Table 4 1. Three (3) of the studies solely reported on outcomes of the Robotic Knee Surgical Systems, three (3) compared the Robotic Knee Surgical Systems to conventional instruments, and one (1) study compared the Robotic Knee Surgical Systems to conventional instruments, patient specific instrumentation (PSI), and computer-assisted navigation (CAS) systems. All of the studies were for the NAVIO™ Surgical System and reported outcomes for UKA. The data provided in these publications is also applicable to the equivalent CORI Robotics.

Table 4-1 Demographic Information for the Robotic Knee Surgical Systems

Primary Author	Year	Robotic System	Indication	Joints (n)	Male (%)	Age, mean±SD (range)	Follow-up, mean±SD
Batailler [39]	2019	NAVIO[1]	UKA	80	33.8	69 ± 9.6 (49-87)	1.64 ± 0.75 years
Battenberg [40]	2019	NAVIO[1]	UKA	128	57.8	64.7 ± 9.6 (45-92)	2.3 years
Canetti [41]	2018	NAVIO[1]	UKA	11	18.0	66.5 ± 6.8 (57-79)	2.87 ± 0.88 years
Gregori [42]	2016	NAVIO[1]	UKA	92	-	-	Periop
Herry [43]	2017	NAVIO[1]	UKA	40	32.5	69 ± 9.6 (49-87)	Periop
Vega Parra [44]	2017	NAVIO[1]	UKA	47	51.0	67 (45-77)	1 years
Sephton [45]	2019	NAVIO[1]	UKA	67	49.0	68 ± 10	Periop
			Total	414	49.0%A (33.8-57.8)	66.8A (45-92)	1.14 years (Periop-2.87)

[1] NAVIO™ Surgical System

4.2.1 Demographic Information

A total of 414 joints were reported in the reviewed literature. Herry et al.[43] and Canetti et al.[41] likely shared the same patient population as Batailler et al.[39] Therefore, these joints were not included in the total, but these publications were not excluded due to different outcomes being reported among the studies. The Robotic Knee Surgical Systems are used intraoperatively to assist with implantation of knee prostheses, and studies report on a combination of intraoperative alignment parameters, clinical outcomes, and safety information. Three (3) studies provided early postoperative follow-up between the perioperative period and one year post-operative time point. Four (4) additional studies reported follow-up of one year or longer, two of which reported outcomes after 2 years of follow-up. The gender of the patients was almost evenly distributed, as men comprised 49% of the total population from all 7 publications. The age of patients undergoing UKA with the Robotic Knee Surgical Systems ranged from 45 to 92 years with an average age of 66.8 years for the total patient population from all 7 publications.

4.2.2 Clinical Outcome

Outcome measures were evaluated in three publications with Knee Society Score (KSS), satisfaction rate, return to sport, Lysholm scale, Forgotten Joint score (FJS), University of California, Los Angeles (UCLA) activity scale, Knee injury and Osteoarthritis Outcome Score (KOOS) and Knee Society Function Score (KSFS) being reported.

KSS, KSFS, and satisfaction rates were the most commonly employed outcome measures, being reported by both Batailler et al.[39] and Canetti et al.[41].These studies reported KSS and KSFS scores ranging from 92.6 to 96.4 and 90 to 97.2, respectively, indicating excellent functional outcomes. Satisfaction was scored on a scale from 1-5 with values corresponding with feeling disappointed to very satisfied. The percentages reported are the number of patients that indicated they were very satisfied with their procedure; this does not include patients that indicated they were just satisfied. Other outcome scores were reported in a single study, and none of these outcomes evidenced reduced function.

Batailler et al.[39] and Canetti et al.[41] compared patients operated on with the NAVIO™ Surgical System to patients who were operated on using conventional instruments. For KSFS and satisfaction rate, no statistically significant differences were observed between the two groups. However, Canetti et al.[41] observed a statistically significant increase in KSS and quicker return to sport for the NAVIO™ Surgical System. As the KSS difference was not observed in the larger cohort of Batailler et al.[39], the observed difference may be due to the smaller sample size. The percentage of patients returning to sports, UCLA, Lysholm scale, and FJS were not statistically significant between the two cohorts.

Overall, patients undergoing knee procedures with the Robotic Knee Surgical Systems showed improved KSS, KSFS, KOOS, and UCLA scores compared to pre-operative values.

4.2.3 Mechanical alignment Accuracy

The Robotic Knee Surgical Systems are intended to assist in planning and executing a procedure involving bone preparation for UKA procedures. Publications have provided accuracy measurements for the Robotic Knee Surgical Systems themselves and compared to conventional instruments. Three (3) publications investigated alignment accuracy in various planes, the incidence of outliers, and restitution of the joint line [39, 42, 43].

The reviewed publications indicate that the Robotic Knee Surgical Systems can produce the desired mechanical axis, hip knee ankle angle, coronal femoral angle, coronal tibial angle, tibial slope, and joint line deviation in the majority of cases. Outliers were reported for most of the angular alignment parameters, and only one study indicated a rate higher than 15% [39]. This increased outlier rate is likely due to the decreased tolerance imposed by the authors as outliers were defined as being within 2° of the desired value compared to the standard 3°.

Batailler et al.[39] and Herry et al.[43] compared alignment with the NAVIO™ Surgical System to conventional instrumentation. Statistically significant differences were not observed between the hip knee ankle angle or tibial slope for medial or lateral UKAs. However, there were statistically fewer outliers for the NAVIO™ Surgical System in the hip knee ankle angle for medial and lateral UKA, the tibial slope for medial UKA, and the coronal tibial angle. In addition, the joint line was significantly less distalized when the NAVIO™ Surgical System was used.

Using the Robotic Knee Surgical Systems results in a knee prosthesis that is well aligned and implanted according to the surgical plan. This is supported by satisfactory angular outcomes in the mean mechanical axis, hip knee ankle angle, coronal femoral angle, coronal tibial angle, and tibial slope. In addition, the joint line was less distalized compared to when conventional instrumentation was utilized.

4.2.4 Adverse Events & Complications

Complications related to the surgery, revision of the implant, and general complications were reported in the 7 included publications. Overall, the revision rate for prostheses implanted using the Robotic Knee Surgical Systems was 1.2% (5/414 procedures). Revisions were due to aseptic loosening without implant malpositioning (3, 0.7%) and unexplained pain (2, 0.5%). Additional reoperations included three (3) arthroscopic partial lateral meniscectomies, two (2) arthroscopic arthrolyses, and one (1) arthrotomy and lavage. Batailler et al.[39] noted that complications that affect robotic-assisted techniques (e.g. pin-site infections, broken pins, or fractures at the pin site) did not occur in their cohort.

4.2.5 Conclusion

Using the Robotic Knee Surgical Systems results in a knee prosthesis that is implanted according to the patient specific surgical plan. This is evidenced by satisfactory angular outcomes and restitution of the joint line. In addition, patients undergoing these procedures with the Robotic Knee Surgical Systems showed improved outcomes scores compared to pre-operative values. The clinical outcomes, alignment accuracy, and adverse events for the Robotic Knee Surgical Systems reported in the literature are similar to those reported for comparable devices.

4.3 Study Purpose

This is a prospective, multi-center study to demonstrate the safety and effectiveness of the CORI Robotics to meet the post-market clinical follow-up requirement in Europe, UK, India and the US. This is a post-market study in all countries involved. In addition, the study may support regulatory approval by the National Medical Products Administration (NMPA) in China.

Study hypotheses are that the CORI surgical system will achieve post-operative leg alignment (± 3°), and an improvement in patient-reported outcome measures. This primary endpoint is aligned to the primary study objective of evaluating the CORI surgical system for UKA and TKA procedures in achieving post-operative leg alignment. Accuracy and alignment are two key variables in successful UKA and TKA procedures. These measures have been previously evaluated with the predicate NAVIO surgical system. The primary endpoint will support the continued evaluation of these variables for the CORI surgical system.

4.4Safety Considerations

Representative language of the indications of use, contraindications and potential adverse effects of CORI Robotics can be found in the IFU.

4.4.1 Intended Use

CORI Robotics is intended to assist the surgeon in providing software-defined spatial boundaries for orientation and reference information to anatomical structures during orthopedic procedures.

4.4.2 Indications

CORI Robotics is indicated for use in surgical knee procedures, in which the use of stereotactic surgery may be appropriate, and where reference to rigid anatomical bony structures can be determined. These procedures include unicondylar knee replacement (UKR) and total knee arthroplasty (TKA). CORI Robotics is indicated for use with cemented implants only.

4.4.3 Contraindications

CORI Robotics is not intended to be used on children, pregnant women, patients who have mental or neuromuscular disorders that do not allow control of the knee joint, or any other patients contraindicated for knee replacement.

4.4.4 Warnings and Precautions

The CORI Robotics user's manual (Document ID: 500230, REAL INTELLIGENCE™ CORI™ for Knee Arthroplasty) states the following warnings and cautions:

- CORI Robotics is a surgical tool designed to provide assistance to the surgeon; it is not a substitute for the surgeon's experience and skill. The surgeon is responsible for implant planning and the conduct of the surgery during which CORI Robotics is being used.
- CORI Robotics and accessories should be used only by, or under the supervision of, a qualified surgeon or qualified member of his or her staff who is familiar with this document and has received training from Smith & Nephew.
- Use of equipment not specifically designated in this manual as compatible with CORI Robotics may result in the system not functioning properly, leading to patient or user injury.
- Refer servicing only to trained service personnel. Equipment damage, personal injury, or death may result if CORI Robotics is not serviced properly.
- To avoid risk of electrical shock, only connect the CORI Robotics Cart to a supply main with protective earth.
- Modification of CORI Robotics can cause the system to malfunction and could result in user and/or patient injury.
- Connecting electrical equipment to the multiple socket output effectively leads to creating a Medical Equipment System, and could result in a reduced level of safety.
- The transformer outlet is only to be used for CORI Robotics components. Do not connect any other device or improper extension cord to the transformer (max. load 600 VA) outlet. Failure to comply with this warning may result in shock hazard or product damage.
- Additional equipment connected to medical electrical equipment must comply with the respective IEC or ISO standards. All configurations shall comply with the requirements for medical electrical systems (see IEC 60601-1). Anyone connecting additional equipment to medical electrical equipment configures a medical system and is therefore responsible that the system complies with the requirements for medical electrical systems. Attention is drawn to the fact that local laws take priority over the above mentioned requirements. If in doubt, contact a qualified Biomedical technician or your local Smith & Nephew representative.

- Any person who connects external equipment to signal input and signal output ports or other connectors has formed a system and is therefore responsible for the system to comply with the requirements of IEC 60601-1. If in doubt, contact a qualified Biomedical technician or your local Smith & Nephew representative.
- Only USB-powered devices, such as USB flash drives, should be connected to CORI USB ports. Any person that connects a self-powered USB device has formed a medical system and is therefore responsible for the system to comply with the requirements of IEC 60601-1. If in doubt, contact a qualified Biomedical technician or your local Smith & Nephew representative.

4.4.5 Environments of Use

CORI Robotics is intended to be used by trained medical professionals in a hospital or clinical setting equivalent to an orthopedic surgery suite. The CORI Robotics Instruments will be used in a sterile environment and must be sterilized prior to use.

4.4.6 Anticipated Risks / Adverse Effects

As with any surgical procedure, there is risk involved. Potential complications accompanying surgery may occur, including allergic reaction (anaphylactic and minor), infection, mild to serious physical injury, localized static shock, delay in the operation, surgical site nerve injury, vascular injuries of the lower extremity, soft tissue damage, major bone gouging at the surgical site, bone fracture, immature implant failure, unstable knee joint, limited or restricted knee range of motion, major blunt impact injury, unintended laceration/puncture wound, and osteonecrosis.

As this is a post-market study and the device is used according to the IFU, the use of CORI Robotics in this study introduces no additional potential risks to the study participant.

4.4.7 Safety Data Collection

All adverse device effects or device deficiencies will be categorised and reported as instructed in Section 12, Adverse Events and Device Deficiencies. During causality assessment activity (assessment of Related vs Unrelated) and expectancy assessment (assessment of Unanticipated vs Anticipated) clinical judgement shall be used and relevant documents, such as the IFU shall be consulted, as foreseeable serious adverse events and the potential risks are summarized there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.

5.OBJECTIVE(S)

To evaluate the safety and effectiveness of REAL INTELLIGENCE™ CORI™ in UKA and TKA procedures.

5.1 Primary Objective

The primary objective of this study is to evaluate the use of CORI Robotics in UKA and TKA procedures in achieving post-operative leg alignment.

5.2 Secondary Objective(s)

The secondary objective of this study is to assess the safety and performance of the CORI Robotics up to 12 months after surgery.

5.3 Other Objective(s)

Other objectives are to determine the Robotics System time and cutting time of the robotic drill of UKA and TKA procedures with the CORI Robotics.

5.4 Claims

No claims to be confirmed by this investigation.

6.INVESTIGATIONAL PRODUCT(S)

6.1Identification

6.1.1 Investigational Product

The CORI Robotics is a computer-assisted orthopedic surgical navigation and burring system. It is designed to aid surgeons in planning and executing a procedure involving bone preparation for unicondylar knee arthroplasty (UKA) and total knee arthroplasty (TKA) procedures.

For the purposes of this study, the CORI Robotics is currently available for the use of the following S+N implant Systems:

Table 6-1 S+N Implant Systems available with CORI Robotics

Implant System	Manufacturer	Region
Journey II Unicompartmental Knee System	Smith+Nephew	India, Germany, United Kingdom, USA
Journey Uni	Smith+Nephew	India, Germany, United Kingdom, USA
STRIDE Unicondylar Knee System*	Smith+Nephew	USA
ZUK Select Knee System*	Smith+Nephew	USA
JOURNEY II Total Knee Systems	Smith+Nephew	India, Germany, United Kingdom, USA
LEGION Hinge Knee System	Smith+Nephew	India, Germany, United Kingdom, USA
GENESIS II Total Knee System	Smith+Nephew	India, Germany, United Kingdom, USA
ANTHEM Total Knee System	Smith+Nephew	India, Germany, United Kingdom, USA

*Only available in the USA.

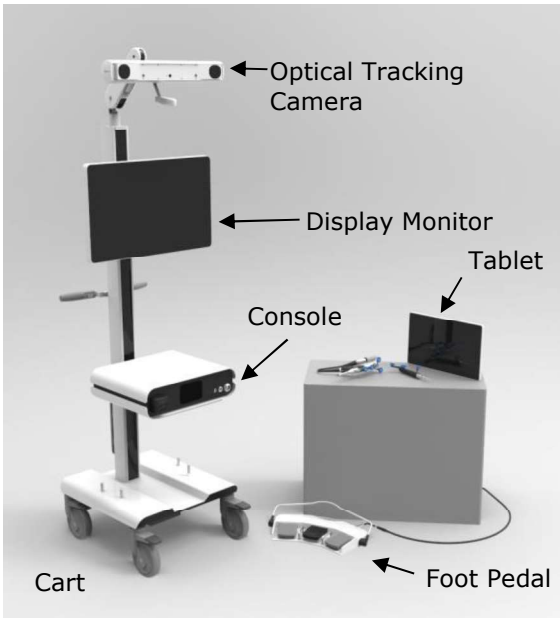
The CORI Robotics is comprised of a console control unit, optical tracking camera, primary and secondary input displays (tablet and optional display monitor), instrument trays and foot pedal (Figure 6-1). The CORI Robotics software consists of a patient and user management module, a surgical planner, and an intra-operative cutting module. The system uses the tracked position of the surgical bur to control its cutting engagement to the bone that is intended to be removed. This cutting control is based on the bur's proximity to the planned target surface of the bone.

The CORI Robotics incorporates a detailed user interface that provides procedure setup, tracking status, visual indicators, and real-time cutting progress during the procedure. The system uses the tracked position of the surgical bur to control its cutting engagement to the bone that is intended to be removed. The cutting control is based on the bur's proximity to the planned target surface of the bone. The CORI Robotics software controls the cutting engagement of the surgical bur based on its proximity to the planned target surface. The cutting control is achieved with two modes:

- Exposure control adjusts the bur's exposure with respect to a guard. If the surgeon encroaches on a portion of bone that is not to be cut, the CORI Robotics retracts the bur inside the guard, disabling cutting.
- Speed control regulates the signal going to the drill motor controller itself and limits the speed of the drill if the target surface is approached. This mode of operation is useful in shaping surfaces of the condyle as well as placing post holes and fixation features for femoral and tibial cut guides.

The surgeon can disable both controls and operate the CORI robotic drill as a standard navigated surgical drill.

Figure 6-1 CORI Robotics



Instrument Tray

- **Console**: It houses the robotic drill tool control, power management, video and audio distribution, central processing unit, and irrigation pump/control.
- **Optical Tracking Camera**: It is used to determine the position of the surgical bur tip and point probe relative to the position of the tibia and femur tracker frames. The position is determined using reflective markers affixed to the robotic drill, point probe, and tibia and femur frames.
- **Foot Pedal**: The left foot pedal allows variable input for robotic drill speed control and provides navigation or confirmation action in certain situations. The right pedal and small circular buttons are used to navigate forward and backward in the workflow and dismiss error messages.
- **Tablet**: The wired display monitor provides a touchscreen interface for the user to interact with the system.
- **Display Monitor**: It provides duplicate display and control of the system user interface.
- **Cart**: It provides a location for the system console, mounting for the optical tracking camera and display monitor, and storage for the foot pedal, tablet, and power cords.
- **CORI Instrument Trays UKA & TKA**: There are two instrument trays, one for UKA and for TKA procedures. Both CORI instrument trays contain reusable, re-sterilizable tools to assist in surgical site preparation, implant placement planning, and bone removal. The tray is comprised of two levels.

The CORI Robotics also includes specific reusable instruments as shown in Figure 6-2.

Figure 6-2 CORI Robotic System Reusable Instruments

CORI Robotic Drill

Point Probe

Femur & Tibia Trackers

Checkpoint Pins

Bone Screw

- **CORI Robotic Drill**: Controls the position and speed of the bur. It is intended for 5 uses and is able to be autoclaved, auto washed, and disinfected.
- **Point Probe**: Tracked instrument used in robotic drill calibration, and bone registration, checkpoint verification.
- **Femur & Tibia Trackers**: Rigid arrays placed on the femur and tibia to track the relative position of bones to point probe and robotic drill tools using reflective markers.
- **Checkpoint Pins**: placed in femur and tibia and checked periodically with the point probe to verify that the tibia and femur tracking arrays have not moved during the procedure.

A full list of the components of the CORI Robotics can be found in Section 22.3 Equipment and Special Instructions.

The CORI Robotics, as well as the single use components, are manufactured by Smith+Nephew, Blue Belt Technologies, 2905 Northwest Blvd. Suite 40, Plymouth, MN 55441, USA

The indications of the compatible S+N Knee Implant Systems can be found below.

Journey Uni & Journey II Uni - Unicompartmental Knee Systems

Unicompartmental knee implants are indicated for restoring either compartment of a knee that has been affected by the following:

- Noninflammatory degenerative joint disease including osteoarthritis, traumatic arthritis, or avascular necrosis;
- Correction of functional deformity;
- Revision procedures where other treatments or devices have failed; and
- Treatment of fractures that are unmanageable using other techniques.
- Unicompartmental knee implants are single use only and are intended for implantation only with bone cement. HA coated unicompartmental knee implants are available outside the US for use without bone cement.

ZUK Unicompartmental Knee

The ZUK system is designed for the surface reconstruction of individual femoral/tibial condyles. Use of this device does not preclude subsequent reconstructive surgery with a stabilizing type device or a total knee replacement.

Indications for Use of the ZUK Unicompartmental Knee are listed below:

- This device is indicated for patients with:
- Painful and/or disabling knee joints due to osteoarthritis or traumatic arthritis.
- Previous tibial condyle or plateau fractures with loss of anatomy or function
- Varus or valgus deformities.
- Revision of previous arthroplasty procedures.
- This device is indicated for cemented use only.
- The ZUK Unicompartmental Knee System is designed for use when load bearing ROM is expected to be less than or equal to 155 degrees.

STRIDE Unicondylar Knee System

The STRIDE Unicondylar Knee System is a unicompartmental prosthetic implant that resurfaces one femoral condyle and one side of the tibial plateau. The femoral component is made of cobalt chrome and the tibial component is composed of a titanium tibial tray with a ultra-high molecular weight polyethylene insert that snaps into place. The device is non-constrained; the articulating surface of the lntra-high molecular weight polyethylene insert is flat and joint stability is maintained by ligaments and other soft tissue surrounding the knee.

The STRIDE Unicondylar Knee Systems are indicated for patients with:

- Painful and/or disabling knee joints due to osteoarthritis or traumatic arthritis.
- Previous tibial condyle or plateau fractures with loss of anatomy or function.
- Varus or valgus deformities.
- Revision of previous arthroplasty procedures.
- These devices are indicated for cemented use only.

Smith+Nephew Total Knee Replacement Systems: JOURNEY II Knee Systems, LEGION Hinge Knee System, and GENESIS II Total Knee System

Smith & Nephew Knee Systems consist of femoral components, tibial components, patellar components, and accessories. Femoral components are manufactured from cobalt chromium alloy or OXINIUM™ oxidized zirconium. Tibial inserts and patella components are manufactured from ultra-high molecular weight polyethylene (UHMWPE) or cross-linked polyethylene (XLPE). Tibial bases are manufactured from titanium 6Al-4V alloy, or cobalt chromium (CoCr) alloy, or ultra-high molecular weight polyethylene (UHMWPE) (for all poly tibial bases). The component material for implantable devices is provided on the outside carton label.

Smith+Nephew Total Knee Replacement Systems are indicated for patients with:

- Rheumatoid arthritis.
- Post-traumatic arthritis, osteoarthritis, or degenerative arthritis.
- Failed osteotomies, unicompartmental replacement, or total knee replacement.
- Posterior stabilized knee systems are designed for use in patients in primary and revision surgery, where the anterior and posterior cruciate ligaments are incompetent and the collateral ligaments remain intact.
- Constrained knee systems are designed for use in patients in primary and revision surgery, where the posterior cruciate ligament and one or both of the collateral ligaments (i.e. medial collateral and/or lateral collateral ligament) are incompetent.
- Hinge knee systems are designed for use in patients in primary and revision surgery, where the posterior cruciate ligament and one or both of the collateral ligaments (i.e. medial collateral and/or lateral collateral ligament) are absent or incompetent.

ANTHEM Total Knee System

The Smith & Nephew ANTHEM Total Knee System consists of femoral components and tibial components. Both the femoral and tibial components are to be used with bone cement.

Anthem Total Knee System is indicated for patients with:

- Rheumatoid arthritis.
- Post-traumatic arthritis, osteoarthritis, or degenerative arthritis.
- Failed osteotomies, unicompartmental replacement, or total knee replacement.
- Posterior stabilized knee systems are designed for use in patients in primary and revision surgery, where the anterior and posterior cruciate ligaments are incompetent and the collateral ligaments remain intact.

For this study only the CORI Robotics is considered the IP and not the implant systems used.

All surgeons using CORI Robotics will have previously been fully trained on the use of the system by S+N staff.

6.1.2 Comparator Treatment<s>

No comparator products are used.

6.1.3 Ancillary Product

No ancillary products are to be provided for this study.

6.2 Product Use

The CORI Robotics has a user manual (Document ID: 500230, REAL INTELLIGENCE™ CORI™ for Knee Arthroplasty). The purpose of this user manual is to serve as the master reference

document for properly trained users in the function and operation of CORI Robotics and its accessories.

In addition, the following devices are packaged with an IFU to ensure that the device is used properly and for the intended purposes:

- IFU REAL INTELLIGENCE™ CORI™ Burs (Document ID: 500172)
- IFU REAL INTELLIGENCE™ CORI™ Flat Markers (Document ID: 500198)
- IFU REAL INTELLIGENCE™ CORI™ Tubing Set (Document ID: 500173)
- IFU REAL INTELLIGENCE™ CORI™ Instrumentation Tray (Document ID: 500229)

The list of reference documents can be found in Appendix 22.2 List of Instructions For Use & User Manuals.

It is the Investigator's responsibility to ensure adherence to the IFU. Sites that are familiar with the use of CORI Robotics / Robotic-assisted surgery systems will be selected so no additional training is required.

6.3Packaging and Labelling

Packaging and labeling are 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 of Investigational Product

All product components of the CORI Robotics System as well as the Smith+Nephew Knee Implant Systems are commercial products in Europe, UK, India and the United States and are being used as approved. Labeling is done as per the standard commercial packaging. No additional labelling will take place.

6.4 Product Accountability Procedures

This study is a post-market study in Europe, UK, India, and the United States. However, the sponsor may provide the study sites with the CORI Robotics System (Console, Optical Tracking Camera, Foot Pedal, Tablet, Display Monitor, Cart, CORI Instrument Trays UKA & TKA) as well as with reusable instrumentation (CORI Robotic Drill, Point Probe, Femur & Tibia Trackers, Checkpoint Pins). Therefore, the following product accountability procedures will be applied for CORI Robotics supplied to study sites.

In instances where CORI Robotics is supplied to site, the investigational site will maintain an inventory of the IP . The Sponsor or its designee will provide a log(s) to facilitate IP inventory control. The log will contain details of receipt, use, returns etc. of IP. All IP 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. As part of monitoring, the Study Monitor will check that site personnel are following the proper procedures for accountability and completing all necessary documentation.

No product accountability procedures will be applied for the S+N Knee Implant Systems as these are commercially available products. Nevertheless, the S+N Knee Implant System as well as the individual component reference and lot numbers (femoral component, tibial baseplate and insert) will be recorded in the eCRF.

Overall accountability for the use of the product is the responsibility of the Investigator or designated individual.

Following completion of enrolment all supplied CORI Robotics systems will be returned to S+N.

For details on the CORI Robotics System and reusable instrumentation please refer to Section 6.1.1 Investigational Product.

6.5 Surgical Technique

All study related procedures with the CORI Robotics must be performed according to the user manual (Document ID: 500230 CORI Robotics for Knee Arthroplasty) and according to the according to the surgical technique and IFU of the specific Smith+Nephew Implant System.

- IFU Smith+Nephew Knee Systems (Document ID: 81090287)
- IFU ZUK (Document ID: 81093274)
- IFU STRIDE (Document ID: 50030)
- IFU ANTHEM Total Knee System (Document ID: 81105696)

Surgeons selected to participate in this study will be familiar with the CORI Robotics and have written evidence of training and expertise in the study procedure. If deemed necessary, 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. Anonymized CORI Robotics Case Reports will be collected for these pre-study cases as proof of experience. If no pre-study cases are completed the case log of the first study case will be collected and analysed as soon as possible following the surgery to ensure the additional data required for the study has been collected.

7.SUBJECT ENROLLMENT AND WITHDRAWAL

7.1Subject Population

A total of 80 subjects will be enrolled in the study in up to 8 sites in Europe, UK, India and the United States.

- 40 subjects will be enrolled for UKA with the use of the CORI Robotics
- 40 subjects will be enrolled for primary TKA with the use of the CORI Robotics

For those subjects, the clinician has decided that the best treatment for the subject is a UKA or TKA facilitated with robotic assisted surgery as a routine medical care. This decision will be made irrespectively of study participation.

The subject will then consent to the study specific treatment with the CORI Robotics System. In case of non-participation, the patient can still receive a robotic assisted UKA or TKA with CORI Robotics or an alternative robotic system (e.g. NAVIO™ Surgical System).It is expected that all subjects will be enrolled within 24 months.

Eligibility criteria are specified to ensure that the subject population of the study represents the target population of the IP.

7.1.1 Vulnerable subjects

No vulnerable subjects will be included in the study.

7.2 Inclusion Criteria

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

1. The subject's treating clinician has decided that REAL INTELLIGENCE™ CORI™ and a compatible Smith+Nephew Knee Implant System is the best treatment for the subject's UKA or TKA and the subject has agreed to the treatment.
2. Subject requires a cemented UKA or TKA as a primary indication that meets either criterion A or B.
    A. Subject requires a cemented UKA as a primary indication due to any of the following conditions:
        1. Non-inflammatory degenerative joint disease, including osteoarthritis
        2. Avascular necrosis
        3. Requires correction of functional deformity
        4. Requires treatment of fractures that were unmanageable using other techniques
    B. Subject requires a cemented TKA as a primary indication due to any of the following condition:
        1. Degenerative joint disease, including osteoarthritis
        2. Rheumatoid arthritis
        3. Avascular necrosis
        4. Requires correction of functional deformity
        5. Requires treatment of fractures that were unmanageable using other techniques
3. Subject is of legal age to consent and considered skeletally mature (≥ 18 years of age at the time of surgery)
4. Subject agrees to consent to and to follow the study visit schedule (as defined in the study protocol and informed consent form), by signing the Ethical Committee (EC) or Institutional Review Board (IRB) approved informed consent form.
5. Subject plans to be available through one (1) year postoperative follow-up.
6. Routine radiographic assessment is possible.
7. Subject able to follow instructions and deemed capable of completing all study questionnaires.

7.3 Exclusion Criteria

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

1.	Subject receives a CORI Robotics UKA or TKA on the index joint as a revision for a previously failed surgery, or need for complex implants, or any other implant than a standard UKA or TKA (e.g. stems, augments, or custom made devices).
2.	Subject has been diagnosed with post-traumatic arthritis.
3.	Subject receives bilateral UKA or TKA.
4.	Subject does not understand the language used in the Informed Consent Form.
5.	Subject does not meet the indication or is contraindicated for UKA or TKA according to specific Smith+Nephew knee system's Instructions For Use (IFU).
6.	Subject has active infection or sepsis (treated or untreated).
7.	Subject is morbidly obese with a body mass index (BMI) greater than 40.
8.	Subject is pregnant or breast feeding at the time of surgery.
9.	Subject, in the opinion of the Investigator, has advanced osteoarthritis or joint disease at the time of surgery and was better suited for an alternate procedure.
10.	Subject has a condition(s) that may interfere with the TKA or UKA survival or outcome (i.e., Paget's or Charcot's disease, vascular insufficiency, muscular atrophy, uncontrolled diabetes, moderate to severe renal insufficiency or neuromuscular disease, or an active, local infection).
11.	Subject in the opinion of the Investigator, has an emotional or neurological condition that would pre-empt their ability or willingness to participate in the study including mental illness, mental retardation, drug or alcohol abuse.
12.	Subject, in the opinion of the Investigator, has a neuromuscular disorder that prohibited control of the index joint.
13.	Subject is a prisoner or meets the definition of a Vulnerable Subject per ISO 14155 Section 3.55[1]

7.4 Screening

Investigators should consecutively screen all subjects presenting with degenerative joint disease of the knee, requiring correction of functional deformity, or treatment of fractures that were unmanageable using other techniques to determine whether they meet all inclusion and none of the exclusion criteria

[1] ISO 14155 Section 3.55 States: Vulnerable subject – Individuals who are unable to fully understand all aspects of the investigation that are relevant to the decision to participated, or who could be manipulated or unduly influenced as a result of compromised position, expectation of benefits or fear of retaliatory response.

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. All screening activities that occur prior to consent shall be referred to as pre-screening.

Part of the screening process will include documentation of women's childbearing potential. For women of childbearing potential, study sites will determine whether the subject is pregnant using their standard clinical practice.

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. Translations of informed consent documents will be available in the participating countries main language(s).

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.

The subject will have sufficient time to consider study participation and ensure all questions have been answered this will usually be at least 24 hours unless approved or documented local site Informed Consent procedures allow for this to be shorter. There is no required interval between the time of consent and the first study procedure being carried out.

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.

Due to the nature of completing Patient Reported Outcome during the study the subject must be able to provide consent. A Legally Authorized Representative signature is not allowed in this study.

ICFs will comply with the Health Information Portability Accountability Act (HIPAA) regulations as well as the EU Global Data Protection Regulation (GDPR) and applicable national regulations and laws.

If new information becomes available during the course of the study that can significantly affect a subject's future health and medical care, Smith + Nephew will ensure that information shall be provided to the subject(s) affected in written form and if relevant, all affected subjects shall be asked to confirm their continuing consent in writing.

7.6 Enrollment

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 two (2) consecutive visits and does not return for a final visit, and study personnel is 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 having the study treatment at a date close to surgery or during surgery 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

Subjects withdrawn from having treatment will not be classed as being enrolled (section 7.6).

Subjects withdrawn from having treatment will be replaced and no further follow-up of the withdrawn subjects is required for the study.

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, took disallowed medications)
- Subject lost to follow-up (section 7.7)

- The Investigator or the Sponsor stop 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, the information will be recorded in the subject's source document and the electronic Case Report Form (eCRF), 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 unicondylar or total knee 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.

7.9Subject Reimbursement and Incentives

Subjects will be reimbursed for the costs of taking part in the study in compliance with local regulations. These costs will only cover study-specific activities or visits including time, travel, parking and inconvenience and will not cover activities or visits associated with the subject's standard clinical care. Payments to the subject will be proportionate to the time and expense involved in study participation and not so large as to unduly encourage the subjects to participate or affect the subject's ability to withdraw prematurely form the study. All arrangements for reimbursement payments to subjects will be approved by the IRB/IEC and/or local site authority as required.

8.STUDY DESIGN

8.1 Study Design

This study is a prospective, multi-center, non-randomized, non-blinded follow-up study to evaluate the use of CORI Robotics in UKA and TKA procedures in achieving post-operative leg alignment. Up to 8 sites will participate within Europe, UK, India and the US.

Subjects will be enrolled in one of two (2) groups based on medical indication and general practice at the site, as shown in Table 8-1. All subjects are treated with knee arthroplasty with the use of the CORI Robotics and a Smith+Nephew Knee Implant System based local regulatory status and medical indication and general practice at the site (see Table 6-1 S+N Implant Systems available with CORI Robotics for this study).

Table 8-1 Overview of Study Groups

Group	Surgical Technique	Knee Implant system	Number of Subjects
Primary UKA	CORI Robotics	Smith+Nephew UKA Implant System	40
Primary TKA	CORI Robotics	Smith+Nephew TKA Implant System	40

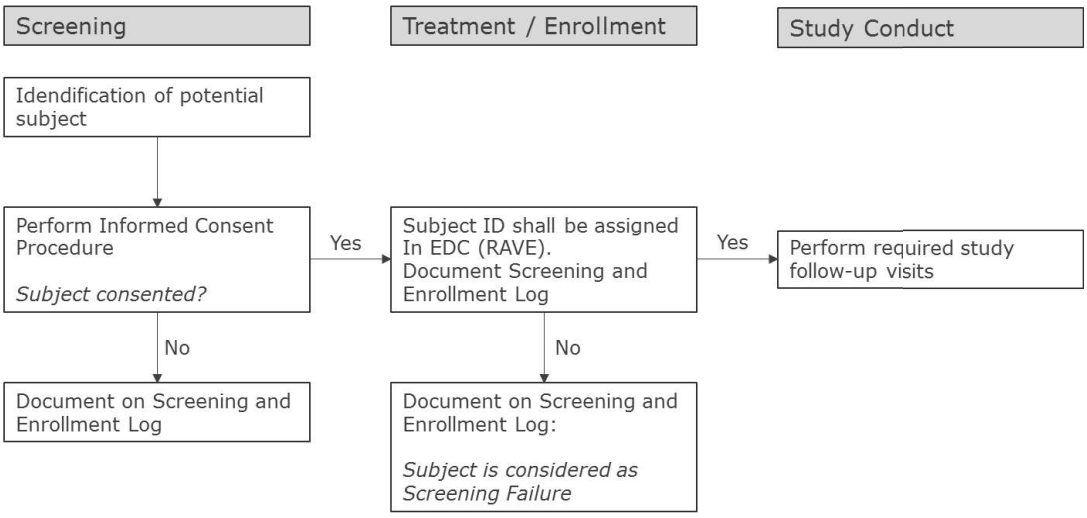
The study is expected to enroll all subjects within a 24 month timeframe. Subjects will be followed-up for a time period of 12 months after surgery.

This study is being conducted in parallel to 2 randomized-controlled studies in China titled: "A Prospective, Multi-center, randomized-controlled Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) procedure" (Protocol ID: CORI.2019.06) and "A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Effectiveness of the REAL INTELLIGENCE™ CORI™ in total knee arthroplasty (TKA) Procedure" (Protocol ID: CORI.2020.08). The study data may be combined for analysis to meet the requirements for regulatory approval of the CORI Robotics by the National Medical Products Administration (NMPA) in China. Further details are described in Section 10 Statistical Design and the Statistical Analysis Plan (SAP).

Figure 8-1 details the different steps of study conduct from screening to enrollment and follow-up.

Subjects may be assigned a subject ID, but then not enrolled in the study (e.g. did not receive the study device or decided not to participate in the study).

Figure 8-1 Study Flowchart



The study design meets the needs of the aforementioned regulatory requirements and has been powered based on recent analyses from the NAVIO Surgical System. This study is designed to demonstrate superiority in the proportion of TKAs post-operatively defined as mechanically aligned against the reference proportion of 73.4% (53). The proportion of mechanically aligned TKAs using the NAVIO™ Surgical System from a recent analysis was estimated to be 92.1% (54). If this assumption holds for this study, then the enrollment of 36 knees for each of the two planned study groups (i.e. the CORI Robotics UKA and CORI Robotics TKA) for a total of 72 knees will individually provide approximately 80% power to show that the lower limit of the two-sided 95% confidence interval for the proportion of mechanically aligned TKAs is greater than that obtained from literature. To account for up to a 10% attrition rate in knees enrolled, 40 knees in each group (80 knees combined, 40 UKA and 40 TKA) will be enrolled in the study.

8.2 Data Management

This study utilizes a validated, 21 CFR Part 11 compliant, electronic data capture system. Access to the electronic data capture system is controlled through Smith and Nephew procedures.

A Data Management Plan (DMP) is written according to Smith and Nephew procedures containing details of the data management process. The following is a brief description of the key points detailed in this plan.

8.2.1 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.

8.2.2 Retention Period

All eCRFs will be archived once the study is completed and will be 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.

8.3 Study Endpoints

8.3.1 Primary Endpoint

The primary endpoint of this study is defined as the evaluation of the proportion of subjects achieving post-operative leg alignment at 6 weeks post-surgery. Achieved leg alignment is defined as ± 3° from the subject's specific target.

This primary endpoint is aligned to the primary study objective of evaluating the CORI surgical system for UKA and TKA procedures in achieving post-operative leg alignment. Accuracy and alignment are two key variables in successful UKA and TKA procedures. These measures have been previously evaluated with the predicate NAVIO surgical system. The primary endpoint will support the continued evaluation of these variables for the CORI surgical system.

8.3.2 Secondary Endpoints

The following secondary endpoints have been defined for this study in order to evaluate the safety and performance of the CORI Robotics:

- Component Alignment 6 weeks post-surgery
- Radiographic assessment (Presence of radiolucent lines, osteolysis & implant migration) 12 months post-surgery
- 2011 Knee Society Score (KSS) at baseline, 6 weeks, 6 and 12 month post-surgery
- Oxford Knee Score (OKS) at baseline, 6 weeks, 6 and 12 month post-surgery
- Forgotten Joint Score (FJS) at 6 weeks, 6 and 12 month post-surgery

- Five-level EuroQol five-dimensional (EQ-5D-5L) VAS & index scores at baseline, 6 weeks, 6 and 12 month post-surgery

Secondary endpoints are aligned to the secondary study objectives of generating safety and performance evidence related to the use of the CORI surgical system. Assessing alignment, radiographic image assessment and patient-reported outcome measures (PROMS) are key variables in determining the success of UKA and TKA procedures. These endpoints have been previously evaluated with the predicate NAVIO surgical system and ongoing assessment of these secondary endpoints under this study will support safety and efficacy of these procedures performed with the CORI surgical system.

8.3.3 Other Endpoints

The following additional endpoints collected during surgery have been defined for this study:

- Leg alignment pre- and post-cementation
- Robotics System time as extracted from the Subject's CORI Robotics Case Report generated by the CORI Robotics Software.
- Cutting time of the robotic drill s extracted from the Subject's CORI Robotics Case Report, generated by the CORI Robotics Software.

8.3.4 Safety Endpoints

Safety endpoints include the collection of the following events:

- All adverse events (AEs) and complications occurring from the time of subject enrollment until study termination or study completion including intra-operative adverse events and complications.
- Device related re-intervention
- Device Deficiencies
- Knee implant revision rate

All AEs will be categorized in terms of seriousness and relatedness to the study device or to the surgical procedure (Adverse Events, Serious Adverse Events, Adverse Device Effects, Serious Adverse Device effects). All Serious Adverse Device Effects will be further categorized as Anticipated or Unanticipated. The definitions for each of these categories are based on ISO 14155. (Including hardware and instrumentation), complications, and revisions.

8.4 Methods Used to Minimize Bias and Maximize Validity

8.4.1 Multiple sites

Subjects will be enrolled at multiple sites, utilizing up to 8 sites in total for the study. This will reduce the effect of observer bias that might arise at any one investigational site as well as maximize the diversity of subjects treated.

8.4.2 Prospective Consecutive Enrolment

Consecutive enrollment will be utilized to enroll subjects who meet the inclusion/exclusion criteria.

8.4.3 Subject Attrition

The required sample size for the study includes adjustment for expected subject attrition.

8.4.4 Pre-specification of Statistical Analysis

The primary 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 as minimize any threats to external validity and yield clinically relevant estimates of effects and precision.

9.STUDY PROCEDURES

9.1Visits and Examinations

9.1.1 Summary

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

Table 9-1: Study Procedures by Visit

Schedule of events	**Pre-Operative Data** **-90 to 0 days**	**Operative Data & Discharge** **Day 0 (+ up to 9 days) [4]**	**6 weeks** **42 ± 14 days**	**6 months[5]** **185 ± 14 days**	**12 months** **365 ± 30 days**
Informed Consent	X				
Inclusion/Exclusion	X				
Demographics/ Medical History	X				
Concomitant Medication Update		X	X	X	X
Operative Data Collection		X			
Knee Implant Disposition		X			
CORI Robotics Case Report (Robotic System time & cutting time)		X			
Discharge Data Collection		X			
Leg alignment Long leg X-ray AP	X	(X)[1]	X		(X)[2]
Standard Lateral X-ray		(X)[1]	X		X
Standard A/P X-ray					X
KSS	X		X	X	X
OKS	X		X	X	X
FJS			X	X	X
EQ-5D-5L	X		X	X	X
Safety Assessment		X	X	X	X
End of Study/Exit			(X)[3]	(X)[3]	(X)[3]

[1] Post-operative standing weight bearing long leg X-rays (A/P & L) may be taken at discharge if standard of care.
[2] Only if standing weight bearing long leg A/P X-ray is taken as a standard of care at 12 months.
[3] Exit form to be completed at the point of withdrawal if the study is not completed.
[4] If any Pre-Operative data is collected on the day of surgery, it must be completed prior to the surgery occurring.
[5] The 6 month visit may be conducted remotely

9.1.2 Screening/Preoperative Visit (-90 to 0 days)

1.	Obtain written informed consent from the subject as detailed in Section 7.5. Any subject who signs an informed consent but fails to meet the entry criteria is considered to be a Screen Failure. Their demographic information must be captured in the appropriate electronic Case Report Form (eCRF) with the reason for screen failure specified. ----- **Do not proceed until consent has been obtained** -----
2.	Obtain demographic information and medical history, including information on all concomitant medications/therapies.
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.	Assign the subject a study number and instruct the subject on treatment procedures.
6.	Collect radiographic images of the affected knee for evaluation of leg alignment (Standing weight bearing A/P long leg X-ray) (x-rays can be taken within 6 months of the surgery date)
7.	Collect the KSS score objective measures (joint alignment, instability, motions & symptoms).
8.	Have the subject complete the KSS score subject questions.
9.	Have the subject complete the OKS patient-reported outcome measure
10.	Have the subject complete the EQ-5D-5L patient-reported outcome measure.
11.	Subjects will be instructed to return for the Operation Visit on a scheduled date.

9.1.3 Operation Visit & Discharge (Day 0 up to Day 9)

If any Pre-Operative data is collected on the day of surgery, it must be completed prior to the surgery occurring.

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.	Query subject regarding any changes in general health and the use of concomitant medications/therapies.
3.	Collect data on the surgical plan: Target Leg alignment as entered into the CORI Robotics.
4.	Perform surgery and collect intra-operative data on the appropriate eCRF. This includes but is not limited to the following information:

- Knee Implant Disposition (recording of tibial baseplate, insert and femoral component name, reference & lot/batch number)
- Surgical data (e.g. duration, blood loss, surgical approach)
- Collect pre- (with the trial implant in place) and post cementation alignment with the use of CORI Robotics.
- Collect the Subject's CORI Robotics Case Report, generated CORI Robotics Software (Robotics System time, cutting time)

5.	Complete discharge eCRF.
6.	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.
7.	Instruct the subject on proper postoperative care/procedures, including any contraindicated treatments/medication(s).
8.	Instruct the subject returning to the site for the next follow up visit 6 weeks (42 ± 14 days) after the surgery date.

9.1.4 Follow-up visits at 6 weeks (42 ± 14 days)

1.	Query subject regarding any changes in general health and the use of concomitant medications/therapies.
2.	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.
3.	Verify with the subject if any revision has occurred since the last visit. If any revision is observed or reported, it must be recorded as instructed in Section 12 - Adverse Events and Device Deficiencies.
4.	Collect the KSS score objective measures (joint alignment, instability, motions & symptoms).
5.	Have the subject complete the KSS score subject questions.
6.	Have the subject complete the OKS patient-reported outcome measure
7.	Have the subject complete the EQ-5D-5L patient-reported outcome measure.
8.	Have the subject complete the FJS patient-reported outcome measure.
9.	Collect the standing weight bearing long leg (A/P) and standard lateral (non-weight bearing) radiographic images of the affected knee. Review the images to complete the appropriate eCRF for leg alignment and component alignment.

10.	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 or make arrangements for delivery of the 6 month PROMs by courier to the subject to be completed remotely.

9.1.5 6 months (185 ± 14 days) after surgery (phone call if remote)

1.	Query subject regarding any changes in general health and the use of concomitant medications/therapies.
2.	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.
3.	Verify with the subject if any revision has occurred since the last visit. If any revision is observed or reported, it must be recorded as instructed in Section 12 - Adverse Events and Device Deficiencies.
4.	Collect the KSS score objective measures (joint alignment, instability, motions & symptoms) (if it is an on-site visit)
5.	Have the subject complete the KSS score subject questions.
6.	Have the subject complete the OKS patient-reported outcome measure
7.	Have the subject complete the EQ-5D-5L patient-reported outcome measure.
8.	Have the subject complete the FJS patient-reported outcome measure.
9.	If the visit was remote arrange for courier to return the completed PROMs to site.
10.	Instruct the subject on follow-up procedures, including returning to the site for the next follow-up visit 12 months (365 ± 30 days) after the surgery date.

9.1.6 Exit Visit 12 months (365 ± 30 days) after surgery

1.	Query subject regarding any changes in general health and the use of concomitant medications/therapies.
2.	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.
3.	Verify with the subject if any revision has occurred since the last visit. If any revision is observed or reported, it must be recorded as instructed in Section 12 - Adverse Events and Device Deficiencies.

4.	Collect standard A/P & lateral radiographic images of the affected knee. Review the images to complete the appropriate eCRF for standard radiographic evaluation (presence of radiolucent lines, osteolysis and implant migration).
5.	In case a standing log leg X-ray is taken as a standard of care, please complete the respective leg alignment eCRF (optional).
6.	Collect the KSS score objective measures (joint alignment, instability, motions & symptoms).
7.	Have the subject complete the KSS score subject questions.
8.	Have the subject complete the OKS patient-reported outcome measure
9.	Have the subject complete the EQ-5D-5L patient-reported outcome measure.
10.	Have the subject complete the FJS patient-reported outcome measure.
11.	Complete Exit Visit eCRF.

9.1.7 Unscheduled Visits

Unscheduled examinations related to the study knee may be conducted at the discretion of the Investigator with all obtained information recorded in the source documents and on the appropriate eCRF. If any adverse events or device deficiencies are observed or reported, they must be recorded as instructed in Section 12. - Adverse Events and Device Deficiencies. The subject should be scheduled to return for the next scheduled study visit within the acceptable time window.

9.1.8 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

9.1.8.1.1 Excluded Concomitant Medications

There are no restrictions on concomitant medications for this study.

9.1.8.1.2 Recording Concomitant Medications in CRF

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

Concomitant Therapies

9.1.8.1.3 Therapies Prohibited During the Study

There are no restrictions on concomitant therapies for this study.

9.1.8.1.4 Recording Concomitant Therapies in the CRF

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

9.1.9 Discontinued Subjects

Discontinued subjects are those who voluntarily discontinue participation, who are withdrawn for reasons of safety or use of prohibited concomitant treatments/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.

9.1.10 Subject Pregnancy

Women of child-bearing potential are not excluded from the study. However, 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 Leg Alignment

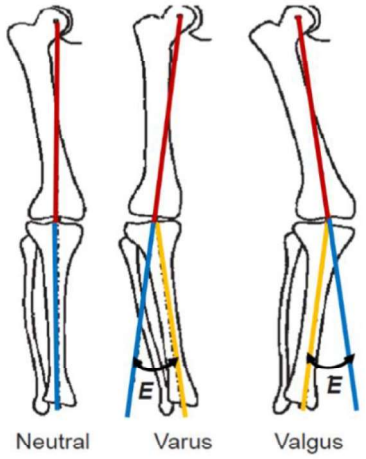
The leg alignment should be measured from an antero-posterior (A/P) view standing weight bearing full leg (‘long leg’) x-ray. The following axes shall be identified:

- Mechanical Axis of the femur: Axis from the center of the femoral head to the center of the distal femur.

- Mechanical Axis of the tibia: Axis from the center of the proximal to the center of the distal tibia.

The angular deviation from the neutral position (180°) shall be measured as shown as "E" in Figure 9-1. The angular deviation from the neutral position shall be recorded in the eCRF.

Figure 9-1 Leg alignment



Red: Mechanical Axis of Femur: Axis from the center of the femoral head to the center of the distal femur

Yellow: Mechanical Axis of Tibia: Axis from the center of the proximal to the center of the distal center of the tibia.

Blue: Neutral position axis (180°).

E: Deviation angle from the neutral position.

Pre-Operative Leg alignment

The pre-operative leg alignment evaluated from a standing weight bearing long leg A/P shall be recorded.

Target Leg alignment (Surgical Plan)

The operative plan for leg alignment as entered in the CORI Robotics shall be recorded in the eCRF for each subject. The planned leg alignment serves as the target for post-operative leg alignment. This may not be a neutral position.

Pre- & Post-Cementation Leg alignment

The pre-cementation leg alignment shall be recorded with the use of the CORI Robotics System (manual screenshot to be taken) with the trials implant is placed.

Once the final implant has been cemented the post-cementation leg alignment shall be recorded with the CORI Robotics System (manual screenshot to be taken).

Post-Operative Leg alignment

The leg alignment shall be assessed post-operatively and 6 weeks after surgery on standing weight bearing long leg A/P X-ray and lateral X-ray. Optionally, leg alignment can be assessed optionally at 12 months, in case a standing weight bearing long leg A/P X-ray is taken at 12 months.

Post-operative leg alignment is achieved when the deviation from the subject specific target does not exceed ±3 degrees.

All leg alignment measures will be added to the eCRF.

9.2.2 Component Alignment

Component alignment will be assessed on long leg standing A/P X-rays and standard non weight bearing lateral X-rays taken 6 weeks after surgery (or at discharge). The following angles will be evaluated on the X-rays and recorded in the eCRF:

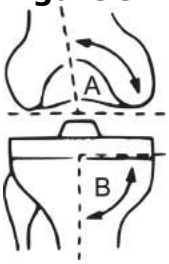
A/P View

Femoral A/P Angle: From the A/P radiograph, the femoral flexion angle is to be obtained using standard radiographic tools. Femoral flexion angle is defined as the angle formed between a line across the base of the femoral condyles and a line that is centered along the femoral canal

Tibial A/P Angle: From the A/P radiograph, the tibial angle denotes the angle formed on the medial side of the knee from intersecting lines parallel to the tibial base plate and a line drawn parallel to the tibial canal (Figure 9-2).

Total Valgus Angle: Is the sum of the femoral flexion angle and the tibial angle.

Figure 9-2 A/P View



A: Femoral A/P Angle

B: Tibial A/P Angle

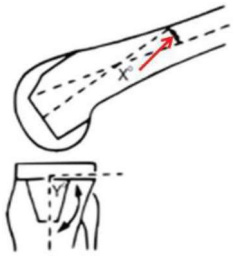
A+B: Total Valgus Angle

Lateral View

Femoral Flexion Angle: The lateral view femoral flexion angle is obtained from the intersection of a line from the center of the femoral implant to the top of the femur with a line through the femoral canal. The angle is measured on the proximal side of the intersection.

Tibial Lateral Angle: The lateral view tibial angle is the angle obtained from the intersection of a line drawn parallel to the bottom of the tibial base insert and a line through the center of the tibial base and the tibial canal (Figure 9-3).

Figure 9-3 Lateral View



X: Femoral Flexion Angle

Y: Tibial Lateral Angle

9.2.3 Standard Radiographic Evaluation

Standard radiographic evaluation on antero-posterior (A/P) and lateral (L) views shall be performed 12 months 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.

9.2.4 2011 Knee Society Score (KSS)

The 2011 Knee Society Score will be collected at the pre-operative visit and 6 weeks, 6- and 12-months after surgery.

The 2011 KSS is a validated tool that combines an objective physician-derived component with a subjective subject-derived component [46, 47]. The KSS consists of 36 questions and provides sub-scores across 4 dimensions as shown in Table 9-2.

Table 9-*2* Knee Society Score 2011

#	Sub-Score	# Questions	Range	Completion by
1	Objective Knee Score	7	0-100	Surgeon
2	Subject Satisfaction Score	5	0-40	Subject
3	Subject Expectation	3	3-15	Subject
4	Functional Knee Score	19	0-100	Subject

The Objective Knee Score is rated by the clinician and assesses a range of clinical outcomes: UKA/TKA 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 the KSS will then be recorded in the eCRF.

9.2.5 Oxford Knee Score (OKS)

The Oxford Knee Score (OKS) will be collected at the pre-operative visit and 6 weeks, 6- and 12-months after surgery.

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 [48, 49]. 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.

9.2.6 Forgotten Joint Score (FJS)

The Forgotten Joint Score (FJS) will be collected at 6 weeks, 6- and 12-months after surgery. A paper questionnaire will be provided by the Sponsor to be completed by the subject.

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 [50]. 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.

9.2.7 Robotic System Time & Cutting Time

The CORI Robotic System Time and the Cutting Time of the robotic drill shall be collected post-operatively.

The CORI Robotics Case Report, including case logs, will be extracted from the CORI system via USB and time data will be extracted for CORI Robotic System Time and the Cutting Time

In the case logs, the following time stamps will be recorded in the log file of the CORI Robotics Case Report:

1. State-Machine transition : [Adjust Camera] --> [Checkpoint Definition]
2. State-Machine transition : [Checkpoint Verification] --> [Remove Bone]
3. State-Machine transition : [Remove Bone] --> [Baseline Stress ROM Collection]

<u>Robotics System Time</u>

Robotics System starts with the checkpoint definition until the bone is removed. This is calculated by the time difference between #3 and #1.

Cutting Time

The Cutting Time of the robotic drill is the time from the start until the end of bone removal and is calculated by the time difference between #3 and #2.

The Robotics System time and the cutting time of the robotic drill will not be recorded in the eCRF as they will be extracted directly from the CORI Robotics Case Report.

9.3 Health Economics/Quality of Life

The EQ-5D-5L questionnaire will be collected at the pre-operative visit as well as 6 weeks, 6- and 12-months after surgery. A paper questionnaire will be provided by the Sponsor to be completed by the subject.

The EQ-5D-5L essentially consists of 2 pages: the EQ-5D descriptive system and the EQ visual analogue scale (EQ VAS).

The descriptive system is used to describe the subject's health state and consists of five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels to choose the most appropriate answer: no problems, slight problems, moderate problems, severe problems, and extreme problems. The subject is asked to indicate his/her health state by marking the most appropriate statement in each of the five areas [51].

The EQ VAS records the subject's self-rated health on a vertical visual analogue scale. The endpoints on the scale are labelled "The best health you can imagine" and "The worst health you can imagine". The VAS can be used as a quantitative measure of health outcome as judged by the individual respondents.

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses for the EQ-5D-5L Score will then be recorded in the eCRF.

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

Smith Nephew'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.

All statistical comparisons of data would describe the test statistic used as well as its distributional assumptions. For continuous variables, in an event of marked deviation from normality assumption, a commensurate non-parametric test would be used as an alternative thereby eliminating the possibility of violation of normality assumptions. 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 treated for a UKA or TKA with the use of the CORI Robotics and a Smith+Nephew Knee Implant System.
- Full analysis set population (FAS): The FAS is a subset of the subjects of the SAF population who have at least one post-operative assessment on any of the effectiveness endpoints or health-related quality of life (HRQoL) endpoints.
- Per-Protocol Population (PP): The PP population is a subset of subjects in the FAS population who do not have major protocol deviations and who satisfied all enrollment eligibility criteria. Major protocol deviations will include but not only restricted to subjects enrolled who do not satisfy the study entry eligibility criteria. All other criteria that will be categorized as major 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 data. All demographic and pre-operative characteristics data will be summarized at baseline. All demographic and baseline characteristics will be summarized using the SAF, FAS and PP analysis populations.

10.4 Efficacy Analysis

10.4.1 Analysis of Primary Endpoint

Leg alignment

The primary endpoint, the proportion of knees achieving post-operative leg alignment, defined as ±3° from the target (pre-operative planned leg alignment) assessed at the 6 weeks study visit in the CORI Robotics UKA (п1) and CORI Robotics TKA (п2) groups.

The proportions as described above will be summarized along with their associated two-sided 95% confidence intervals (CIs), estimated using exact binomial methods.

The hypothesis of superiority in leg alignment in both groups will incorporate the use of the Intersection Union Test (IUT) where superiority will be inferred if and only if the outcomes from the simultaneous comparisons relative to the literature-specified rate provided of 73.4% yield lower limits of their two-sided 95% CIs both greater than 73.4% (i.e. both lower limits of the 95% CIs from the two groups must be greater than 73.4%) [52]. No multiplicity adjustments are required through the use of the IUT. The leg alignment will additionally be summarized using summary statistics for the pooled CORI Robotics UKA and CORI Robotics TKA groups (п).

As supportive analysis on the primary endpoint, the difference between the target and actual leg alignment achieved postoperatively will be summarized for each group (i.e. CORI Robotics UKA versus CORI Robotics TKA) as well as for the combined groups using summary statistics for continuous variables. Ninety-five (95) % CIs based on the Student's t-distribution will be calculated for the means.

The primary endpoint and the supportive analysis will be summarized using the FAS analysis population as primary and then PP analysis population for sensitivity.

10.4.2 Analysis of Secondary Endpoint

All analyses on the secondary endpoints will be carried out separately in the CORI Robotics UKA and CORI Robotics TKA groups.

Component Alignment

Femoral components (internal rotation, valgus and anterior tilt) and tibial components (internal rotation, valgus, and posterior slope) will be summarized using descriptive summary characteristics for continuous variables.

Standard Radiographic Assessment

Radiolucent lines (mm) by zone and visit will be summarized using descriptive statistics for continuous variables.

2011 Knee Society Score (KSS)

The 2011 KSS objective, function and satisfaction scores will be summarized at the pre-operative and postoperative visits using continuous summary characteristics. For each of these 3 KSS scores, independent repeated measures Analysis of Covariance (ANCOVA) models (to account for the correlation between subjects with bilateral knees) will be used to model the KSS scores as the dependent variable. As a minimum, each model will contain a visit (pre-operative and postoperative) and the investigational site as a fixed term with a repeated specification for the knee. Pre-operative prognostic and demographic variables not only restricted to age, BMI and sex, but that can also be ascertained to have an impact on the KSS scores will be introduced as covariates in the final model. 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 it's associated p-value ≤ 0.1. Model based means (adjusted means or Least Square Means, LSMeans) and corresponding standard errors associated with each KSS score at the pre-operative visit and postoperative visits will be presented. Model based changes (and corresponding standard errors) from the pre-operative visit to each subsequent postoperative as well as their corresponding 95% CIs will additionally be summarized. If the p-value associated with the visit term in the model is significant (i.e. $p < 0.05$), then the 95% CIs corresponding to the model based change (LS Mean) from the pre-operative to each postoperative visit will indicate where significant differences (changes) from the pre-operative at postoperative are found.

The 2011 KSS subject expectation score will be summarized at the pre-operative and postoperative follow-up visits using descriptive characteristics for continuous variables.

Oxford Knee Score (OKS)

The OKS (0-48) will be summarized at the preoperative and postoperative visits using continuous summary characteristics. The repeated measures ANCOVA model to account for the correlation between subjects in case of bilateral knees analogous to that specified for the 2011 KSS will be used.

Forgotten Joint Score (FJS)

The transformed FJS score (0-100) will be summarized at the postoperative visits using continuous summary characteristics. The repeated measures ANCOVA model to account for the correlation between subjects in case of bilateral knees analogous to that specified for the 2011 KSS will be used.

EQ-5D-5L Score

The HRQoL Index score and VAS score will be summarized using summary statistics for continuous variables pre-operatively and at all postoperative visits. In the case of bilateral knees, repeated measures ANCOVA models will account for correlation between subjects with bilateral knees each for the index score and VAS analogous to that specified for the 2011 KSS will be used.

All secondary endpoints will be summarized using the FAS analysis population.

10.4.3 Analysis of Other Endpoint(s)

The analyses for other endpoints (will be carried out separately in the CORI Robotics UKA and CORI Robotics TKA groups.

Leg alignment pre- and post-cementation

Leg alignment pre- and post-cementation will be summarized using descriptive summary characteristics for continuous variables.

Robotics System Time & Cutting Time

Robotic System and cutting times will be summarized using summary statistics for continuous variables. Standard Robotics System and cutting times will be obtained from literature and included in the SAP. The average operating (μ_{11}) and cutting times (μ_{21}) and their commensurate 95% CIs will be summarized compared to the obtained literature-specified (i.e. μ_{10} and μ_{20} respectively) using the t-test.

The following are the possible outcomes, where i=1 represents operating time and i=2 represents cutting time:

If the lower limit (LL) of the 95% CI for μ_{i1} is > μ_{i0}, then it is concluded that μ_{i1} is significantly greater than μ_{i0}.

If the upper limit (UL) of the 95% CI for μ_{i1} is > μ_{i0}, then it is concluded that μ_{i1} is significantly less than μ_{i0}.

If (LL of 95% CI for $\mu_{i1} \leq \mu_{i0} \leq$ UL for 95% CI of μ_{i1}), then it is concluded that μ_{i1} on-study is comparable to that specified in the literature (μ_{i0}).

All other endpoints will be summarized using the FAS analysis population.

10.5 Safety Analyses

All safety analyses will be carried out separately for each of the groups (CORI Robotics UKA and CORI Robotics TKA groups) and overall as follows:

- The number of adverse events will be reported both overall and by seriousness, relationship to study device and anticipation.
- The number of subjects experiencing adverse events will be summarised both overall and by seriousness, relationship to study device and anticipation.
- An overall AE summary table that will summarize as number (n) and percentages (%), the overall incidence according to subjects with at least one AE; subjects with at least one AE by worst severity (mild, moderate, or severe); subjects with at least one AE by worst outcome (resolved, ongoing/unresolved, or death); subjects with an AE that led to study discontinuation) and; subjects with at least one AE by worse relatedness to device. Other events such as SAEs, ADEs, SADEs or UADEs will also be similarly summarized using the number (n) and percentages (%).
- Incidence of device-related re-interventions that occur on-study will be summarized as number (n) and percentages as well as by type.
- A listing of device deficiencies that occur on-study will be provided.
- Knee implant revision rate will be summarized as proportions with 95% CIs estimated using exact binomial methods.

All safety endpoints will be summarized using the SAF analysis population.

10.6 Interim Analyses

Not applicable.

11. SAMPLE SIZE JUSTIFICATION

Parratte et al.[53] looked at the effects of postoperative mechanical axis alignment on the survival of TKAs. They found that of the 398 TKAs reviewed in the paper there were 292 (73.4%) which post-operatively were defined as mechanically aligned (i.e. with a mechanical axis of 0˚ ± 3˚).

This study is designed to demonstrate superiority in the proportion of TKAs post-operatively defined as mechanically aligned against the reference proportion of 73.4% from above.

The proportion of mechanically aligned TKAs using the NAVIO™ Surgical System from a recent analysis was estimated to be 92.1% [54]. If this assumption holds for this study, then the enrollment of 36 knees for each of the two planned study groups (i.e. the CORI Robotics UKA and CORI Robotics TKA) for a total of 72 knees will individually provide approximately 80% power to show that the lower limit of the two-sided 95% confidence interval for the proportion of mechanically aligned TKAs is greater than that obtained from literature. To account for up to a 10% attrition rate in knees enrolled, 40 knees in each group (80 knees combined, 40 UKA, 40 TKA) will be enrolled in the study.

12. ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 Definitions

The categories of adverse events are shown in table 12.1-1. The definitions for each of these categories are given in the subsequent sections.

Table 12.1-1: Categories of Adverse Event

<table>
<tr><th></th><th>NOT DEVICE-RELATED</th><th colspan="2">DEVICE- OR PROCEDURE- RELATED</th></tr>
<tr><td>Non-Serious</td><td>Adverse Event (AE)</td><td colspan="2">Adverse Device Effect (ADE)</td></tr>
<tr><td rowspan="3">Serious</td><td rowspan="3">Serious Adverse Event (SAE)</td><td colspan="2">Serious Adverse Device Effect (SADE) (See 12.1.3)</td></tr>
<tr><td>Anticipated</td><td>Unanticipated</td></tr>
<tr><td>Anticipated Serious Adverse Device Effect (ASADE)</td><td>Unanticipated Serious Adverse Device Effect (USADE)</td></tr>
</table>

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 or comparators.

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 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) foetal distress, foetal 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. A list of potential ASADE for the CORI Robotics is provided in but not limited to Table 12.1-2. Please also refer to Section 4.4.6 Anticipated Risks / Adverse Effects and the current IFUs (Appendix 22.2).

Table 12.1-2 Potential Anticipated Serious Adverse Device Effects (ASADE)

#	Potential Harm	Description
1	Allergic Reaction to Materials	Hypersensitivity caused by exposure to material constituents of the product that leads to local inflammatory reaction and tissue damage. Contact with an allergen may cause swelling and redness of the skin in minor cases. A severe anaphylactic reaction may occur.
2	Bone Fracture	Any break or fracture to any bone. (Applicable to displaced and non-displaced fractures) The bone break could be reduced (set) and immobilized during the same surgery during which it occurred if it is detected. If the fracture occurs after the surgery, additional medical attention would be required. Subsequent healing returns normal body function for the subject.
3	Burn	3rd degree burn extending through the dermis which requires excision. 4th degree burn extending into the subcutaneous tissue, muscle and bone with eschar formation. Burns may be caused by thermal or chemical burns.
4	Cardiac Arrhythmia - symptomatic	Variation from the normal heart rhythm symptomatic.
5	Cement Leakage	Cement can end up in an unintended location in the joint. Cement leakage may cause early wear of poly or pain to the subject and may require revision surgery.
6	Unstable knee joint	The implant components are placed in such a way that there is too much laxity in the ligaments. The subject experiences instability throughout the range of motion, There is an increased risk of early loosening/ wear of the implant. This may impact the stability and wear of implant components. Implants loosening could lead to early revision surgery.
7	Restricted Range of Motion	The implants are placed in such a way that excessive forces are placed on the ligaments (ACL, PCL, MCL, and LCL). This leads to an unintended reduction in the range of motion or progression of disease in a non- operative compartment. This may be serious, if the subject's range of motion has been worsened compared to the range of motion prior to surgery, or it has been restored sub-optimally.

#	Potential Harm	Description
8	Infection	Invasion and multiplication of microorganisms in body tissues, especially microorganisms causing local cellular injury due to competitive metabolism, toxins, intracellular replication, or antigen-antibody response. The infection may lead to a diseased state in the receiving host if the host has inadequate resistance and/or lacks immunity to overcome the invasion by the pathogen. Most typically, the resultant disease state can be treated through the use of antibiotics. When the pathogen is particularly virulent, or when the host has low resistance, the disease state may lead to a permanent impairment of some aspect of bodily function or, in extreme cases, to death. Infections caused by a transfer of body fluids during orthopedic surgery can in most cases be treated by a course of antibiotics. Severe infections that can occur by the transfer of body fluids during the procedure include HIV and hepatitis.
9	Delay	A delay in the operation time exceeding 60 minutes of intra-operative case time. A wound being open longer would more likely result in soft tissue edema, increased blood loss, muscle necrosis as a result of extended tourniquet time and a higher chance of infection.
10	Immature implant failure	Implant components wear before their intended service life resulting in early revision surgery.
11	Neurological Injury	Damage to the nerve systems of the subject's leg. A neurological injury could result in temporary or permanent paralysis.
12	Physical Injury - Serious	A physical injury that necessitates medical intervention.
13	Soft Tissue Damage	Damage to ligaments or tendons leading to loss of stability in the knee joint. In severe cases of ligament damage, additional surgery may be required.
14	Surgeon Operates on Wrong Part of Anatomy	The clinical impacts of operating on the wrong subject anatomy relate to the resultant function of the skeletal element that was treated and the need to repeat treatment for the desired skeletal element. The impact on the subject may be additional surgery under full anesthesia.

#	Potential Harm	Description
15	Vascular Injury - Main Low-extremity vessels	Damage to the vascular systems of the subject's leg. In severe cases, dis-vascularization occurs that is, the subject loses blood flow to the leg when a clot forms in significant arteries of the leg. Additional surgery would be required to correct blood flow. If blood flow to the leg is not restored, the patient's leg may need to be amputated.

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.

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 if

a) suitable action had not been taken,
b) intervention had not been made, or
c) 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 2020 v2.1 – 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.

The investigator will inform the regulatory agency and IRB/IEC of adverse events as per the requirements listed below:

Unanticipated SADE's and DD's that could have led to SADE 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 12.3-12-1: Evaluation and Reporting of AE

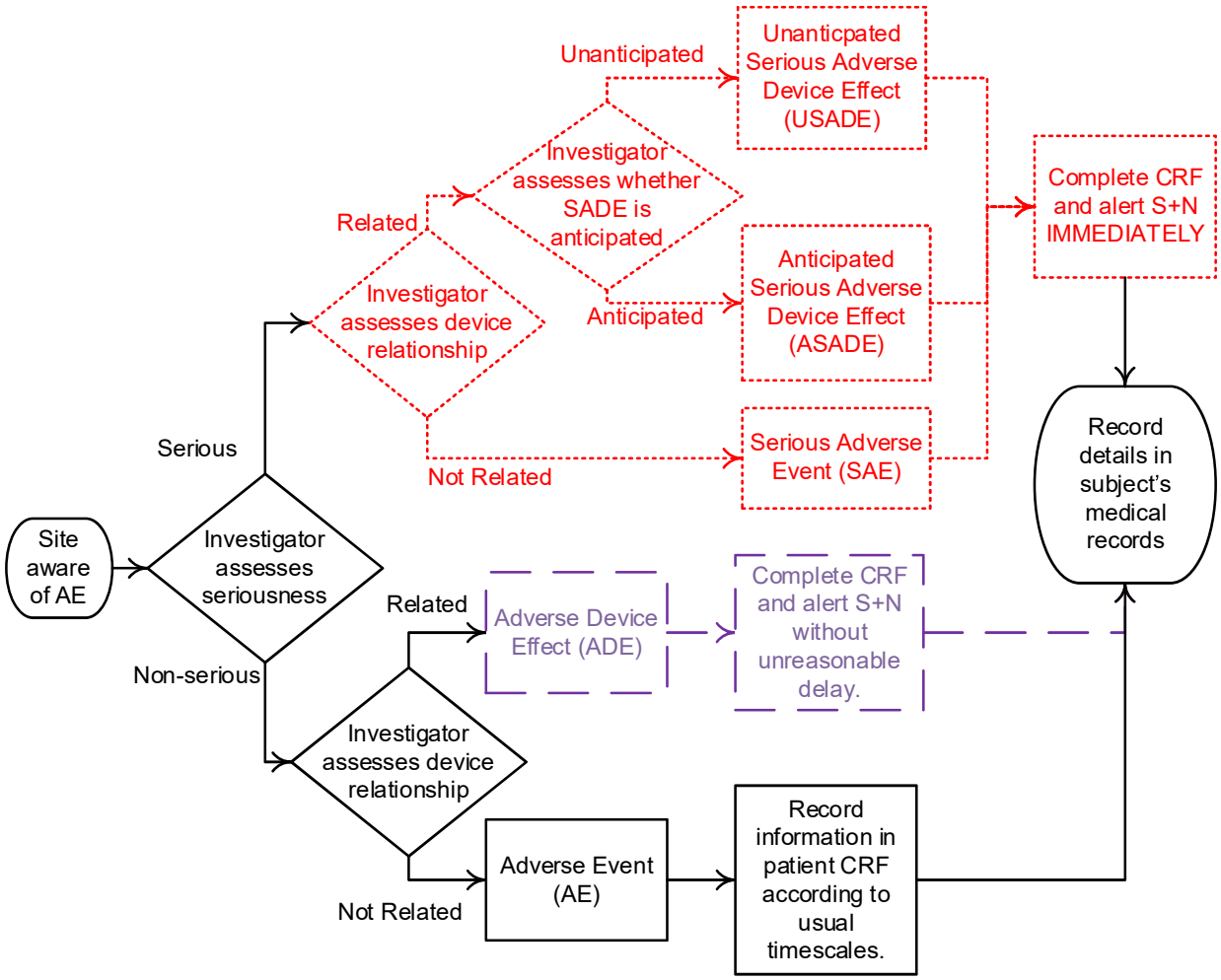
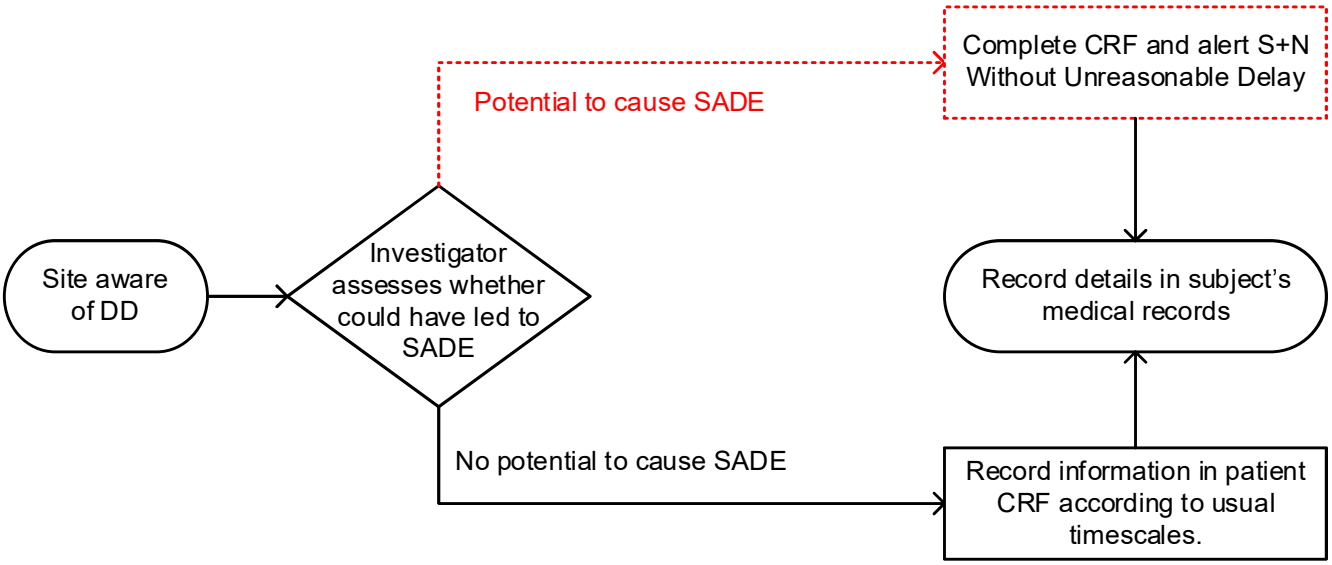


Figure 12-2: Evaluation and Reporting of DD



12.4 Unblinding of Investigational Product

Not Applicable.

12.5 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.

12.5.1 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.

13. 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 22.7 Principal Investigator Obligations (ISO 14155) of this protocol. Sub-Investigators, who are individual member of the investigation site team designated and supervised by the Principal Investigator at an investigation site to perform clinical investigation-related procedures or to make important clinical investigation-related and medical treatment decisions, may have responsibilities delegated to them by the Principal Investigator. However, the Principal Investigator retains overall responsibility for the clinical investigation at the site.

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.

The Coordinating Investigator appointed by the Sponsor will assist in coordinating the work in the multicentre clinical investigation.

14. 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.

14.1 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.

14.2 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 Clinical Trial Agreement and documented IRB/IEC approval.

14.3 Interim Monitoring Visit

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

14.4 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 remove close-out visit may be conducted.

14.5 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, regardless of location and format.

15. 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 (FRM-402046 Protocol/GCP Deviation Log). Significant and/or recurrent protocol/GCP deviations will be documented on a protocol deviation form (FRM-400347 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. If it is deemed necessary full clinical Corrective and Preventive Action (CAPA) will be initiated.

It is not allowed to use waivers to allow planned deviation of the study protocol.

An investigator may be early terminated from the study upon identification of serious protocol deviations whereby there are concerns for patient safety or data quality (especially those not reported to the sponsor by the site). Early termination may also occur if there are repeated protocol deviations which have previously been addressed via corrective and preventative actions thereby suggesting an issue with site compliance.

Protocol deviations requiring reporting to the IRB/IEC should be done so in the timeframe stipulated by the IRB/IEC.

16. 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.

17. CONFIDENTIALITY OF THE STUDY

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

18. 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.

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.

The clinical study is financed by the sponsor. All financial arrangements between the sponsor and investigation sites/investigators are documented separate clinical trial agreements.

19. END OF STUDY

The end of this study is defined by the last follow-up visit that occurs in the whole study population. Due to defined visit windows, the last follow-up visit must not necessarily be of the last subject treated. Subject's will return to standard of care as prescribed by the individual sites if further follow-up is needed. The study is expected to last 36 months (enrolment period: 24 months, Follow-up period: 12 months).

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.

An End of Study CRF needs to be completed for all subjects including any subject that does not complete the study, to document the reason for termination.

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to other parties (Investigator, IRB/IEC, Sponsor and regulatory authorities). If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB/IEC and the study sites and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance with study protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination of futility

Study may resume once concerns about safety, study protocol compliance, data quality are addressed and satisfy the Sponsor and IRB/IEC.

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

20. PUBLICATION POLICY

20.1 Publication of Study Data

The study will be registered in a publicly accessible database (ClinicalTrials.gov and Clinical Trials Registry - India (CTRI)) and the results will be made available within that database.

It is intended that the results of this study will be submitted for publication within a manuscript.

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, including, but not limited to the Health Insurance Portability and Accountability Act of 1996.

20.2 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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22. APPENDICES

22.1 Protocol Amendment

22.1.1 Protocol Amendment 1

22.1.1.1 General Purpose

This amendment has been completed to:

1) increase the pre-operative visit window from 28 days to 90 days and to allow pre-operative activities to occur on the day of surgery as long as they occur prior to the surgery itself.
2) allow the 6-month visit to be conducted remotely.

22.1.1.2 Rationale

1) Following the COVID pandemic and the cancellations of elective surgery the waiting lists for surgery have increased globally. Extending the visit window will aid sites in being able to include subjects whose surgery is longer than 28 days from their initial pre-operative visit without having to schedule an additional pre-operative visit.
2) No x-rays are taken at the 6-month visit so the subject does not need to come in to site. The PROMs collected at the visit can be sent to the subject who can complete them whilst on the phone to a member of the study team. The PROMs will then be securely sent back to site and entered into the EDC. The KSS would not have the "objective" (clinician-generated) component of the questionnaire completed if the visit is remote. However, per the 2011 Knee Society Knee Scoring System Licensed User Manual [55] outcomes are only scored using the patient reported responses. Data derived from items on the "objective" (clinician-generated) component of the questionnaire is collected for background information and to facilitate comparison of patient outcome with the old KSCR.

22.1.1.3 Effect on Study Status

1) The amendment will ensure more potential subjects can be included in the study and reflect the consequences of the COVID pandemic on the current routine clinical schedules. There is no impact on any subjects that are enrolled prior the amendment being effective as the amendment is lengthening rather than reducing the pre-operative visit window.
2) There will be no impact on any subjects reaching the 6-month visit prior to the amendment being effective because they will have the 6-month visit on site.

The database will be updated according to the new protocol once approved.

22.1.1.4 Details

At the time of the amendment the protocol template was also updated throughout to ensure it is compliant with the current effective protocol template (TMP-800052/TMP-CD-05 Rev 3). The major changes are included in the table below.

Section	Current Text 18/Jun/2020 Version 4.0	Revised Text 08/Nov/2022 Version 5.0
Front Page	Sponsor	Sponsor and funding source:
Front Page	N/A	Single Identification Number of Clinical Investigation: N/A
Front Page	N/A	Summary of Revision History V4.0, 18/Jun/2020 V3.0, 08/Jun/2020 V2.0, 29/Apr/2020 V1.0, 24/Feb/2020
2. Synopsis	N/A	Sponsor and Funding Source: Smith & Nephew Inc, 1450 E. Brooks Road, Memphis, Tennessee 38116, USA
2. Synopsis Study Design	Prospective, multi-center, cohort study, 2 arms	• Prospective • Multi-center – up to 8 sites, • Cohort study, • 2 arms • 140 subjects (70 x UKA, 70 x TKA) • 1 year follow-up
2. Synopsis Study Type	Post-market study	Post-market study Interventional, non-randomised, non-blinded
2. Synopsis Comparison Group(s)*: (*if applicable)	N/A	Comparison Group(s)*: N/A (*if applicable)
2. Synopsis Primary Objective:	To evaluate the use of CORI Robotics in unicondylar knee arthroplasty (UKA) and total knee arthroplasty (TKA) procedures in achieving post-operative leg alignment.	To evaluate the use of CORI Robotics in UKA and TKA procedures in achieving post-operative leg alignment.
2. Synopsis Secondary Objective(s):	To generate safety and performance evidence supporting the use of CORI Robotics procedures.	To assess the safety and performance of the CORI Robotics up to 12 months after surgery.
2. Synopsis Other Objective(s):	To collect Robotics System time and cutting time of the robotic drill	To determine the Robotics System time and cutting time of the robotic

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	from the CORI Robotics Case Report.	drill of UKA and TKA procedures with the CORI Robotics.
2. Synopsis Safety Data	• All adverse events (AEs) and complications occurring from the time of subject enrollment until study termination or study completion including intra-operative adverse events and complications. • Device Deficiencies • Knee implant revision rate All AEs will be categorized in terms of seriousness and relatedness to the study device or to the surgical procedure. All Serious Adverse Device Effects will be further categorized as Anticipated or Unanticipated. The definitions for each of these categories are based on ISO 14155:2011.	Deleted section as repeated lower in Synopsis
2. Synopsis Targeted Global Regions:	Europe, India, and the US	Europe, UK, India, and the US
2. Synopsis Inclusion Criteria	1. The subject's treating clinician has decided that REAL INTELLIGENCE™ CORI™ and a compatible Smith+Nephew Knee Implant System is the best treatment for the subject's unicondylar knee arthroplasty (UKA) or total knee arthroplasty (TKA) and the subject has agreed to the treatment.	1. The subject's treating clinician has decided that REAL INTELLIGENCE™ CORI™ and a compatible Smith+Nephew Knee Implant System is the best treatment for the subject's UKA or TKA and the subject has agreed to the treatment. 7. Subject able to follow instructions and deemed capable of completing all study questionnaires.
2. Synopsis Study Duration	**Estimated Timelines** • Study period: 25 months (12 months enrolment) • Start enrolment: July 2020	Estimated total study timeline: 36 months (Enrolment period: 24 months, Follow-up period: 12 months)

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	• Last subject first visit: June 2021 • Last subject last visit: July 2022	
2. Synopsis Primary Endpoint	Post-operative leg alignment via radiographic assessment (the proportion of subjects achieving post-operative leg alignment 6 weeks after surgery, defined as ± 3° from target)	The evaluation of the proportion of subjects achieving post-operative leg alignment at 6 weeks post-surgery. Achieved leg alignment is defined as ± 3° from the subject's specific target.
2. Synopsis Secondary endpoint(s):	• Component Alignment • Radiographic assessment (Presence of radiolucent lines, osteolysis & implant migration) • 2011 Knee Society Score (KSS) • Oxford Knee Score (OKS) • Forgotten Joint Score (FJS) • Five-level EuroQol five-dimensional (EQ-5D-5L) VAS and index scores	• Component Alignment 6 weeks post-surgery • Radiographic assessment (Presence of radiolucent lines, osteolysis & implant migration) 12 months post-surgery • 2011 Knee Society Score (KSS) at baseline, 6 weeks, 6 and 12 month post-surgery • Oxford Knee Score (OKS) at baseline, 6 weeks, 6 and 12 month post-surgery • Forgotten Joint Score (FJS) at 6 weeks, 6 and 12 month post-surgery Five-level EuroQol five-dimensional (EQ-5D-5L) VAS and index scores at baseline, 6 weeks, 6 and 12 month post-surgery
2. Synopsis Other exploratory endpoint(s):	Each enrolled subject's CORI Robotics Case Report will be collected to document the robotic system time and cutting time of the robotic drill	• Leg alignment pre- and post-cementation • Robotics System time as extracted from the Subject's CORI Robotics Case Report generated by the CORI Robotics Software. • Cutting time of the robotic drill s extracted from the Subject's

Section	Current Text 18/Jun/2020 Version 4.0	Revised Text 08/Nov/2022 Version 5.0
		CORI Robotics Case Report, generated by the CORI Robotics Software.
2. Synopsis Safety Data	N/A	Additional text: All AEs will be categorized in terms of seriousness and relatedness to the study device or to the surgical procedure (Adverse Events, Serious Adverse Events, Adverse Device Effects, Serious Adverse Device effects). All Serious Adverse Device Effects will be further categorized as Anticipated or Unanticipated. The definitions for each of these categories are based on ISO 14155. (Including hardware and instrumentation), complications, and revisions.
2. Synopsis Study Schedule	Pre-Operative: -28 to 0 days Operative Data & Discharge: Day 1 (+ up to 9 days) 6-Month Follow-Up: Day 185 ± 14	Pre-Operative: -90 to 0 days Operative Data & Discharge: Day 0 (+ up to 9 days) 6-Month Follow-Up*: Day 185 ± 14 * The 6 month visit may be conducted remotely.
4.1 Background	N/A	Additional text: A summary of known and potential risks and benefits to humans of CORI Robotics can be found in the Instructions for Use (IFU).
4.3 Study Purpose	This is a prospective, multi-center study to demonstrate the safety and effectiveness of the CORI Robotics to meet the post-market clinical follow-up requirement in Europe, India and the US. In addition, the study may support regulatory approval by the	This is a prospective, multi-center study to demonstrate the safety and effectiveness of the CORI Robotics to meet the post-market clinical follow-up requirement in Europe, UK, India and the US. This is a post-market study in all countries involved. In addition, the study may support

Section	Current Text 18/Jun/2020 Version 4.0	Revised Text 08/Nov/2022 Version 5.0
	National Medical Products Administration (NMPA) in China.	regulatory approval by the National Medical Products Administration (NMPA) in China. Study hypotheses are that the CORI surgical system will achieve post-operative leg alignment (± 3°), and an improvement in patient-reported outcome measures. This primary endpoint is aligned to the primary study objective of evaluating the CORI surgical system for UKA and TKA procedures in achieving post-operative leg alignment. Accuracy and alignment are two key variables in successful UKA and TKA procedures. These measures have been previously evaluated with the predicate NAVIO surgical system. The primary endpoint will support the continued evaluation of these variables for the CORI surgical system.
4.4 Safety Considerations	N/A	Representative language of the indications of use, contraindications and potential adverse effects of CORI Robotics can be found in the IFU.
4.4.6 Anticipated Risks / Adverse Effects	4.4.6 Potential Adverse Effects	4.4.6 Anticipated Risks / Adverse Effects Additional text: As this is a post-market study and the device is used according to the IFU, the use of CORI Robotics in this study introduces no additional potential risks to the study participant.
4.4.7 Safety Data Collection	N/A	All adverse device effects or device deficiencies will be categorised and reported as instructed in Section 12, Adverse Events and Device

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		Deficiencies. During causality assessment activity (assessment of Related vs Unrelated) and expectancy assessment (assessment of Unanticipated vs Anticipated) clinical judgement shall be used and relevant documents, such as the IFU shall be consulted, as foreseeable serious adverse events and the potential risks are summarized there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered.
5. Objectives	N/A	To evaluate the safety and effectiveness of REAL INTELLIGENCE™ CORI™ in UKA and TKA procedures.
5.1 Primary Objective	The primary objective of this study is to evaluate the use of CORI Robotics in UKA (phase 1) and TKA procedures in achieving post-operative leg alignment.	The primary objective of this study is to evaluate the use of CORI Robotics in UKA and TKA procedures in achieving post-operative leg alignment.
6.1.1 Investigational Product	The CORI Robotics is currently avaible for the use of the following S+N implant Systems:	For the purposes of this study, the CORI Robotics is currently available for the use of the following S+N implant Systems: Additional text: For this study only the CORI Robotics is considered the IP and not the implant systems used. All surgeons using CORI Robotics will have previously been fully trained on the use of the system by S+N staff.
6.1.2 Comparator Treatment<s>	N/A	No comparator products are used.

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6.1.3 Ancillary Product	N/A	No ancillary products are to be provided for this study.
6.2 Product Use	N/A	Additional text: It is the Investigator's responsibility to ensure adherence to the IFU. Sites that are familiar with the use of CORI Robotics / Robotic-assisted surgery systems will be selected so no additional training is required.
6.3.1 Labelling of Investigational Product	N/A	Additional text: No additional labelling will take place.
6.4 Product Accountability Procedures	N/A	Clarification added: In instances where CORI Robotics is supplied to site, Additional text for when CORIs are supplied to site: Overall accountability for the use of the product is the responsibility of the Investigator or designated individual. Following completion of enrolment all supplied CORI Robotics systems will be returned to S+N.
6.5 Surgical Technique	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. Anonymized CORI Robotics Case Reports will be collected for these pre-study cases as proof of experience.	If deemed necessary, 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. Anonymized CORI Robotics Case Reports will be collected for these pre-study cases as proof of experience. If no pre-study cases are completed the case log of the first study case will be collected and analysed as soon as possible following the surgery to ensure the additional

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		data required for the study has been collected.
7.1 Subject Population	N/A	Additional text: It is expected that all subjects will be enrolled within 24 months. Eligibility criteria are specified to ensure that the subject population of the study represents the target population of the IP.
7.1.1 Vulnerable Subjects	N/A	No vulnerable subjects will be included in the study.
7.2 Inclusion Criteria	1. The subject's treating clinician has decided that REAL INTELLIGENCE™ CORI™ and a compatible Smith+Nephew Knee Implant System is the best treatment for the subject's unicondylar knee arthroplasty (UKA) or total knee arthroplasty (TKA) and the subject has agreed to the treatment.	1. The subject's treating clinician has decided that REAL INTELLIGENCE™ CORI™ and a compatible Smith+Nephew Knee Implant System is the best treatment for the subject's UKA or TKA and the subject has agreed to the treatment. 7. Subject able to follow instructions and deemed capable of completing all study questionnaires.
7.4 Screening	N/A	Additional text: Part of the screening process will include documentation of women's childbearing potential. For women of childbearing potential, study sites will determine whether the subject is pregnant using their standard clinical practice.
7.5 Informed Consent	N/A	Additional text: Translations of informed consent documents will be available in the participating countries main language(s).

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		The subject will have sufficient time to consider study participation and ensure all questions have been answered this will usually be at least 24 hours unless approved or documented local site Informed Consent procedures allow for this to be shorter. There is no required interval between the time of consent and the first study procedure being carried out. Due to the nature of completing Patient Reported Outcome during the study the subject must be able to provide consent. A Legally Authorized Representative signature is not allowed in this study.
7.8.1 Withdrawal from Treatment	N/A	Additional text: Subjects withdrawn from having treatment will not be classed as being enrolled (section 7.6). Subjects withdrawn from having treatment will be replaced and no further follow-up of the withdrawn subjects is required for the study.
8.1 Study Design	This study is being conducted in parallel to a randomized-controlled study in China titled: "A Prospective, Multi-center, randomized-controlled Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) and total knee arthroplasty (TKA) procedures" (Protocol ID:	This study is being conducted in parallel to 2 randomized-controlled studies in China titled: "A Prospective, Multi-center, randomized-controlled Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) procedure" (Protocol ID: CORI.2019.06) and "A Prospective, Multi-center, Randomized Controlled

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	CORI.2019.06). The study data will be combined for analysis to meet the requirements for regulatory approval of the CORI Robotics by the National Medical Products Administration (NMPA) in China. Further details are described in Section 10 Statistical Design and the Statistical Analysis Plan (SAP).	Study to Evaluate the Safety and Effectiveness of the REAL INTELLIGENCE™ CORI™ in total knee arthroplasty (TKA) Procedure" (Protocol ID: CORI.2020.08). The study data will be combined for analysis to meet the requirements for regulatory approval of the CORI Robotics by the National Medical Products Administration (NMPA) in China. Further details are described in Section 10 Statistical Design and the Statistical Analysis Plan (SAP). Additional text: The study design meets the needs of the aforementioned regulatory requirements and has been powered based on recent analyses from the NAVIO Surgical System. This study is designed to demonstrate superiority in the proportion of TKAs post-operatively defined as mechanically aligned against the reference proportion of 73.4% (53). The proportion of mechanically aligned TKAs using the NAVIO™ Surgical System from a recent analysis was estimated to be 92.1% (54). If this assumption holds for this study, then the enrollment of 63 knees for each of the two planned study groups (i.e. the CORI Robotics UKA and CORI Robotics TKA) for a total of 126 knees will individually provide 80% power to show that the lower limit of the two-sided 95% confidence interval for the proportion of mechanically aligned TKAs is greater than that obtained from literature. To account for up to a 10% attrition rate in knees enrolled, 70 knees in each group (140 knees

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		combined, 70 UKA and 70 TKA) will be enrolled in the study.
8.2 Data Management	N/A	This study utilizes a validated, 21 CFR Part 11 compliant, electronic data capture system. Access to the electronic data capture system is controlled through Smith and Nephew procedures. A Data Management Plan (DMP) is written according to Smith and Nephew procedures containing details of the data management process. The following is a brief description of the key points detailed in this plan.
8.2.1 Data Review and Quality Assurance	N/A	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.

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		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.
8.2.2 Retention Period	N/A	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.
8.3.1 Primary Endpoint	The primary endpoint of this study is defined as the evaluation of the proportion of subjects achieving post-operative leg alignment. Achieved leg alignment is defined as ± 3° from the subject's specific target.	The primary endpoint of this study is defined as the evaluation of the proportion of subjects achieving post-operative leg alignment at 6 weeks post-surgery. Achieved leg alignment is defined as ± 3° from the subject's specific target. This primary endpoint is aligned to the primary study objective of evaluating the CORI surgical system for UKA and TKA procedures in achieving post-operative leg alignment. Accuracy and alignment are two key variables in successful UKA and TKA procedures. These measures have been previously evaluated with the predicate NAVIO surgical system. The primary endpoint will support the continued evaluation of these variables for the CORI surgical system.

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8.3.2 Secondary Endpoints	The following secondary endpoints have been defined for this study in order to evaluate the safety and performance of the CORI Robotics: • Component Alignment • Radiographic assessment (Presence of radiolucent lines, osteolysis & implant migration) • 2011 Knee Society Score (KSS) • Oxford Knee Score (OKS) • Forgotten Joint Score (FJS) • Five-level EuroQol five-dimensional (EQ-5D-5L) VAS & index scores	The following secondary endpoints have been defined for this study in order to evaluate the safety and performance of the CORI Robotics: • Component Alignment 6 weeks post-surgery • Radiographic assessment (Presence of radiolucent lines, osteolysis & implant migration) 12 months post-surgery • 2011 Knee Society Score (KSS) at baseline, 6 weeks, 6 and 12 month post-surgery • Oxford Knee Score (OKS) at baseline, 6 weeks, 6 and 12 month post-surgery • Forgotten Joint Score (FJS) at 6 weeks, 6 and 12 month post-surgery • Five-level EuroQol five-dimensional (EQ-5D-5L) VAS & index scores at baseline, 6 weeks, 6 and 12 month post-surgery Secondary endpoints are aligned to the secondary study objectives of generating safety and performance evidence related to the use of the CORI surgical system. Assessing alignment, radiographic image assessment and patient-reported outcome measures (PROMS) are key variables in determining the success of UKA and TKA procedures. These endpoints have been previously evaluated with the predicate NAVIO surgical system and ongoing assessment of these

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		secondary endpoints under this study will support safety and efficacy of these procedures performed with the CORI surgical system.
8.3.4 Safety Endpoints	N/A	Additional text: All AEs will be categorized in terms of seriousness and relatedness to the study device or to the surgical procedure (Adverse Events, Serious Adverse Events, Adverse Device Effects, Serious Adverse Device effects). All Serious Adverse Device Effects will be further categorized as Anticipated or Unanticipated. The definitions for each of these categories are based on ISO 14155. (Including hardware and instrumentation), complications, and revisions.
Table 9 1: Study Procedures by Visit	Pre-Operative Data -28 to 0 days Operative Data & Discharge Day 1 (+ up to 9 days) [1.] Post-operative standing weight bearing long leg X-rays (A/P & L) may be taken at discharge already	Pre-Operative Data -90 to 0 days Operative Data & Discharge Day 0 (+ up to 9 days) [4] [1.] Post-operative standing weight bearing long leg X-rays (A/P & L) may be taken at discharge if standard of care Addition of: [4.] If any Pre-Operative data is collected on the day of surgery, it must be completed prior to the surgery occurring. [5.] The 6 month visit may be conducted remotely.

Section	Current Text 18/Jun/2020 Version 4.0	Revised Text 08/Nov/2022 Version 5.0
9.1.2 Screening / Preoperative Visit	9.1.2 Screening / Preoperative Visit 5. Instruct the subject on treatment procedures. 6. Collect radiographic images of the affected knee for evaluation of leg alignment (Standing weight bearing A/P long leg X-ray).	9.1.2 Screening / Preoperative Visit (-90 to 0 days) 5. Assign the subject a study number and instruct the subject on treatment procedures. 6. Collect radiographic images of the affected knee for evaluation of leg alignment (Standing weight bearing A/P long leg X-ray) (x-rays can be taken within 6 months of the surgery date)
9.1.3 Operation Visit & Discharge	Operation Visit & Discharge (Day 0)	9.1.3 Operation Visit & Discharge (Day 0 up to Day 9) If any Pre-Operative data is collected on the day of surgery, it must be completed prior to the surgery occurring.
9.1.4 Follow-up visits at 6 weeks (42 ± 14 days)	10. 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.	10. 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 or make arrangements for delivery of the 6 month PROMs by courier to the subject to be completed remotely.
9.1.5 6 months (185 ± 14 days) after surgery	9.1.5 6 months (185 ± 14 days) after surgery 4. Collect the KSS score objective measures (joint alignment, instability, motions & symptoms).	9.1.5 9.1.5 6 months (185 ± 14 days) after surgery (phone call if remote) 4. Collect the KSS score objective measures (joint alignment, instability, motions & symptoms) (if it is an on-site visit) Addition:

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		9. If the visit was remote arrange for courier to return the completed PROMs to site.
9.1.7 Unscheduled visits	Unscheduled examinations may be conducted at the discretion of the Investigator with all obtained information recorded in the source documents and on the appropriate eCRF. The subject should be scheduled to return for the next scheduled study visit within the acceptable time window.	Unscheduled examinations related to the study knee may be conducted at the discretion of the Investigator with all obtained information recorded in the source documents and on the appropriate eCRF. If any adverse events or device deficiencies are observed or reported, they must be recorded as instructed in Section 12. - Adverse Events and Device Deficiencies. The subject should be scheduled to return for the next scheduled study visit within the acceptable time window.
10.6 Interim Analysis	A first interim analysis is planned for H2 2020. More specific details on the interim analyses will be included in the SAP.	Not applicable.
12.1.1 Adverse Event	An Adverse Event (AE) is any untoward medical occurrence, unintended disease of untoward clinical sign (including abnormal laboratory findings) in subjects, users or other persons, whether or not causally related to the IP/Ancillary Product. Note 1: This definition includes events related to the IP, comparator or ancillary products. 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 IP	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

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		related to the use of investigational medical devices or comparators.
12.1.2 Adverse Device Effect	An Adverse Device Effect (ADE) is an adverse event that, in the opinion of the investigator, is related to the use of the IP.	An Adverse Device Effect (ADE) is an adverse event related to the use of an investigational medical device. Addition: Note 3: This includes "comparator" if the comparator is a medical device.
12.1.3 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, in the view of either the Investigator or the Sponsor, it led to any of the following:	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:
12.1.5 Guidance Regarding the Determination of Unanticipated Events:	During causality assessment activity, clinical judgement shall be used and the relevant documents, such as the Investigator's Brochure, the Clinical Protocol or the Risk Analysis Report shall be consulted, as all the foreseeable serious adverse events and the potential risks are listed and assessed there. The presence of confounding factors, such as concomitant medication/treatment, the natural history of the underlying disease, other concurrent illness or risk factors shall also be considered [MEDDEV 2.7/3 Rev 3 Sec 8].	Deleted
12.1.6 Device Deficiency	A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability,	A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or

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	safety, or performance. DD includes malfunctions, use errors and inadequate labeling.	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.
12.3 Reporting procedures	AE of any kind and DD will be recorded in the applicable eCRF and source notes. The Investigator will evaluate all AE for a relationship to the device and procedure, if applicable, seriousness, and severity. The following timescales should be followed for the AE/DD information to be entered into the eCRF and reported to the Sponsor	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, if applicable, 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

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	or designee (see Figure 12-1 & Figure 12-2): • 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) For ADE and DD, 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 eCRF 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 the criteria for expedited reporting to the regulatory authorities. The investigator will inform the IRB/IEC of adverse events according to the IRB/IEC requirements.	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. The investigator will inform the regulatory agency and IRB/IEC of

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		adverse events according to as per the requirements listed below: Unanticipated SADE's and DD's that could have led to SADE will be reported to IEC/IRB and regulatory authorities within 10 working days. All other events will be reported on a periodic/annual basis.
14.1 Contract Research Organization	The Sponsor has engaged Contract Research Organization (CRO) to assist in conducting this study. When appropriate, the CRO is referred to in study documents as "Sponsor's agent."	Deleted 14.1 Contract Research Organization
14.3 Interim Monitoring Visit	N/A	Regular interim monitoring visits will be performed by the Sponsor or qualified person designated by the Sponsor.
14.4 Close-Out Visit	N/A	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 remove close-out visit may be conducted.
15 Protocol Deviations	N/A	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

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		discovered during monitoring visits will be compiled in a Protocol / GCP Deviation Log (FRM-402046 Protocol/GCP Deviation Log). Significant and/or recurrent protocol/GCP deviations will be documented on a protocol deviation form (FRM-400347 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. If it is deemed necessary full clinical Corrective and Preventive Action (CAPA) will be initiated. It is not allowed to use waivers to allow planned deviation of the study protocol. An investigator may be early terminated from the study upon identification of serious protocol deviations whereby there are concerns for patient safety or data quality (especially those not reported to the sponsor by the site). Early termination may also occur if there are repeated protocol deviations which have previously been addressed via corrective and preventative actions thereby suggesting an issue with site compliance. Protocol deviations requiring reporting to the IRB/IEC should be done so in the timeframe stipulated by the IRB/IEC.
18. Statements of Compliance	N/A	The clinical study is financed by the sponsor. All financial arrangements between the sponsor and

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		investigation sites/investigators are documented separate clinical trial agreements.
19. End of Study	The end of this study is defined by the last follow-up visit that occurs in the whole study population. Due to defined visit windows, the last follow-up visit must not necessarily be of the last subject treated. 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 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	The end of this study is defined by the last follow-up visit that occurs in the whole study population. Due to defined visit windows, the last follow-up visit must not necessarily be of the last subject treated. Subject's will return to standard of care as prescribed by the individual sites if further follow-up is needed. The study is expected to last 36 months (enrolment period: 24 months, Follow-up period: 12 months). 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. An End of Study CRF needs to be completed for all subjects including any subject that does not complete the study, to document the reason for termination. This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or

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		termination, will be provided by the suspending or terminating party to other parties (Investigator, IRB/IEC, Sponsor and regulatory authorities). If the study is prematurely terminated or suspended, the Investigator will promptly inform the IRB/IEC and the study sites and will provide the reason(s) for the termination or suspension. Circumstances that may warrant termination or suspension include, but are not limited to: • Determination of unexpected, significant or unacceptable risk to participants • Demonstration of efficacy that would warrant stopping • Insufficient compliance with study protocol requirements • Data that are not sufficiently complete and/or evaluable • Determination of futility Study may resume once concerns about safety, study protocol compliance, data quality are addressed and satisfy the Sponsor and IRB/IEC. 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
20.1 Publication of Study Data	N/A	The study will be registered in a publicly accessible database (ClinicalTrials.gov and Clinical Trials Registry - India (CTRI)) and the

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		results will be made available within that database. It is intended that the results of this study will be submitted for publication within a manuscript.
21 References	N/A	55. 2011 Knee Society Knee Scoring System Licensed User Manual - https://www.kneesociety.org/assets/2011KSS%20Support%20Materials.pdf
22.1 Protocol Amendment 1	N/A	22.1.1 General Purpose This amendment has been completed to: 1) increase the pre-operative visit window from 28 days to 90 days and to allow pre-operative activities to occur on the day of surgery as long as they occur prior to the surgery itself. 2) allow the 6-month visit to be conducted remotely. 22.1.2 Rationale 1) Following the COVID pandemic and the cancellations of elective surgery the waiting lists for surgery have increased globally. Extending the visit window will aid sites in being able to include subjects whose surgery is longer than 28 days from their initial pre-operative visit without having to schedule an additional pre-operative visit. 2) No x-rays are taken at the 6-month visit so the subject does not need to come in to site. The PROMs collected at the visit can be sent to the subject who can complete them whilst on the phone to a member of the study team. The PROMs will then be securely sent back to site and entered into the EDC. The KSS would

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		not have the "objective" (clinician-generated) component of the questionnaire completed if the visit is remote. However, per the 2011 Knee Society Knee Scoring System Licensed User Manual [55] outcomes are only scored using the patient reported responses. Data derived from items on the "objective" (clinician-generated) component of the questionnaire is collected for background information and to facilitate comparison of patient outcome with the old KSCR. 22.1.3 Effect on Study Status 1) The amendment will ensure more potential subjects can be included in the study and reflect the consequences of the COVID pandemic on the current routine clinical schedules. There is no impact on any subjects that are enrolled prior the amendment being effective as the amendment is lengthening rather than reducing the pre-operative visit window. 2) There will be no impact on any subjects reaching the 6-month visit prior to the amendment being effective because they will have the 6-month visit on site. The database will be updated according to the new protocol once approved. 22.1.4 Details At the time of the amendment the protocol template was also updated throughout to ensure it is compliant with the current effective protocol template (TMP-800052/TMP-CD-05

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		Rev 3). The major changes are included in the table below. Addition of this table 22.1.5 Approval/Notification These updates will be submitted for EC/IRB approval. The changes will only be implemented after EC/IRB approval confirmation.
22.5 Clinical Study Sites	N/A	Smith + Nephew will maintain a list of the name and address of involved sites in the Trial Master File. This list is available upon request.
22.6 Contract Research Organization	N/A	S+N will use the following external organisations in the conduct of this study: • IQVIA – providing Clinical Research Associates • Veranex (Quartesian) – providing data management services
22.7 Principal Investigator Obligations (ISO 14155)	21.4 Principal Investigator Obligations (ISO14155:2011)	Wording updated to ensure ISO 14155:2020 compliance
Section numbering / protocol version and date updated throughout		

22.1.1.5 Approval/Notification

These updates will be submitted for EC/IRB approval. The changes will only be implemented after EC/IRB approval confirmation.

22.1.2 Protocol Amendment 2

22.1.2.1 Protocol Version Details

Protocol Type	Version and Date of protocol being amended	Amendment Number	Version and Date of amended protocol
Master	5.0; 08Nov2023	4	6.0; 15Jan2024

22.1.2.2 General Purpose and Rationale

The purpose of the amendment and the rationale for the changes are as follows:

1. Adjustment to the sample size calculation used in the CORI.2019.07 study. On a review of the sample size it was found that an error had led to too many patients being planned under the assumptions provided. A calculation was re-run under the same assumptions as the original sample size which found that the reduction of sample size allowed the study to still be appropriately powered and avoided recruiting further patients unnecessarily.
2. Update to the Insurance provision paragraph to reflect the fact this is a global study protocol and remove reference to a UK only guideline.
3. Protocol template update. At the time of the amendment the protocol template was also updated throughout to ensure it is compliant with the current effective protocol template (TMP-800052/TMP-CD-05 Rev 4).

22.1.2.3 Summary of Changes

22.1.2.3.1 Sample Size Changes

Synopsis, Section 11, Throughout (Where the Total Number of Subjects is Stated)

Old Text - Synopsis:

140 CORI Robotics procedures:

- 70 unicondylar knee arthroplasty (UKA)
- 70 total knee arthroplasty (TKA)

The statistical justification is provided separately for UKA and TKA and is based on data collected from the NAVIO™ Surgical System. N=70 subjects per arm, based on post-operative alignment (±3 degrees) with expected 92.1% NAVIO™ Surgical System vs. 73.4% from a historical control.

New Text - Synopsis

80 CORI Robotics procedures:

- 40 unicondylar knee arthroplasty (UKA)
- 40 total knee arthroplasty (TKA)

The statistical justification is provided separately for UKA and TKA and is based on data collected from the NAVIO™ Surgical System. N=40 subjects per arm, based on post-operative alignment (±3 degrees) with expected 92.1% NAVIO™ Surgical System vs. 73.4% from a historical control.

Old Text – Section 11:

Parratte et al.[53] looked at the effects of postoperative mechanical axis alignment on the survival of TKAs. They found that of the 398 TKAs reviewed in the paper there were 292 (73.4%) which post-operatively were defined as mechanically aligned (i.e. with a mechanical axis of 0˚ ± 3˚).

This study is designed to demonstrate superiority in the proportion of TKAs post-operatively defined as mechanically aligned against the reference proportion of 73.4% from above.

The proportion of mechanically aligned TKAs using the NAVIO™ Surgical System from a recent analysis was estimated to be 92.1% [54]. If this assumption holds for this study, then the enrollment of 63 knees for each of the two planned study groups (i.e. the CORI Robotics UKA and CORI Robotics TKA) for a total of 126 knees will individually provide 80% power to show that the lower limit of the two-sided 95% confidence interval for the proportion of mechanically aligned TKAs is greater than that obtained from literature. To account for up to a 10% attrition rate in knees enrolled, 70 knees in each group (140 knees combined, 70 UKA, 70 TKA) will be enrolled in the study.

New Text – Section 11:

Parratte et al.[53] looked at the effects of postoperative mechanical axis alignment on the survival of TKAs. They found that of the 398 TKAs reviewed in the paper there were 292 (73.4%) which post-operatively were defined as mechanically aligned (i.e. with a mechanical axis of 0˚ ± 3˚).

This study is designed to demonstrate superiority in the proportion of TKAs post-operatively defined as mechanically aligned against the reference proportion of 73.4% from above.

The proportion of mechanically aligned TKAs using the NAVIO™ Surgical System from a recent analysis was estimated to be 92.1% [54]. If this assumption holds for this study, then the enrollment of 36 knees for each of the two planned study groups (i.e. the CORI Robotics UKA and CORI Robotics TKA) for a total of 72 knees will individually provide approximately 80% power to show that the lower limit of the two-sided 95% confidence interval for the proportion of

mechanically aligned TKAs is greater than that obtained from literature. To account for up to a 10% attrition rate in knees enrolled, 40 knees in each group (80 knees combined, 40 UKA, 40 TKA) will be enrolled in the study.

22.1.2.3.2 Insurance

Section 18

Old Text:
Public/Products Liability Insurance has been purchased by Smith & Nephew plc. Worldwide and incorporates coverage for personal injury in respect of clinical studies. The Sponsor agrees to operate in good faith and in accordance with ABHI (Association of British Healthcare Industries) guidelines regarding compensation for injury arising in the course of clinical studies.

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

22.1.2.3.3 Protocol Template Update

Section 7

Addition of a new section:
7.9 Subject Reimbursement and Incentives
Subjects will be reimbursed for the costs of taking part in the study in compliance with local regulations. These costs will only cover study-specific activities or visits including time, travel, parking and inconvenience and will not cover activities or visits associated with the subject's standard clinical care. Payments to the subject will be proportionate to the time and expense involved in study participation and not so large as to unduly encourage the subjects to participate or affect the subject's ability to withdraw prematurely form the study. All arrangements for reimbursement payments to subjects will be approved by the IRB/IEC and/or local site authority as required.

Section 13

13. Investigator Obligations
Old Text:
The Principal Investigator will comply with the commitments outlined in the in the Statement of Investigator, provided by the Sponsor, and with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Appendix 22.7 Principal Investigator Obligations (ISO 14155) of this protocol.

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.

New Text:
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 22.7 Principal Investigator Obligations (ISO 14155) of this protocol. Sub-Investigators, who are individual member of the investigation site team designated and supervised by the Principal Investigator at an investigation site to perform clinical investigation-related procedures or to make important clinical investigation-related and medical treatment decisions, may have responsibilities delegated to them by the Principal Investigator. However, the Principal Investigator retains overall responsibility for the clinical investigation at the site.

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.

The Coordinating Investigator appointed by the Sponsor will assist in coordinating the work in the multicentre clinical investigation.

22.1.2.3.4 Corrections

Various typographical, grammatical and formatting errors were corrected within the document. In addition, use of abbreviations was standardized, and terms were added to/removed from the abbreviations list as necessary.

22.2 List of Instructions for Use & User Manuals

- CORI Robotics user's manual (Document ID: 500185, REAL INTELLIGENCE™ CORI™ for Knee Arthroplasty)
- IFU REAL INTELLIGENCE™ CORI™ Burs (Document ID: 500172)
- IFU REAL INTELLIGENCE™ CORI™ Flat Markers (Document ID: 500198)
- IFU REAL INTELLIGENCE™ CORI™ Irrigation (Document ID: 500173)
- IFU REAL INTELLIGENCE™ CORI™ Instrumentation Tray (Document ID: 500229)
- IFU Smith+Nephew Knee Implant Systems (Document ID: 81090287)
- IFU ZUK (Document ID: 81093274)
- IFU STRIDE (Document ID: 50030)

- IFU ANTHEM Total Knee System (Document ID: 81105696)

22.3 Equipment and Special Instructions

The following section provides a list of components of the CORI Robotics:

Table 22-1: CORI Components

Article	Description
ROB10000	CORI Starter Kit
ROB10024	REAL INTELLIGENCE CORI
ROB10025	REAL INTELLIGENCE Tracking Camera
ROB10026	REAL INTELLIGENCE Foot Pedal
ROB10027	REAL INTELLIGENCE Tablet
ROB10028	REAL INTELLIGENCE Transportation Case

Table 22-2: CORI Robotics Cart

Article	Description
ROB10002	REAL INTELLIGENCE Robotics Cart Column
ROB100021	REAL INTELLIGENCE Robotics Cart Base 120
ROB100022	REAL INTELLIGENCE Robotics Cart Base 220

Table 22-3: CORI Robotics Monitor

Article	Description
ROB10003	REAL INTELLIGENCE 24 in.Touch Screen

Table 22-4: CORI Robotics Tray and Instrumentation

Article	Description
ROB10001	REAL INTELLIGENCE Robotics Instruments
ROB10010	REAL INTELLIGENCE Bone Pins 4 mm x 127 mm
ROB10011	REAL INTELLIGENCE Bone Pins 4 mm x 152 mm
ROB10012	REAL INTELLIGENCE Checkpoint Pins

Article	Description
ROB10013	REAL INTELLIGENCE Robotic Drill
ROB10014	REAL INTELLIGENCE Robotic Drill Tracker
ROB10015	REAL INTELLIGENCE Robotic Drill Attachment
ROB10016	REAL INTELLIGENCE Robotic Drill Guard
ROB10017	REAL INTELLIGENCE Point Probe
ROB10018	REAL INTELLIGENCE Femur Tracker
ROB10019	REAL INTELLIGENCE Tibia Tracker
ROB10020	REAL INTELLIGENCE Tracker Clamp
ROB10021	REAL INTELLIGENCE Drill Guide
ROB10022	REAL INTELLIGENCE Checkpoint Tool
ROB10050	REAL INTELLIGENCE Robotics Instruments Tray
ROB10051	REAL INTELLIGENCE Robotics Pin Caddy
ROB10052	REAL INTELLIGENCE Robotics Pin Caddy Lid
71441351	Rasp
74013489	Speed Pin Driver
71935186	SCOTT CEMENT CURETTE
71935187	CEMENT CURETTE
ROB10086	REAL INTELLIGENCE Plane Visualizer

Table 22-5: CORI Robotics Shipping Inserts

Article	Description
ROB10055	REAL INTELLIGENCE Shipping Insert (A)
ROB10056	REAL INTELLIGENCE Shipping Insert (B)
ROB10057	REAL INTELLIGENCE Shipping Insert (C)
ROB10058	REAL INTELLIGENCE Shipping Insert (F)

Table 22-6: CORI Robotics Lids

Article	Description
ROB10087	Universal Base Tray Lid
ROB10088	Universal Insert Lid (A)
ROB10089	Universal Insert Lid (B)

Article	Description
ROB10090	Universal Insert Lid (C)
ROB10054	Universal Insert Lid (F)
ROB10091	Universal Insert Lid (G)
ROB10097	Universal Insert Lid (H)
ROB10098	Universal Insert Lid (I)
ROB10095	Universal Insert Lid (J)

Table 22-7: CORI Robotics Instrument Reduction Modules - Kits

Article	Description
ROB10004	JOURNEY II Uni Medial
ROB10085	JOURNEY II Uni Lateral
ROB10005	JOURNEY II TKA Essentials
ROB10006	JOURNEY II Distal Burring
ROB10007	JOURNEY II CR Module
ROB10008	JOURNEY II BCS Module
ROB10009	JOURNEY II XR Module
ROB10067	JOURNEY II Options Module

Table 22-8: CORI Robotics JOURNEY II UK Inserts

Article	Description
ROB10053	ROBOTICS FINISHING INSERT (F)
74036185	LEFT MEDIAL BASEPLATE TRIALS
74036127	MEDIAL INSERT TRIALS
74036174	RESECTION FEMORAL FINISHING TRIALS LM/RL
74036187	RIGHT MEDIAL BASEPLATE TRIALS
74036190	RESECTION FEMORAL FINISHING TRIALS RM/LL
74036196	LATERAL BASEPLATE TRIALS
74036198	LATERAL INSERT TRIALS
74036190	RESECTION FEMORAL FINISHING TRIALS RM/LL
74036196	LATERAL BASEPLATE TRIALS
74036174	RESECTION FEMORAL FINISHING TRIALS LM/RL

Table 22-9: CORI Robotics JOURNEY II Instrument Reduction Inserts

Article	Description
ROB10060	ROBOTICS FINISHING BASE
ROB10066	TIBIA FINISIHING INSERT (F)
ROB10092	LEFT TRIAL BASE
ROB10062	FEMUR TRIAL INSERT LEFT (FF)
ROB10064	TIBIA TRIAL INSERT LEFT (C)
ROB10093	RIGHT TRIAL BASE
ROB10063	FEMUR TRIAL INSERT RIGHT (FF)
ROB10065	TIBIA TRIAL INSERT RIGHT (C)
ROB10061	DISTAL BURRING INSERT (GG)
ROB10068	CR POLY TRIAL INSERT LEFT (II)
ROB10069	CR POLY TRIAL INSERT RIGHT (II)
ROB10070	CAM TRIAL INSERT LEFT
ROB10072	JOURNEY II BCS Finishing Insert (A)
ROB10071	CAM TRIAL INSERT RIGHT
ROB10079	JOURNEY II Robotics XR Poly Trial Insert Left (CC)
ROB10080	JOURNEY II Robotics XR Poly Trial Insert Right (CC)
ROB10094	JOURNEY II XR Tibia Finishing Insert (J)
ROB10096	JOURNEY II XR TIBIA IMPACTOR INSERT (GG)
ROB10073	JOURNEY II BCS Poly Trial Insert Left (HH)
ROB10074	JOURNEY II BCS Poly Trial Insert Right (HH)
ROB10075	JOURNEY II BCS Constrained Insert Left (HH)
ROB10076	JOURNEY II BCS Constrained Insert Right (HH)
ROB10077	JOURNEY II CR Deep Dish Insert Left (HH)
ROB10078	JOURNEY II CR Deep Dish Insert Right (HH)
ROB10081	JOURNEY II XR Poly Upslope Trial Insert Left (HH)
ROB10082	JOURNEY II XR Poly Upslope Trial Insert Right (HH)
ROB10083	J2 Robotics Universal Spacer Trial Insert (CC)
ROB10099	REAL INTELLIGENCE Flex Base

Table 22-10: Total Knee Instruments

Article	Description
ROB00003	TKA Femur Cut Adapter
ROB00005	TKA Femur Distal Cut Guide – Small

Article	Description
ROB00006	TKA Femur Distal Cut Guide – Med
ROB00007	TKA Femur Distal Cut Guide – Lg
ROB00014	TKA Femur Stabilizer – Small
ROB00015	TKA Femur Stabilizer – Med
ROB00016	TKA Femur Stabilizer – Lg
ROB00018	TKA Drill Guide – Journey II
ROB00024	TKA Drill Guide – Genesis II/Legion
ROB00025	TKA Left Tibia Twin Peg Cut Guide
ROB00026	TKA Right Tibia Twin Peg Cut Guide
ROB00060	TKA Distal FMR Punches – 38mm
ROB00061	TKA Distal FMR Punches – 45mm

Table 22-11: CORI Robotics Disposables

Article	Description
4951	Tablet Drape
ROB10031	Tubing Set
ROB10032 PFSDV0016	Flat Markers
ROB10033	6 mm Bullet Bur
ROB10034	6 mm Chip Breaker Bullet Bur
ROB10035	5 mm Cylindrical Bur
ROB10036	6 mm Cylindrical Bur
74013401	Speed Pins (110 mm)
74013490	Speed Pins (80 mm)

Table 22-12: CORI Robotics Country Bundles

Article	Description
ROB20000	CORI Robotics USA
ROB20001	CORI Robotics EMEA Bundle 1
ROB20002	CORI Robotics EMEA Bundle 2
ROB20003	CORI Robotics EMEA Bundle 3
ROB20004	CORI Robotics EMEA Bundle 4
ROB20005	CORI Robotics EMEA Bundle 5

Article	Description
ROB20006	CORI Robotics EMEA Bundle 6
ROB20007	CORI Robotics APAC Bundle 1
ROB20008	CORI Robotics APAC Bundle 2
ROB20009	CORI Robotics APAC Bundle 3
ROB20010	CORI Robotics APAC Bundle 4
ROB20011	CORI Robotics APAC Bundle 5
ROB20012	CORI Robotics ROW Bundle 1
ROB20013	CORI Robotics ROW Bundle 2
ROB20014	CORI Robotics ROW Bundle 3
ROB20015	CORI Robotics ROW Bundle 4
ROB20016	CORI Robotics ROW Bundle 5

Table 22-13: CORI Robotics Welcome Box

Article	Description
ROB10299	Welcome Box USA
ROB10300	Welcome Box ROW 1
ROB10301	Welcome Box ROW 2
ROB10302	Welcome Box ROW 3
ROB10303	Welcome Box ROW 4
ROB10304	Welcome Box ROW 5
ROB10305	Welcome Box EMEA 1
ROB10306	Welcome Box EMEA 2
ROB10307	Welcome Box EMEA 3
ROB10308	Welcome Box EMEA 4
ROB10309	Welcome Box EMEA 5
ROB10310	Welcome Box APAC 1
ROB10311	Welcome Box APAC 2
ROB10312	Welcome Box APAC 3
ROB10313	Welcome Box APAC 4
ROB10314	Welcome Box APAC 5
ROB10315	Welcome Box APAC 6

Table 22-14: CORI Robotics Product Documents / Other

Article	Description
ROB10400	REAL INTELLIGENCE Implant Database v2.85
ROB10401	REAL INTELLIGENCE Archiving USB
ROB10402	REAL INTELLIGENCE Supporting Documents
ROB10403	REAL INTELLIGENCE CORI Quick Start Guide
ROB10404	REAL INTELLIGENCE CORI Tray Guide
ROB10400	REAL INTELLIGENCE Implant Database v2.85

Table 22-15: CORI Robotics Power Cords

Article	Description
ROB10199	Power Cord North America
ROB10200	Power Cord ROW 1
ROB10201	Power Cord ROW 2
ROB10202	Power Cord ROW 3
ROB10203	Power Cord ROW 4
ROB10204	Power Cord ROW 5
ROB10205	Power Cord EMEA 1
ROB10206	Power Cord EMEA 2
ROB10207	Power Cord EMEA 3
ROB10208	Power Cord EMEA 4
ROB10209	Power Cord EMEA 5
ROB10210	Power Cord EMEA 6
ROB10211	Power Cord APAC 1
ROB10212	Power Cord APAC 2
ROB10213	Power Cord APAC 3
ROB10214	Power Cord APAC 4
ROB10215	Power Cord APAC 5

22.4 Health Economic Outcome Measures/Quality of Life measures

Not applicable

22.5 Clinical Study Sites

Smith + Nephew will maintain a list of the name and address of involved sites in the Trial Master File. This list is available upon request.

22.6 Contract Research Organization

S+N will use the following external organisations in the conduct of this study:

- IQVIA – providing Clinical Research Associates
- Veranex (Quartesian) – providing data management services

22.7 Principal Investigator Obligations (ISO 14155)

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.
   b. The PI is responsible for ensuring adequate training and qualification of the investigation site team and for maintaining oversight of their activities. The principal investigator may delegate tasks to qualified members of the investigation site team but retains responsibility for the clinical investigation (see also 7.6). This also applies when activities are outsourced to an external organization by the principal investigator in which case he/she shall implement procedures to ensure the integrity of all tasks performed and any data generated by this external organization.
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 an investigation site team that is: qualified by education, training, and experience to assume responsibility for the proper conduct of the clinical investigation in accordance with this document; evidence of such qualifications for members of the investigation site team shall be documented through up-to-date CVs or other relevant documentation,.
   c. has adequate facilities.
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.
      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 their 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 their 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 their 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 their medical condition allows.

d. The Principal Investigator may not enroll a subject without obtaining informed consent of the subject or their 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. Statement indicating that a description of the clinical investigation has or shall be registered in a publicly accessible database

xiii. 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 and no loss of benefits to which the subject is otherwise entitled;
   iii. A statement declaring that discontinuation/withdrawal and thereby revoking the informed consent 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 that the subject acknowledges the information provided during the informed consent process and that (s)he had ample time to consider participation
   vi. A statement confirming that the subject or their 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 their 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 their 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 as well as maintain documentation of the type and location of these source documents,,
   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. Comply with the procedure for the safe return of investigational devices including potentially hazardous devices and, in the case of reported device deficiencies, collaborate with the sponsor to provide the necessary information allowing an accurate analysis where appropriate. requirements and provide any information need to analyze device deficiencies, if applicable.
m. allow and support the Sponsor to perform monitoring and auditing activities,
n. be accessible to the monitor and respond to questions during monitoring visits,
o. determine the cause and implement appropriate corrective and preventative actions to address significant noncompliance,
p. allow and support regulatory authorities and the IEC when performing auditing activities,
q. ensure that all clinical-investigation-related records are retained as required taking measures to prevent accidental or premature destruction, and
r. 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.

Note, for studies conducted under 21 CFR Part 812 Investigational Device Exemption Regulations, an investigator shall prepare and submit the following complete, accurate, and timely reports:

1. Unanticipated Adverse Device Effects An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
2. Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
3. Progress. An investigator shall submit progress reports on the investigation to the sponsor, the monitor, and the reviewing IRB at regular intervals, but in no event less often than yearly.
4. Deviations from the investigational plan. An investigator shall notify the sponsor and the reviewing IRB of any deviation from the investigational plan to protect the life or physical well-being of a subject in an emergency. Such notice shall be given as soon as possible, but in no event later than 5 working days after the emergency occurred. Except in such an emergency, prior approval by the sponsor is required for changes in or deviations from a plan, and if these changes or deviations may affect the scientific soundness of the plan or the rights, safety, or welfare of human subjects, FDA and IRB also is required.
5. Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.

Investigational device including clinical procedure risks and their disclosure. The PI shall:

a. Evaluate risks according to ISO 14971 before starting a trial,
b. Summarize benefit-risk analysis in trial documents,
c. Add residual risk and their nature, occurrence, severity, and outcome to the IB,
d. Include in CIP all anticipated adverse device effects and a rationale for the related benefit-risk ratio,
e. Include any anticipated adverse device effect in the consent form.

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Envelope Summary Events	**Status**	**Timestamps**
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Certified Delivered	Security Checked	11-Mar-2024 | 08:24
Signing Complete	Security Checked	11-Mar-2024 | 08:36
Completed	Security Checked	11-Mar-2024 | 08:36
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You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
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To advise Smith Nephew - Sub of your new email address

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