Smith+Nephew

Clinical Protocol	**Study Number:** CORI.2019.06
A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) Procedure	**Version**: 4.0-Master, 07 Sep 2022
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Sponsor Name and Address:	Smith & Nephew, Inc., 1450 E. Brooks Road, Memphis, TN 38116, United States
Investigational Product(s)	REAL INTELLIGENCE™ CORI™ (referred as "CORI" throughout this document)
Single Identification Number of Clinical Investigation	CORI.2019.06
Protocol Author(s):	Manvendra Saxena, Clinical Study Manager Babajide Olayinka, Senior Biostatistician
Summary of Revision History	Version 2.0 04 Sep 2020 Version 2.1 14 Jan 2021 Version 3.0-Master 03 Mar 2021 Version 4.0-Master 07 Sep 2021

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, Randomized Controlled Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) Procedure", version 4.0-Master, dated 07Sep2022, and agree to abide by all provisions set forth herein.
I agree to comply with the Investigator's Obligations stipulated in Section 22.6 Principal Investigator Obligations according to ISO 14155:2020 and all applicable local legislation and regulations.
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the conduct of the described clinical investigation without the prior written consent of Smith & Nephew Inc.

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

1.2 COORDINATING INVESTIGATOR APPROVAL

☐ I have read the attached protocol entitled "A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) Procedure", version 4.0-Master, dated 07Sep2022, and agree to abide by all provisions set forth therein.

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

1.3 SPONSOR APPROVAL

Name and Title	Signature and Date / DocuSign Stamp
Rachael Winter, Senior Director, Global Clinical Operations	DocuSigned by: Rachael Winter Signer Name: Rachael Winter Signing Reason: I approve this document Signing Time: 25-Nov-2022 | 08:41:03 GMT A32F12A80F1B4490986E80ACCB7471CB
Julian Yang, Director, China Clinical Affairs	DocuSigned by: Julian Yang Signer Name: Julian Yang Signing Reason: I approve this document Signing Time: 22-Nov-2022 | 01:39:38 GMT 7874D1D26E584792AFFC91EBB7CEF6D0
Julie Lankiewicz, Clinical Strategy Director Robotics	DocuSigned by: Julie Lankiewicz Signer Name: Julie Lankiewicz Signing Reason: I approve this document Signing Time: 21-Nov-2022 | 14:14:22 GMT 59CD0029AA274067A40E4605966E81DA
Michael Robinson, Independent Statistician signing on behalf of Director Biostatistics & Data Management	DocuSigned by: Michael Robinson Signer Name: Michael Robinson Signing Reason: I approve this document Signing Time: 22-Nov-2022 | 14:40:41 GMT 0E27C33EB43441FB820C99CBC38E7E89

Luca Orlandini, VP Medical Affairs	DocuSigned by: Signer Name: Luca Orlandini Signing Reason: I approve this document Signing Time: 22-Nov-2022 | 22:31:50 GMT FC872951AC1C4261B85EC7A7CD09ACDC
Lisa Ewing, Director, Regulatory Affairs Orthopedics & Robotics	DocuSigned by: Lisa Ewing Signer Name: Lisa Ewing Signing Reason: I approve this document Signing Time: 21-Nov-2022 | 16:00:24 GMT 2E1A455324AA4FAD8477965D1980CCED
Kerry Geng, Senior. Director, Head of Regulatory Affairs and Quality	DocuSigned by: Kerry Geng Signer Name: Kerry Geng Signing Reason: I approve this document Signing Time: 21-Nov-2022 | 09:15:58 GMT 915D993DECAC45C6B47B47118A847FBA
Kate Drysdale Senior Clinical Compliance and Training Manager	DocuSigned by: Kate Drysdale Signer Name: Kate Drysdale Signing Reason: I approve this document Signing Time: 22-Nov-2022 | 08:49:59 GMT C3124B89DAB7491083D68451D2B9ED3C

2 SYNOPSIS

Title of Study:	A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) procedure
Study Design:	Prospective, multi-center, randomized controlled study
Study Type:	Post-market study in Australia, New Zealand, South Korea & China (Hong Kong) Pre-market study in China Mainland
Study Product:	REAL INTELLIGENCE™ CORI™ (CORI) is a computer-assisted orthopedic surgical navigation and burring system. CORI 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 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 software consists of a patient and user management module, a surgical planner, and an intra-operative cutting module.
Comparison Groups	Conventional approach with conventional manual instrumentation will be used as the comparison group.
Study Purpose:	This is a prospective randomized controlled study to demonstrate the safety and effectiveness of CORI and to register CORI in China mainland.

Primary Objective:	To evaluate the use of CORI in unicondylar knee arthroplasty (UKA) procedures in achieving post-operative leg alignment as compared to procedures using conventional manual instruments.
Secondary Objective(s):	To generate safety and performance evidence supporting the use of CORI procedures. To assess the safety and performance of CORI up to 12 months after surgery as compared to procedures using conventional manual instruments.
Other Objective(s):	To collect CORI system time and cutting time of the robotic drill from the CORI Case Report.
Sample Size:	140 in total: • 70 CORI procedure for UKA • 70 Conventional procedures for UKA 1. The statistical justification for CORI UKA is based on data collected from the NAVIO™ Navigation System, the former generation of CORI. 2. N=70 subjects per arm, based on post-operative alignment (±3 degrees) with expected 92.1% NAVIO™ vs. 73.4% from a historical control.
Number of Study Sites:	Up to 8 sites
Targeted Global Regions:	Australia, China Mainland, China (Hong Kong), South Korea, and New Zealand

Inclusion Criteria:	1. Subject is a suitable candidate for a UKA procedure using CORI and a compatible Smith & Nephew (S+N) Knee implant system. 2. Subject requires a cemented UKA as a primary indication that meets any of the following conditions: a) Non-inflammatory degenerative joint disease, including osteoarthritis b) Avascular necrosis c) Requires correction of functional deformity d) 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 Ethics 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. Applicable routine radiographic assessment is possible.
Exclusion Criteria:	1. Subject receives a UKA 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 (e.g., stems, augments, or custom-made devices). 2. Subject has been diagnosed with post-traumatic arthritis

	3. Subject receives simultaneous bilateral UKA OR a unilateral UKA with contralateral TKA. 4. Subject has one or more of the following arthroplasties that are not fully healed and well-functioning, as determined by the investigator: -Contralateral primary TKA or UKA, however, the subject can only have one knee enrolled in this study. 5. Subject does not understand the language used in the Informed Consent Form. 6. Subject does not meet the indication or is contraindicated for UKA according to specific S+N knee system's Instructions for Use (IFU). 7. Subject has active infection or sepsis (treated or untreated). 8. Subject is morbidly obese with a body mass index (BMI) greater than 40. 9. Subject is pregnant or breast feeding at the time of surgery. 10. 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. 11. Subject currently enrolled in another orthopedic clinical trial study. 12. Subject has a condition(s) that may interfere with the 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).

	13. 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, intellectual disability, drug or alcohol abuse. 14. Subject, in the opinion of the Investigator, has a neuromuscular disorder that prohibited control of the index joint. 15. Subject is a prisoner or meets the definition of a Vulnerable Subject per ISO 14155:2020 Section 3.55.
Study Duration:	**Estimated timeline:** • Study period: 36 months • Start enrolment: April 2022 • Last subject first visit: March 2024 • Last subject last visit: April 2025
Primary endpoint:	Post-operative leg alignment via radiographic assessment (the proportion of subjects achieving planned post-operative leg alignment 6 weeks after surgery, defined as ± 3° from target)
Secondary endpoint(s):	• Component Alignment • Radiographic assessment (Presence of radiolucent lines, osteolysis & implant migration) • 2011 Knee Society Score (2011 KSS) • Oxford Knee Score (OKS) • Forgotten Joint Score (FJS-12) • Five-level EuroQol five-dimensional (EQ-5D-5L) Visual Analogue Scale (VAS) and index scores

Other exploratory endpoint(s):	Each enrolled subject's CORI Case Report will be collected to document the system time and cutting time of the robotic drill.
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 14155:202020 and applicable local laws and regulations.

STUDY SCHEDULE

Schedule of events	Pre-Operative Data -90 to 0 days	Operative Data & Discharge Day 1 (+ up to 9 days)	6 weeks 42 ± 14 days	6 months 185 ± 14 days	12 months 365 ± 30 days
Informed Consent	x				
Demographics/ Medical History	x				
Inclusion/Exclusion	x				
Preoperative Examinations (e.g. ECG, Blood Routine Examination, Biochemical Examination, Coagulation Examination)[1]	x				
Pregnancy Test[2]	x				
Concomitant Medication	x				
Concomitant Medication Update		x	x	x	x
Operative Data Collection		x			
CORI Case Report (System time & cutting time)		x			
Discharge Data Collection		x			
Leg alignment Long leg X-ray AP[3]	x	(x)[4]	x		(x)[5]

Standard Lateral X-ray		(x)[4]	x		x
Standard A/P X-ray					x
KSS	x		x	x	x
OKS	x		x	x	x
FJS-12			x	x	x
EQ-5D-5L	x		x	x	x
Safety Assessment		x	x	x	x
End of Study/Exit			(x)[6]	(x)[6]	x

1 Only applicable at site in China
2 Only Applicable at site in China
3 Pre-operative long leg X-rays (A/P) collected 6-months prior to the date of surgery is admissible.
4 Post-operative standing weight bearing long leg X-rays (A/P) and standard lateral X-rays may be taken at discharge.
5 Only if standing weight bearing long leg A/P X-ray is taken as a standard of care at 12 months.
6 Exit form to be completed at the point of withdrawal if the study is not completed

3 CONTENTS

Table of Contents

3.1 List of Tables

3.2 LIST OF FIGURES

3.3 List of Abbreviations and definitions

Abbreviation	Definition
ADE	Adverse Device Effect(s)
AE	Adverse Event(s)
ACL	Anterior Cruciate Ligament
ANCOVA	Analysis of Covariance
A/P	Antero-posterior
ASADE	Anticipated Serious Adverse Device Effect
AVN	Avascular Necrosis
BMI	Body Mass Index
CAS	Computer-assisted navigation systems
CE	Conformité Européene
CI	Confidence Interval
CORI	REAL INTELLIGENCE™ CORI™
eCRF	Electronic Case Report Form(s)
CRO	Contract Research Organization
CTA	Clinical Trial Agreement
CV	Curriculum Vitae
DD	Device Deficiency(ies)
DMP	Data Management Plan
ECG	Electrocardiogram
EDC	Electronic Data Capture
EQ-5D-5L	Five-level EuroQol five-dimensional
FAS	Full Analysis Set Population
FDA	Food and Drug Administration
FJS-12	Forgotten Joint Score
FU	Follow-Up

Abbreviation	Definition
GCP	Good Clinical Practice
GDPR	EU Global Data Protection Regulation
HIPAA	Health Information Portability Accountability Act
HKA	Hip-Knee-Ankle
HRQoL	Health Related Quality of Life
IB	Investigator's Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFU	Instructions for Use
IP	Investigational Product
IRB	Institutional Review Board
ISF	Investigator Site File
ITT	Intention to Treat population
2011 KSS	Knee Society Score, 2011
LCL	Lateral Collateral Ligament
LL	Lower Limit
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™ Navigation System
NMPA	National Medical Products Administration
OA	Osteoarthritis
OKS	Oxford Knee Score
OR	Operating room
PCL	Posterior Cruciate Ligament
PI	Principal Investigator
PICF	Patient Informed Consent Form

Abbreviation	Definition
PMA	Pre-Market Authorization
PP	Per-protocol Population
PSI	Patient specific instrumentation
RA	Rheumatoid Arthritis
RCT	Randomized Controlled Trial
S+N	Smith & Nephew, Inc., 1450 E. Brooks Road, Memphis, TN 38116, United States
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 and 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 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 a 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 Australia, 660,000 primary TKAs and 60000 primary UKAs have been performed in 2018. Since 2003, the number of knee replacement procedures undertaken has increased by 128% [18].

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 [19, 20]. 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) [20, 21]. 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 [22]. Malalignment of components in any anatomical plane can cause major complications including aseptic loosening, instability, poor function, polyethylene wear, and pain [22-24]. Additionally, implant malposition and malalignment of the joint can result in failure of the prosthesis [25]. 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 [26].

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 [27]. For partial knee procedures, approximately 30-60% of UKAs have been reported to be malaligned using conventional manual instruments [28]. The importance of alignment can be demonstrated by observing higher revision rates of UKA attributed to malposition or malalignment of partial knees [28, 29] while roughly 25% of TKAs have been revised for instability or malalignment [30].

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 [31]. 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 CORI. 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 navigation systems to conventional instruments have demonstrated that robotic platforms produce fewer positioning errors in both UKA and TKA [32-34]. 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 [35-37].

For China, CORI is an investigational device - for details of the full literature review, pre-clinical, clinical, safety data and a risk analysis refer to the Investigator's Brochure (IB).

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 Navigation Knee Surgical Systems.

Use of the Navigation Knee Surgical Systems was reported in 7 publications with 1 being a prospective study and the remaining 6 being retrospective studies shown in Table 4.2-4-1. Three (3) of the studies solely reported on outcomes of the Navigation Knee Surgical Systems, three (3) compared the Navigation Knee Surgical

Systems to conventional instruments, and one (1) study compared the Navigation Knee Surgical Systems to conventional instruments, patient specific instrumentation (PSI), and computer-assisted navigation (CAS) systems. All of the studies were for the NAVIO™ Navigation System (NAVIO) and reported outcomes for UKA. The data provided in these publications is also applicable to the equivalent CORI.

Table 4.2-4-1 Demographic Information for the Navigation Knee Surgical Systems

Primary Author	Year	Navigation System	Indication	Joints (n)	Male (%)	Age, mean±SD (range)	Follow-up, mean±SD
Batailler [38]	2019	NAVIO[1]	UKA	80	33.8	69 ± 9.6 (49-87)	1.64 ± 0.75 years
Battenberg [39]	2019	NAVIO[1]	UKA	128	57.8	64.7 ± 9.6 (45-92)	2.3 years
Canetti [40]	2018	NAVIO[1]	UKA	11	18.0	66.5 ± 6.8 (57-79)	2.87 ± 0.88 years
Gregori [41]	2016	NAVIO[1]	UKA	92	-	-	Periop
Herry [42]	2017	NAVIO[1]	UKA	40	32.5	69 ± 9.6 (49-87)	Periop
Vega Parra [43]	2017	NAVIO[1]	UKA	47	51.0	67 (45-77)	1 year
Sephton [44]	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.[42] and Canetti et al.[40] likely shared the same patient population as Batailler et al.[38] 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 Navigation 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 NAVIO 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-12), 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.[38] and Canetti et al.[40].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.[38] and Canetti et al. compared patients operated on with NAVIO 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. observed a statistically significant increase in KSS and quicker return to sport for NAVIO. As the KSS difference was not observed in the larger cohort of Batailler et al.[38], the observed difference may be due to the smaller sample size. The percentage of patients returning to sports, UCLA,

Lysholm scale, and FJS-12 were not statistically significant between the two cohorts.

Overall, patients undergoing knee procedures with NAVIO showed improved KSS, KSFS, KOOS, and UCLA scores compared to pre-operative values.

4.2.3 Mechanical Alignment Accuracy

The Navigation 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 Navigation 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 [38, 41, 42].

The reviewed publications indicate that the Navigation 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% [38]. 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.[38] and Herry et al.[42] compared alignment with NAVIO 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 NAVIO 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 NAVIO was used.

Using the Navigation 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 distal 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 Navigation 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.[38] 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 Navigation 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 Navigation knee surgical systems showed improved outcomes scores compared to pre-operative values. The clinical outcomes, alignment accuracy, and adverse events for the Navigation 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, randomized controlled study to demonstrate the safety and effectiveness of CORI to support the regulatory approval by the National Medical Products Administration (NMPA) in China. Data collected in this study may also be used to maintain product registration in global markets including, but not limited to, Australia (Therapeutic Goods Administration (TGA)) and Europe (Conformité Européene (CE)).

4.4 SAFETY CONSIDERATIONS

CORI's intended use, indications and contraindications can be found in the User's Manual & Instructions for Use (IFU) for Australia, China (Hong Kong), South Korea, and New Zealand or the Investigator's Brochure for China Mainland.

4.4.1 Intended Use

CORI 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 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 is indicated for use with cemented implants only.

4.4.3 Contraindications

CORI 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 Environments of Use

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

4.4.5 Potential 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.

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

- CORI 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 is being used.

- CORI 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 S+N.
- Use of equipment not specifically designated in this manual as compatible with CORI 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 is not serviced properly.
- To avoid risk of electrical shock, only connect the CORI Cart to a supply main with protective earth.
- Modification of CORI 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 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.

5 OBJECTIVE(S)

5.1 PRIMARY OBJECTIVE

The primary objective of this study is to evaluate the use of CORI in UKA procedures in achieving post-operative leg alignment as compared to procedures using conventional manual instruments.

5.2 SECONDARY OBJECTIVE(S)

The secondary objective of this study is to generate safety and performance evidence supporting the use of CORI procedures. To assess the safety and performance of CORI up to 12 months after surgery as compared to procedures using conventional manual instruments.

5.3 OTHER OBJECTIVE(S)

Other objectives are to collect the system time and cutting time of the robotic drill from the CORI Case Report.

5.4 CLAIMS

No claims to be confirmed by this investigation.

6 INVESTIGATIONAL PRODUCT(S) AND COMPARATOR

6.1 IDENTIFICATION

6.1.1 Investigational Product

CORI 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.

CORI is currently avaible for the use of the following S+N UKA implant Systems, the implant system will be selected according to the registration status in each country.

Table 6.1-6-1 S+N Implant Systems available with CORI

Implant System	Manufacturer
Journey II Unicompartamental Knee System	Smith & Nephew, Inc.
Journey Uni	Smith & Nephew, Inc.

CORI 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 6.1-6-1). CORI 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.

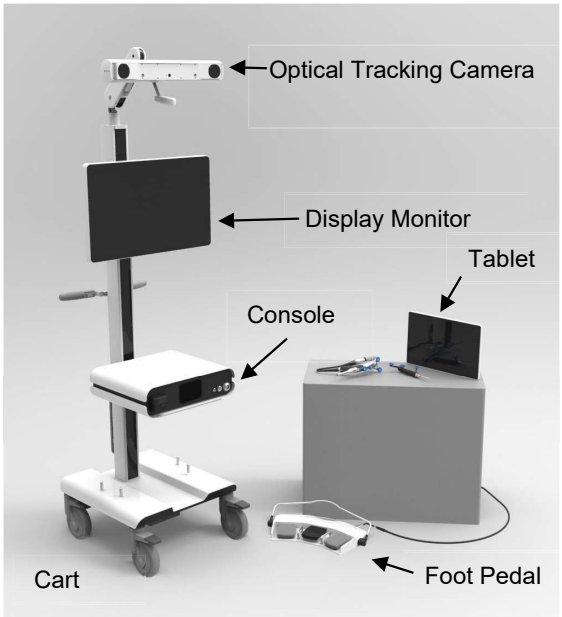
CORI incorporates a detailed user interface that provides procedure setup, tracking status, visual indicators, and real-time cutting progress during the procedure. The system uses the tracked position of the surgical bur to control its cutting engagement to the bone that is intended to be removed. The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

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, CORI 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 CORI robotic drill as a standard navigated surgical drill.

Figure 6.1-6-1 CORI



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 unicondylar knee arthroplasty (UKA) and for total knee arthroplasty (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**.**

  *Only UKA related components will be used for the study.

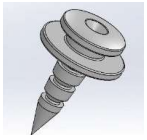
CORI also includes specific reusable instruments as shown in Figure 6.1-6-2.

Figure 6.1-6-2 CORI Reusable Instruments

CORI Robotic Drill

Point Proble

Femur & Tibia Trackers



Checkpoint Pins

Bone Screw

- **CORI Robotic Drill:** Controls the position and speed of the bur. It is intended for 75 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.

Details on single use instruments of CORI can be found in Section 22.3.

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

6.1.2 Comparator Treatment

CORI will be compared to conventional manual instrumentation currently available in Australia, China (Hong Kong), New Zealand, South Korea, and China Mainland.

Arthroplasty has traditionally used conventional manual instruments to guide placement of the implant and determine bone resection in reference to anatomical landmarks. Manual instruments include intramedullary or extramedullary rods that centralize and align the components according to the surgical plan as shown in Figure 6.1-6-3 & Figure 6.1-6-4.

Figure 6.1-6-3 Extramedullary rod

Figure 6.1-6-4 Intramedullary rod

6.1.3 Ancillary Product(s)

Not applicable.

6.2 PRODUCT USE

CORI has a user's manual (Document ID: 500230, REAL INTELLIGENCE™ CORI™ for Knee Arthroplasty). The purpose of this user's manual is to serve as the master reference document for properly trained users in the function and operation of CORI 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™ Irrigation (Document ID: 500173)
- IFU REAL INTELLIGENCE™ CORI™ Instrumentation Tray (Document ID: 500229)

For Australia, Hong Kong, South Korea, and New Zealand the list of reference documents can be found in Appendix Section 22.3Instruction For Use & User Manual.

For China mainland, details of the use of CORI can be found in the Investigator's Brochure.

6.3 PACKAGING 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 System are commercial products in the Australia, China(Hong Kong), South Korea, and New Zealand and are being used as approved. Labeling is done as per the standard commercial packaging.

In China mailand, CORI is a an investigational product. The standard commercial packaging as marketed in the US is used. However, additional labels will be included on the commercial packaging to meet the regulatory requirements for investigational devices in countries where the devices are not approved for marketing.

Compatible S+N Knee Implant Systems are commercial products in Australia, China (Hong Kong), New Zealand, and China mainland and are being used as approved.

6.3.2 Comparator Product

Conventional approach with conventional manual instrumentation will be used as the comparison group and there will be no packaging involved with the conventional approach.

S+N Knee Implant Systems are commercial products in Australia, Hong Kong, New Zealand, South Korea, and China mainland and are being used as approved.

6.4 PRODUCT ACCOUNTABILITY PROCEDURES

This study is a post-market study in Australia, Hong Kong, South Korea, and New Zealand. However, the sponsor provides the study sites with CORI System (Console, Optical Tracking Camera, Foot Pedal, Tablet, Display Monitor, Cart, CORI Instrument Trays UKA) 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 at all study sites.

The investigational site will maintain an inventory of the investigational product. 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.

For details on CORI and reusable instrumetation please refer to Section 6.1.1 Investigational Product.

6.5 SURGICAL TECHNIQUE

All study related procedures with CORI must be performed according to the user's manual (Document ID: 500230 CORI Robotics for Knee Arthroplasty for Australia, Hong Kong, South Korea, and New Zealand, as well as Investigator's Brochure for China) and according to the according to the surgical technique and IFU of the specific S+N Implant System.

Surgeons selected to participate in this study will be familiar with CORI and have written evidence of training and expertise in the study procedure. The Surgeon will conduct Pre-study in order to establish the expertise of the individual surgeons. The exact number of pre-study cases may be adjusted depending on the level of the individual experience of the surgeon.

CORI Case Reports Forms of the non-randomized cases will be collected as proof of surgeons' experience and for inclusion in the safety analysis set (applicable only at sites in China).

6.6 MEDICAL PROCEDURE

There are 3 basic steps in unicondylar knee arthroplasty. The first step is preparing the bone and removing the cartridge from the damaged knee compartment. This will be completed using either the CORI robotic drill or an oscillating saw. The surgeon will then position the metal implants on the damaged side of the femur and tibia using several orthopaedic tools. Finally, a spacer will be inserted between the metal implants to reduce friction when the knee flexes and extends. At various times during

the procedure, the hip-knee-ankle angle (HKA) will be checked using the CORI advanced tracking system or via the use of intramedullary and / or extramedullary rods. How the angle is measured will depend on which treatment arm the subject is randomized to receive. All unicondylar knee arthroplasty is completed using general anaesthetic by a surgical team trained in both the CORI system and the use of standard manual instrumentation.

7 SUBJECT ENROLLMENT AND WITHDRAWAL

7.1 SUBJECT POPULATION

At least 145 subjects will be enrolled into the study. At least 5 of these subjects will be treated with CORI directly to fulfil the learning needs of the surgeons prior to enrolling, a further 140 subjects who will be enrolled in the randomized stage of the study in up to 8 sites in Australia, Hong Kong, New Zealand, South Korea, and China mainland. Seventy (70) subjects will be enrolled for UKA with the use of the CORI and 70 subjects will be enrolled for UKA with the use of conventional manual instrumentation. Vulnerable subjects will not be enrolled in this study.

7.2 INCLUSION CRITERIA

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

1	Subject is a suitable candidate for a UKA procedure using CORI and a compatible S+N Knee Implant System.
2	Subject requires a cemented UKA as a primary indication that meets any of the following conditions: a) Non-inflammatory degenerative joint disease, including osteoarthritis b) Avascular necrosis c) Requires correction of functional deformity d) 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 Ethics 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	Applicable routine radiographic assessment is possible.

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 UKA 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 (e.g. stems, augments, or custom made devices).
2	Subject has been diagnosed with post-traumatic arthritis
3	Subject receives simultaneous bilateral UKA OR a unilateral UKA with contralateral TKA.
4	Subject has one or more of the following arthroplasties that are not fully healed and well-functioning, as determined by the investigator: -Contralateral primary TKA or UKA, however, the subject can only have one knee enrolled in the study.
5	Subject does not understand the language used in the Informed Consent Form.
6	Subject does not meet the indication or is contraindicated for UKA according to specific S+N knee system's Instructions for Use (IFU).
7	Subject has active infection or sepsis (treated or untreated).
8	Subject is morbidly obese with a body mass index (BMI) greater than 40.
9	Subject is pregnant or breast feeding at the time of surgery.
10	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.
11	Subject currently enrolled in another orthopedic clinical trial study.

12	Subject has a condition(s) that may interfere with the 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).
13	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, intellectual disability, drug or alcohol abuse.
14	Subject, in the opinion of the Investigator, has a neuromuscular disorder that prohibited control of the index joint.
15	Subject is a prisoner or meets the definition of a Vulnerable Subject per ISO 14155:2020 Section 3.55.[1]

[1] ISO 14155:2020 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 participate, or who could be manipulated or unduly influenced as a result of a compromised position, expectation of benefits or fear of retaliatory response

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.

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.

In China sites, part of the screening process will include documentation of women's childbearing potential. If the woman is not of childbearing potential this should be documented in the medical history (e.g., surgically postmenopausal, postmenopausal [i.e., at least one year without menses]). For women of childbearing potential, their method of birth control should be documented in the source.

7.5 INFORMED CONSENT

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

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

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

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

ICFs will comply with applicable laws and regulations in Australia (Privacy Act 1988), China, South Korea, and New Zealand (Privacy Act 1993). 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 ENROLMENT

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

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

7.7 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he/she does not appear for the scheduled study visit for two (2) consecutive visits, 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

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 is lost to follow-up
- The Investigator or the Sponsor terminates the study for any reason
- 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 withdraw or are withdrawn by the investigator cannot be re-enrolled in the study. Withdrawn subjects will not be replaced.

If at any point during the study, the unicondylar 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 the Study

Study participation is voluntary, and subjects may withdraw from the study at any time. Where subjects withdraw consent, the Investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's right to privacy. The reason for withdrawal will be recorded in the eCRF and source documents.

7.8.4 Use of Data Following Withdrawal

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

8 STUDY DESIGN

8.1 STUDY DESIGN

This study is a prospective, multi-center, randomized controlled, non-blinded follow-up study to evaluate the use of CORI in UKA procedure in achieving post-operative leg alignment. Up to 8 sites will participate within Australia, China (Hong Kong), New Zealand, South Korea, and China Mainland.

The pre-randomized stage of the study will comprise of at least 5 subjects enrolled and treated with CORI directly in order to fulfil the learning needs of the surgeons. Subjects who will comprise the randomized stage of the study will be enrolled and randomized into one of two (2) groups, as shown in Table 8.1-8-1.

All groups are treated with knee arthroplasty with a S+N Knee Implant System. (The implant system will be selected according to the registration status in each country).

Table 8.1- 8-1 Overview of Study Groups

Surgery	Knee Implant system	Surgical Technique (Groups)	Number of Subjects
Primary UKA	S+N UKA Implant System (Journey II Unicompartamental Knee System, Journey Uni)	CORI	70
		Conventional manual instrumentation	70

Figure 8.1-8-1 Study Recruitment Timeline

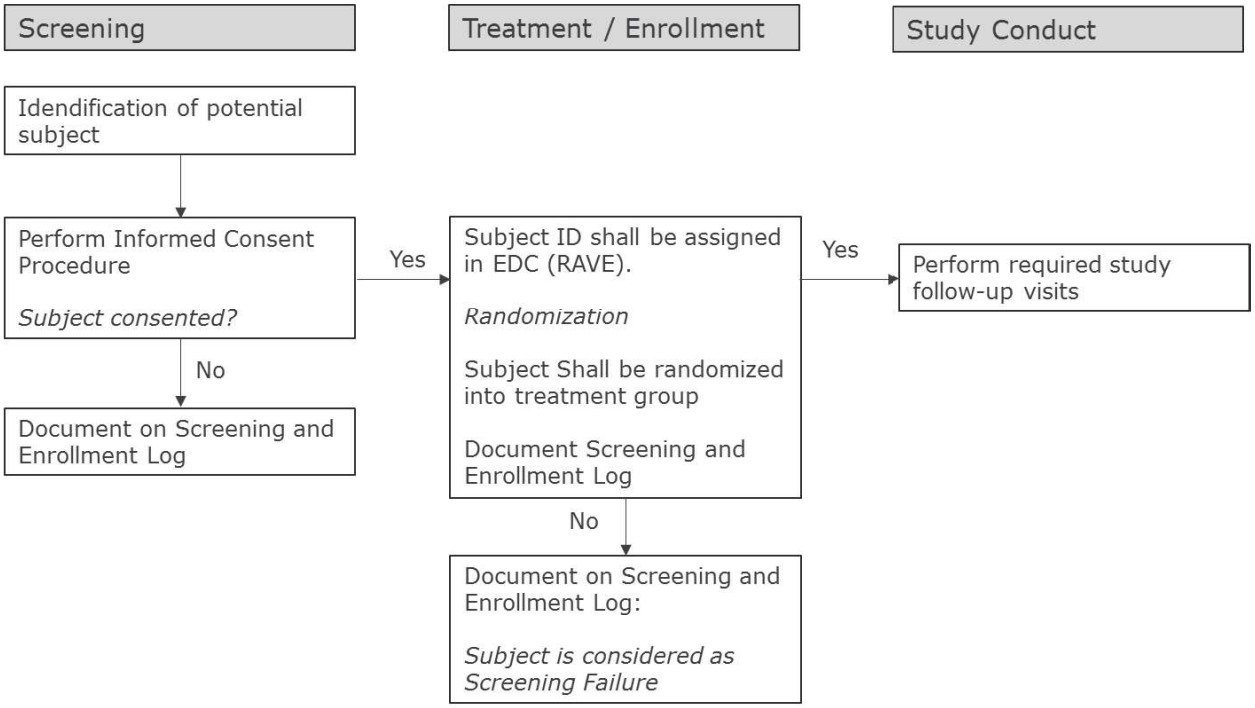
The study is expected to enroll all subjects within a 12-month timeframe. Subjects will be followed-up for a time period of 12 months after surgery. Figure 8.1-8-1 details the Study Recruitment timeline.

This study is being conducted in parallel to a global cohort study titled: "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" (Protocol ID: CORI.2019.07). The study data may be combined for analysis. Further details are described in Section 10 Statistical Design and the Statistical Analysis Plan (SAP).

Figure 8.1-8-2 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 8.1-8-2 Study Flowchart



8.2 ALLOCATION AND BLINDING

8.2.1 Treatment Allocation

Subjects will be randomly assigned to the CORI navigational or conventional manual instrumentation groups according to a balanced randomization procedure using a 1:1 allocation ratio. To ensure balanced group assignment within each investigational site, a block (by investigational site) randomization schedule will be generated. Only sites will be included that are willing to perform both, CORI Navigated and conventional instrumentation UKA procedures. Subjects who satisfy all inclusion and exclusion criteria will be randomized in a 1:1 randomization allocation ratio. The block size should be sufficiently small to allow approximately equal allocation of subjects in each group should the study be terminated prematurely whilst also being large enough so as the next treatment cannot be guessed.

8.2.2 Blinding

The study is non-blinded.

8.3 DATA MANAGEMENT

This study utilizes a validated, encrypted electronic data capture system that is 21 CFR Part 11 compliant. Access to the electronic data capture system is restricted by study role in accordance with 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.

8.3.1 Data Review and Quality Assurance

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

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

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

8.3.2 Retention Period

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

8.4 STUDY ENDPOINTS

8.4.1 Primary Endpoint

The primary endpoint of this study is defined as the evaluation of the proportion of subjects achieving planned post-operative leg alignment. Achieved leg alignment is defined as ± 3° from the subject's specific target in comparison with conventional manual instrumentation.

8.4.2 Secondary Endpoints

The following secondary endpoints have been defined for this study in order to evaluate the safety and performance of CORI in comparison with conventional manual instrumentation up to 12 months post-operatively:

- Component Alignment
- Radiographic assessment (Presence of radiolucent lines, osteolysis & implant migration)
- 2011 Knee Society Score (2011 KSS)
- Oxford Knee Score (OKS)
- Forgotten Joint Score (FJS-12)
- Five-level EuroQol five-dimensional (EQ-5D-5L) VAS & index scores

8.4.3 Other Endpoints

The following additional endpoints have been defined for this study:

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

8.4.4 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

8.5 METHODS USED TO MINIMIZE BIAS AND MAXIMIZE VALIDITY

8.5.1 Multiple sites

After fulfillment of all eligibility criteria (including informed consent), subjects will be enrolled and randomized at multiple sites, utilizing up to 8 sites in total for the study. Subject enrollment will continue until the completion of recruitment of a minimum of 140 subjects. File records and enrollment registration forms for screening work must be retained and submitted to the Sponsor as needed.

8.5.2 Prospective Consecutive Enrolment

Subjects meeting all inclusion/exclusion criteria will be randomly allocated to one of two treatment groups (CORI Navigational versus conventional manual instrumentation) in a 1:1 allocation ratio. Blocked randomization to balance this allocation ratio by investigational site and overall will be implemented through a

network-based randomization system. A randomization number is allocated only when subjects have signed the Informed Consent Form and satisfy all study eligibility criteria.

8.5.3 Subject Attrition

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

8.5.4 Pre-specification of Statistical Analysis

The 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 all analyses to be performed will further be pre-specified in the Statistical Analysis Plan (SAP) so as to minimize any threats to external validity and yield clinically relevant estimates of effects and precision.

9 STUDY PROCEDURES

9.1 VISITS AND EXAMINATIONS

9.1.1 Summary

For a summary of the required procedures by visit, refer to the Study Schematic Table 9.1.1-9-1 Study Procedures by Visit.

Table 9.1.1-9-1 Study Procedures by Visit

Schedule of events	Pre-Operative Data -90 to 0 days	Operative Data & Discharge Day 1 (+ up to 9 days)	6 weeks 42 ± 14 days	6 months 185 ± 14 days	12 months 365 ± 30 days
Informed Consent	x				
Demographics/ Medical History	x				
Inclusion/Exclusion	x				
Preoperative Examinations (eg. ECG, Blood Routine Examination, Biochemical Examination, Coagulation Examination)[1]	x				
Pregnancy Test[2]	x				
Concomitant Medication	x				
Concomitant Medication Update		x	x	x	x
Operative Data Collection		x			
CORI Case Report (System time & cutting time)		x			
Discharge Data Collection		x			
Leg alignment Long leg X-ray AP[3]	x	(x)[4]	x		(x)[5]
Standard Lateral X-ray		(x)[4]	x		x
Standard A/P X-ray					x

KSS	x		x	x	x
OKS	x		x	x	x
FJS-12			x	x	x
EQ-5D-5L	x		x	x	x
Safety Assessment		x	x	x	x
End of Study/Exit			(x)[6]	(x)[6]	x

[1] Only applicable at sites in China
[2] Only Applicable at site in China
[3] Pre-operative long leg X-rays (A/P) collected 6-months prior to the date of surgery is admissible
[4] Post-operative standing weight bearing long leg X-rays (A/P) and standard lateral X-rays may be taken at discharge.
[5] Only if standing weight bearing long leg A/P X-ray is taken as a standard of care at 12 months.
[6] Exit form to be completed at the point of withdrawal if the study is not completed.

9.1.2 Screening/Pre-operative Visit

1. Obtain written informed consent from the subject as detailed in Section 7.5.
   ----- Do not proceed until the 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. 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).
7. Collect the 2011 KSS score objective measures (joint alignment, instability, motions & symptoms).
8. Have the subject complete the 2011 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. The subject will be randomized to treatment group (CORI or Manual conventional instrumentation).
12. Subjects will be instructed to return for the Operation Visit on a scheduled date.

9.1.3 Operation Visit & Discharge (Day 1+up to 9 days)

1. Prior to surgery, 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.
4. Perform surgery and collect intra-operative data on the appropriate eCRF. This includes but is not limited to the following information:
    - Knee Implant Data
    - 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.
    - Collect the Subject's CORI Case Report, generated CORI Software (System time, cutting time) for CORI group.
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.
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 2011 KSS score objective measures (joint alignment, instability, motions & symptoms).
5. Have the subject complete the 2011 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-12 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.

9.1.5 6 months (185 ± 14 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 the 2011 KSS score objective measures (joint alignment, instability, motions & symptoms).
5. Have the subject complete the 2011 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-12 patient-reported outcome measure.
9. 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 and 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 long leg X-ray is taken as a standard of care, please complete the respective leg alignment eCRF (optional).

6. Collect the 2011 KSS score objective measures (joint alignment, instability, motions & symptoms).
7. Have the subject complete the 2011 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-12 patient-reported outcome measure.
11. Complete Exit Visit eCRF.

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.

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

Excluded Concomitant Medications

There are no restrictions on concomitant medications for this study.

Recording Concomitant Medications in the eCRF

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

Therapies Prohibited During the Study

There are no restrictions on concomitant therapies for this study.

Recording Concomitant Therapies in the eCRF

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 medications/therapies, who are lost to follow-up, refer to Section 7.8 for further details. Where possible, the next scheduled study 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

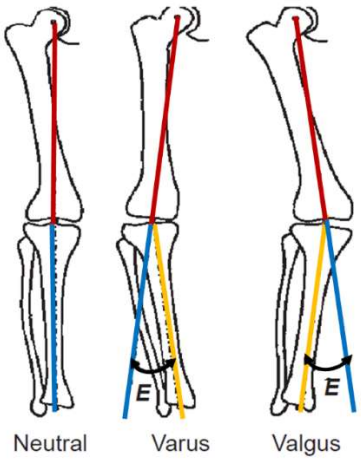
9.2.1 Leg alignment

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 9.2-9-1. The angular deviation from the neutral position shall be recorded in the eCRF.

Figure 9.2-9-1 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 standing A/P shall be recorded.

Target Leg alignment (Surgical Plan)

The operative plan for leg alignment as entered in CORI 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 (for CORI UKA only)

The pre-cementation leg alignment shall be recorded with the use of CORI (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 CORI (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.

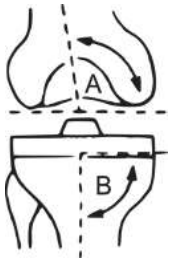
9.2.2 Component Alignment

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 9.2-9-2).
- **Total Valgus Angle:** Is the sum of the femoral flexion angle and the tibial angle.

Figure 9.2.2-9-2 A/P View



A: Femoral A/P Angle
B: Tibial A/P Angle
A+B: Total Valgus Angle

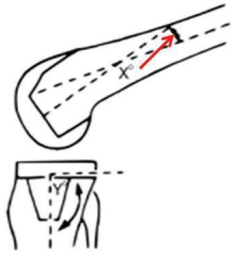
Lateral View

- **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 9.2.2-9-3 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 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 (2011 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 [45, 46]. The 2011 KSS consists of 34 questions and provides sub-scores across 4 dimensions as shown in Table 9.2.4-9-2.

Table 9.2.4-9-2 2011 Knee Society Score

#	Sub-Score	# Questions	Completion by
1	Objective Knee Score	4	Surgeon

2	Symptoms	3	Subject
2	Subject Satisfaction Score	5	Subject
3	Subject Expectation	3	Subject
4	Functional Knee Score	19	Subject

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

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses for the 2011 KSS will then be recorded in the eCRF.

9.2.5 Oxford Knee Score (OKS)

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

The 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 [47, 48]. 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-12)

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

A paper questionnaire will be provided by the Sponsor to be completed by the subject. Responses for the FJS-12 will then be recorded in the eCRF.

9.2.7 CORI System Time & Cutting Time

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

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

In the case logs, the following time stamps will be recorded in the log file of the CORI 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]

CORI System Time

CORI 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 CORI 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 Case Report.

9.3 HEALTH ECONOMICS/QUALITY OF LIFE

9.3.1 EQ-5D-5L

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 [50].

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

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

All statistical comparisons of data will 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:

- Enrolled Population: This is defined as subjects enrolled and/or randomized to either CORI or Conventional manual instrumentation groups. A total of 140 patients will be competitively enrolled and or/randomized in the study across all the sites including the sites in China.
- Safety Population (SAF): This is defined as all subjects who were treated for UKA (include non-randomized subjects in China as CORI is a pre-market

product in China) with the use of CORI or conventional manual instrumentation.

- Intent-to-Treat Population (ITT): The ITT population is a subset of the randomized population which is defined as subjects randomized to either CORI or conventional manual instrumentation groups who have at least one post-operative assessment on any of the effectiveness endpoints or health-related quality of life (HRQoL) endpoints. Data summarized on the ITT population will be based on the intervention the subject was randomized to receive which may be different from the intervention the subject actually received.
- 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 (or preoperative) data. All demographic and pre-operative characteristics data will be summarized at baseline. All demographic and baseline characteristics will be summarized using the enrolled SAF, ITT and PP analysis populations.

10.4 EFFECTIVENESS 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 CORI UKA (π_1) and conventional manual instrumentation UKA (π_0) groups.

The hypotheses are as follows:

- H_0(null): $\pi_1 <= \pi_0$ versus
- H_1 (alternate): $\pi_1 > \pi_0$.

The proportions as described above will be supported with the use of a two-sided 95% confidence intervals (CI), estimated using exact binomial methods.

Superiority of π_1 over π_0 will be inferred if and only if the lower limit of the 95% CI for π_1 is greater than the upper limit of the 95% CI for π_0 .

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 UKA and the Conventional manual instrumentation UKA) 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.

For missing primary endpoint data, the Missing Value Treated as Failure (MVTF) missing value imputation method will be used. This is considered a conservative imputation method as all missing data on the primary endpoint will be considered as a failure, i.e. not attaining the pre-specified target alignment. More specific details of this imputation method will be included in the SAP.

10.4.2 Analysis of Secondary Endpoints

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. These would additionally be stratified by surgical technique within each group (CORI Navigational versus Conventional Manual Instrumentation).

Standard Radiographic Assessment

The presence of radiographic observations: implant loosening, implant migration, and osteolysis and other pertinent radiographic findings will be summarized as counts (n) and percentages (%) by visit. These would additionally be stratified by surgical technique within each group (CORI Navigational versus Conventional Manual Instrumentation).

Radiolucent lines (mm) by zone and visit will be summarized using descriptive statistics for continuous variables. These would additionally be stratified by surgical technique within each group (CORI Navigational versus Conventional Manual Instrumentation).

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 change from preoperative to postoperative KSS scores as the dependent variable. As a minimum, each model will contain a group (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 its associated p-value $\leqslant$ 0.1. Model based means (adjusted means or Least Square Means, LSMeans) and corresponding standard errors associated with each change from preoperative to postoperative KSS score will be presented by group. Model based

differences (and corresponding standard errors) between the CORI Navigational and Conventional manual instrumentation groups and their corresponding 95% CIs will additionally be summarized. If the p-value associated with the group term in the model is significant (i.e. $p < 0.05$), then the 95% CIs corresponding to the model based differences between the CORI Navigational and Conventional manual instrumentation groups will additionally be presented.

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. Change from preoperative to postoperative visits will also be summarized. 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-12)

The transformed FJS-12 score (0-100) will be summarized at the postoperative visits using continuous summary characteristics. Change from preoperative to postoperative visits will also be summarized. 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. Change from

preoperative to postoperative visits will also be summarized. 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.

The 2011 KSS, transformed FJS-12 and EQ-5D-5L scores will additionally be summarized by group (i.e. the CORI Navigational and Conventional manual instrumentation groups) and visit using descriptive statistics for continuous variables.

The Multiple Imputation (MI) missing value imputation method will be used as the imputation method for missing 2011 KSS, FJS-12, OKS, and EQ-5D-5L endpoints. Details of the MI method will be included in the SAP.

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 summarized separately in the CORI Navigational and Conventional manual instrumentation groups).

Leg alignment pre- and post-cementation (CORI UKA only)

Leg alignment is classified as normal, varus deformity and valgus deformity. Shift tables to summarize the changes from pre- to post-cementation will be created.

CORI System Time & Cutting Time

CORI System and cutting times will be summarized using summary statistics for continuous variables. The average operating and cutting times summarized using summary statistics for continuous variables. Additionally, 95% CIs based on the t-statistic will be presented.

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

10.5 SAFETY ANALYSES

All safety analyses will be summarized separately for each of the groups (i.e. CORI Navigational and Conventional manual instrumentation groups) as follows:

- The number of adverse events will be reported by seriousness, relationship to study device and anticipation.
- The number of subjects experiencing adverse events will be summarised 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

A first interim analysis is planned for after completion of the 6 weeks visit in order to support the China NMPA registration. More specific details on the interim analyses will be included in the SAP.

11 SAMPLE SIZE JUSTIFICATION

Parratte et al.[51] 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 $0^{\circ} \pm 3^{\circ}$).

This study is designed to demonstrate superiority in the proportion of knees achieving post-operative leg alignment in the CORI Navigational group over the Conventional manual instrumentation group.

The proportion of mechanically aligned TKAs using NAVIO from a recent analysis was estimated to be 92.1% [52]. This proportion is expected to be equivalent if NAVIO was used to determine the proportion of mechanically aligned UKAs. Using these assumptions, enrollment of 63 UKAs per group will provide 80% power to show that the lower limit of the two-sided 95% confidence interval for the proportion of mechanically aligned UKAs 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) will be enrolled into the randomized stage of the study. A minimum of an additional 5 subjects who will be treated with CORI directly to fulfil the learning needs of the surgeons will be enrolled at the pre-randomized study stage, thus leading to a minimum total study enrollment of 145 subjects.

12 ADVERSE EVENTS AND DEVICE DEFICIENCIES

12.1 DEFINITIONS

The categories of adverse events are shown in Table 12.1-12-1. The definitions for each of these categories are given in the subsequent sections.

Table 12.1-12-1 Categories of Adverse Event

	NOT DEVICE-RELATED	**DEVICE- OR PROCEDURE-RELATED**	
NON-SERIOUS	ADVERSE EVENT (AE)	ADVERSE DEVICE EFFECT (ADE)	
SERIOUS	SERIOUS ADVERSE EVENT (SAE)	SERIOUS ADVERSE DEVICE EFFECT (SADE) (SEE 12.1.3)	
		ANTICIPATED	**UNANTICIPATED**
		ANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (ASADE)	UNANTICIPATED SERIOUS ADVERSE DEVICE EFFECT (USADE)

12.1.1 Adverse Event

An Adverse Event (AE) is any untoward medical occurrence, unintended disease or injury or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

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

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

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

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

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

12.1.2 Adverse Device Effect

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

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

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

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

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

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

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

12.1.3 Related Serious Adverse Events and Serious Adverse Device Effects

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

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

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

12.1.4 Anticipated/Unanticipated Serious Adverse Device Effect

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

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

A list of potential ASADE for CORI is provided in Table 12.1.4-12-2. Please also refer to Section 4.4.5 Potential Adverse Effects.

Table 12.1.4-12-2 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.
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

#	Potential Harm	Description
		flow. If blood flow to the leg is not restored, the patient's leg may need to be amputated.

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].

12.1.6 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.

12.1.7 Device Deficiency

A Device Deficiency (DD) is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. DD includes malfunctions, use errors and inadequate labeling.

Note 1: DD includes malfunctions, use errors and inadequacy in the information supplied by the manufacturer including labelling.

Note 2: This definition includes device deficiencies related to the investigational medical device or the comparator.

Device deficiencies that did not lead to an adverse event but could have led to a medical occurrence

a) if either suitable action had not been taken,
b) if intervention had not been made, or
c) if circumstances had been less fortunate,

are considered Device Deficiencies with potential to cause SADE and shall be reported as specified in section 12.3.

12.2 AE CODING DICTIONARY

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

12.3 Reporting Procedures

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

- ADE and DD – without unreasonable delay
- SAE, SADE and DD with potential to cause SADE – immediately (i.e. within 24 hours of the investigator being informed about the event)
- All other events – according to usual timescales

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

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

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

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

The investigator should inform the regulatory agency and IRB/IEC of adverse events as per the requirements of each site. The detailed information is described in Safety Monitoring Plan.

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

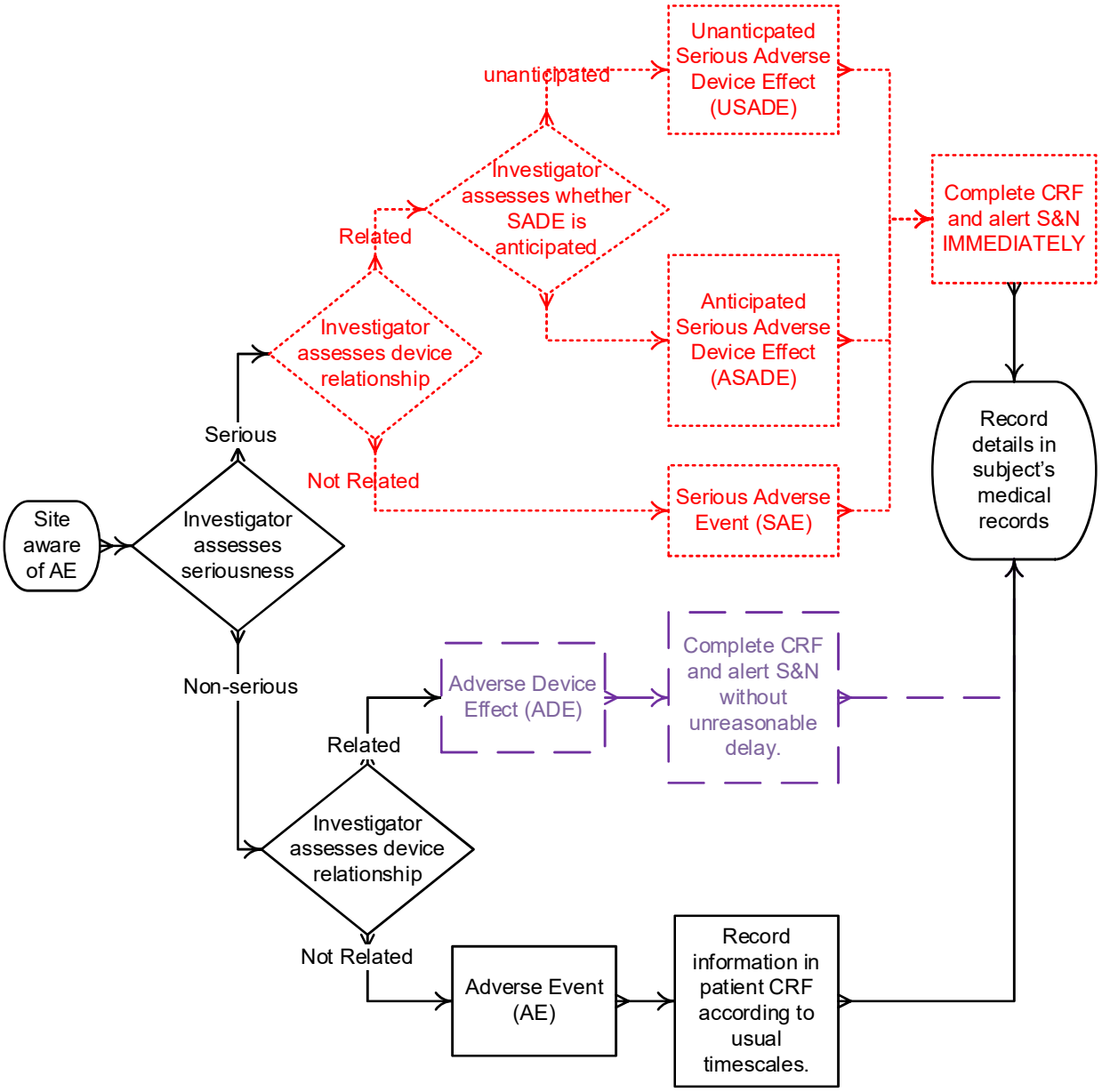
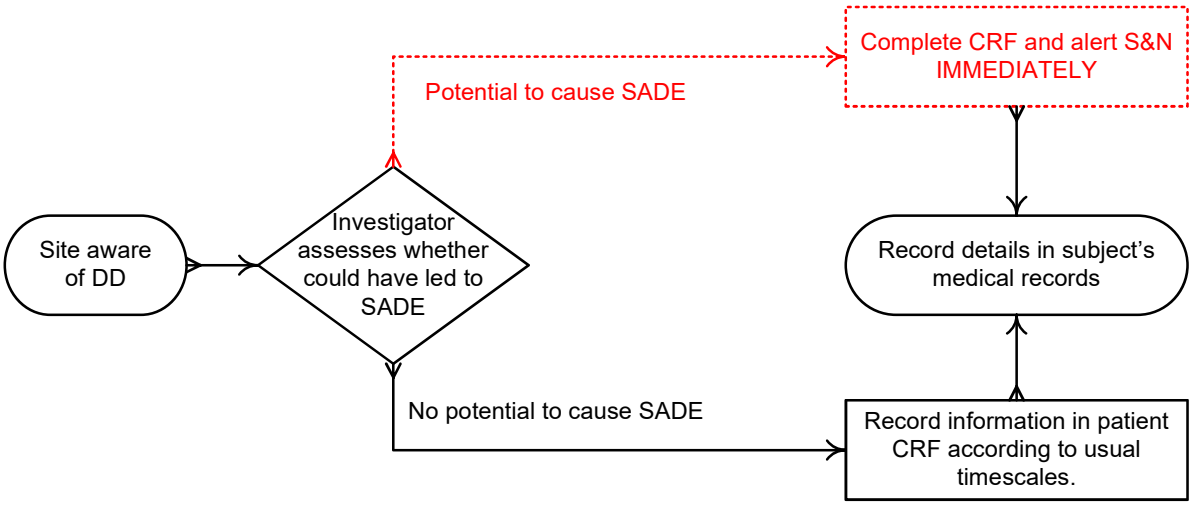


Figure 12.3-12-2 Evaluation and Reporting of DD



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 eCRF or the 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 that 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 in the Statement of Investigator, provided by the Sponsor, and with Good Clinical Practice (GCP), and all applicable regulatory requirements as outlined in Appendix-Principal Investigator Obligations as well as all applicable local laws and regulations.

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 any changes that affect their financial disclosure status occur during the course of the study and up to one year after study completion.

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 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."

14.2 Site Qualification Visit

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

14.3 Site Initiation Visit

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

14.4 Interim Monitoring Visit

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

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.

14.6 CLOSE-OUT VISIT

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

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 (TMP-CD-31-02 Protocol/GCP Deviation Log). Significant and/or recurrent protocol/GCP deviations will be documented on a protocol deviation form (TMP-CD-31-01 Protocol/GCP Deviation) including identified root cause and, as necessary, appropriate corrective and preventive actions will be put in place and and signed off by the study personnel.

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 or IEC. Protocol amendments need to be approved by the IRB or 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 Sponsor agrees to operate in good faith and in accordance with the local guidelines regarding compensation for injury resulting from participation in an industry-sponsored clinical trial.

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 requirement for subject follow up in these instances will be considered as part

of these processes. The sponsor may decide to discontinue a specific study site under the following conditions:

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

20 PUBLICATION POLICY

20.1 PUBLICATION OF STUDY DATA

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

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. The 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 General Purpose

The purpose of the protocol amendment is to meet the requirements of the Hongkong site during the EC approval session. The protocol amendment for version 2.1 is minor.

The purpose to have the 2nd protocol amendment into version 3.0-Master is to update the protocol from Template B into Template D and also update the information within the protocol.

The purpose of amending version 3.0 to version 4.0-Master is to expand the pre-surgery visit window from -28 to -90 days. South Korea has also been added as a location for where the study will be conducted and staged bilateral subjects can now be enrolled. Subject has one or more of the following arthroplasties that are not fully healed and well-functioning, as determined by the investigator: Contralateral primary TKA or UKA, however, the subject can only have one knee enrolled in this study. . An additional exclusion was added to restrict the enrolment of subjects who currently enrolled in another study orthopaedic clinical trial study at least 1 year prior to screening. Some of the changes in this version are being made to maintain alignment with the changes required by the regulatory authorities in China.

22.1.2 Rationale

The rationale to 1st time updates the protocol is due to the protocol title inconsistency with other documents. Since the amendment is change that do not materially affect the study which is simply update the protocol title from "procedures" into "Procedure".

The rationale to 2nd time updates the protocol is due to the protocol template updated from version B to version D. And also, the information inside of the protocol need to be further updated.

The rationale to 3rd time update is to allow more patient to enrol in the study and update the information based on ISO14155 2020 and to maintain alignment with the changes required by the regulatory authorities in China.

22.1.3 Effect on Study Status

Not applicable. The amendment in version 2.0, 2.1 and 3.0-Master was in effect and implemented prior to subject enrolment.
The amendment in Version 4.0-Master will not impact the status of study, however, patient enrolment may improve.

22.1.4 Details

1st Update from Version 2.0 to Version 2.1

Section	Current Text Version 2.0 (04SEP2020)	Revised Text Version 2.1 (14JAN2021)
header	A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) procedures Version: 2.0, 04SEP2020	A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) Procedure Version: 2.1, 14JAN2021
Section 1.2.1&1.2.2	A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Effectiveness of REAL	A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Effectiveness of REAL

	INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) procedures", version 2.0, dated 04SEP2020	INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) Procedure", version 2.1, dated 14JAN2021
Synopsis	A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) procedures	A Prospective, Multi-center, Randomized Controlled Study to Evaluate the Safety and Effectiveness of REAL INTELLIGENCE™ CORI™ in unicondylar knee arthroplasty (UKA) Procedure

2nd Update from Version 2.1 to Version 3.0-Master

Section	Current Text Version 2.1 (14JAN2021)	Revised Text Version 3.0-Master (03MAR2021)
Cover Page	Original Text	Added "Single Identification Number of Clinical Investigation: CORI.2019.06"
Cover Page	Protocol Author(s): Rahel Meister, Senior Clinical Study Manager Babajide Olayinka, Senior Biostatistician	Protocol Author(s): Michelle Li, Associate Clinical Study Manager Rahel Meister, Senior Clinical Study Manager Babajide Olayinka, Senior Biostatistician
Header	Version: 2.1, Date: 14JAN2021	Version: 3.0-Master, Date: 03MAR2021

Footer	TMP-CD-05-01 – Clinical Protocol-Device – Revision B; SOP-CD-05 Clinical Protocols	TMP-CD-05-01 – Clinical Protocol-Device – Revision D; SOP-CD-05 Clinical Protocols
Section 1.1 &1.2	Protocol Version: 2.1, Date: 14JAN2021	Protocol Version: 3.0-Master, Date: 03MAR2021 Merge the Signature and Date into same column
Section 1.1	I agree to comply with the Investigator's Obligations stipulated in Section 22.5 Principal Investigator Obligations according to ISO 14155:2011. and applicable laws and regulation in China (NMPA) of the protocol.	I agree to comply with the Investigator's Obligations stipulated in Section 6 Principal Investigator Obligations according to ISO 14155:2011 and all applicable local legislation and regulations
Section 1.2	Refer to version 2.0 for full sponsor approval. Approval of the head of China clinical operations indicates approval both of the changes to the protocol and of the changes being processed and approved as a minor amendment. Astrid Yung Associate Director, Clinical Strategy and Operations	Full stakeholders signature list

Sections 2 and 7.3	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.	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, intellectual disability, or drug or alcohol abuse.
Section 2	Study Duration: **Estimated timeline:** •Study period: 25 months (12 months enrolment) •Start enrolment: December 2020 •Last subject first visit: February 2022 •Last subject last visit: April 2020	Study Duration: **Estimated timeline:** •Study period: 25 months (12 months enrolment) •Start enrolment: March 2021 •Last subject first visit: March 2022 •Last subject last visit: May 2023
Section 2	Safety Data: 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	Safety Data: 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

	Unanticipated. The definitions for each of these categories are based on ISO 14155:2011 and applicable local laws and regulations. in China. (Including hardware and instrumentation), complications, and revisions.	categories are based on ISO 14155:2011 and applicable local laws and regulations.
Section 3.1 &3.2 & 3.3	Original Table of Content, List of Tables & List of Figures	Updated Table of Content, List of Tables & List of Figures Numbering updated for all tables and figures throughout the protocol
Section 3.4	KSS - Knee Society Score	2011 KSS - Knee Society Score, 2011 HKA – Hip-Knee-Ankle
Section 5.1	The primary objective of this study is to evaluate the use of CORI in UKA procedures in achieving post-operative leg alignment as compared to procedures using standard instruments.	The primary objective of this study is to evaluate the use of CORI in UKA procedures in achieving post-operative leg alignment as compared to procedures using conventional manual instruments.
Section 5.2	The secondary objective of this study is to assess the safety and performance of CORI up to 12 months after surgery as compared to procedures using conventional manual instruments.	The secondary objective of this study is to generate safety and performance evidence supporting the use of CORI procedures. To assess the safety and performance of CORI up to 12 months after surgery as compared to procedures using conventional manual instruments.

Section 5.3	Other objectives are to determine the system time and cutting time of the robotic drill of UKA procedures with CORI.	Other objectives are to collect the system time and cutting time of the robotic drill from the CORI Case Report.
Section 6	Title: NVESTIGATIONAL PRODUCT(S)	Title: NVESTIGATIONAL PRODUCT(S) AND COMPARATOR
Section 6.1.1	**Figure 6.1-6-1 CORI Reusable Instruments** **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.	**Figure 6.1-6-2 CORI Reusable Instruments** **CORI Robotic Drill**: Controls the position and speed of the bur. It is intended for 75 uses and is able to be autoclaved, auto washed, and disinfected.
Section 6.1.3	Not Exist	Added new section "Ancillary Product(s)->Not applicable.
Section 6.2	For Australia, Hong Kong and New Zealand the list of reference documents can be found in Appendix Section 22.2 Instruction For Use & User Manual.	For Australia, Hong Kong and New Zealand the list of reference documents can be found in Appendix Section 22.3 Instruction For Use & User Manual.
Section 6.3.1	The standard commercial pacaing as marketed in the US is used. However, additional labels will be included on the commercial packaing to meet the regulatory requirements for investational devices in countries	The standard commercial packaging as marketed in the US is used. However, additional labels will be included on the commercial packaging to meet the regulatory requirements for investigational devices in countries where the

	where the devices are not approved for marketing.	devices are not approved for marketing.
Section 6.6	Not Exist	New added section "Medical Procedure-> There are 3 basic steps in unicondylar knee arthroplasty. The first step is preparing the bone and removing the cartridge from the damaged knee compartment. This will be completed using either the CORI robotic drill or an oscillating saw. The surgeon will then position the metal implants on the damaged side of the femur and tibia using several orthopaedic tools. Finally, a spacer will be inserted between the metal implants to reduce friction when the knee flexes and extends. At various times during the procedure, the hip-knee-ankle angle (HKA) will be checked using the CORI advanced tracking system or via the use of intramedullary and / or extramedullary rods. How the angle is measured will depend on which treatment arm the subject is randomized to receive. All unicondylar knee arthroplasty is completed using general anaesthetic by a surgical team trained in both the

		CORI system and the use of standard manual instrumentation.
Section 7.3	Exclusion Criteria No. 1-7	Exclusion Criteria No. 7-13
Section 7.5	The subject, or their legally authorized representative	The subject, or their legally authorized representative (if applicable)
Section 7.8.2	• Subject noncompliance (e.g., did not follow instructions, took disallowed medications) • Subject lost to follow-up • The Investigator or the Sponsor stops the study for any reason and decides to withdraw subject(s) from the study • Concurrent illness • Adverse Events/Adverse Device Effects • Any other significant reason identified by the Investigator Subjects who drop out or are withdrawn will not be-re-entered into the study at a later date.	• Subject noncompliance (e.g., did not follow instructions, took disallowed medications) • Subject is lost to follow-up • The Investigator or the Sponsor terminates the study for any reason • Concurrent illness • Adverse Events/Adverse Device Effects • Any other significant reason identified by the Investigator. Subjects who withdraw or are withdrawn by the Investigator cannot be-re-enrolled in the study.
Section 7.8.3	Study participation is voluntary, and subjects may withdraw at any point during the study without giving their reason for	Study participation is voluntary, and subjects may withdraw from the study at any time. Where subjects withdraw consent, the Investigator

	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 eCRF and source documents.	should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's right to privacy. The reason for withdrawal will be recorded in the eCRF and source documents.
Section 8.1-Figure 8-1		
Section 8.2.1	Within the Primary UKA segment of the study, subjects will be randomly assigned to the CORI Navigational or Conventional manual instrumentation groups according to a balanced randomization procedure using a 1:1 allocation ratio.	Subjects will be randomly assigned to the CORI navigational or conventional manual instrumentation groups according to a balanced randomization procedure using a 1:1 allocation ratio.
Section 8.3	Not Exist	New added section "DATA MANAGEMENT" This study utilizes a validated, encrypted electronic data capture system that is 21 CFR Part 11 compliant. Access to the electronic data capture system is restricted by study role in accordance with 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. 8.3.1 Data Review and Quality Assurance Data will be transcribed from the data source to an electronic Case Report Form (eCRF). All data requested on the eCRFs are considered required. Data points not collected and/or recorded will be considered deviations unless otherwise specified. Data collection is the responsibility of the clinical trial staff at the site under the supervision of the Principal Investigator. The Principal Investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The Principal Investigator must provide his/her electronic signature on the appropriate eCRFs to be documented in compliance with local regulations. Changes to data

		previously submitted to the sponsor will require a new signature by the Investigator to acknowledge/approve the changes. Visual and computer data review will be performed in line with Smith and Nephew procedures to identify possible data discrepancies. Manual and automatic queries will be created within the electronic data capture system, and will be issued by Smith and Nephew to the site for appropriate response. Site staff are responsible for resolving all queries in the electronic data capture system. 8.3.2 Retention Period All eCRFs will be archived once the study is completed and will kept for a period of no less than five years after the later of the following dates: the date of which the study is terminated or completed or; the date that the records are no longer required supporting marketing applications.
Section 8.4.3	robotic drills	robotic drills
Section 8.5.1	In order to eliminate selection bias, investigators will	Original Sentence deleted

	continuously screen eligible subjects.	
Section 8.5.2	Subjects meeting all inclusion/exclusion criteria will be randomly allocated into any of two study groups (CORI Navigational versus conventional manual instrumentation groups) in a 1:1 allocation ratio.	Subjects meeting all inclusion/exclusion criteria will be randomly allocated to one of two treatment groups (CORI Navigational versus conventional manual instrumentation) in a 1:1 allocation ratio.
Section 8.5.4	The details of the analyses 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.	The details of all analysis to be performed will further be pre-specified in the Statistical Analysis Plan (SAP) so as to minimize any threats to external validity and yield clinically relevant estimates of effects and precision.
Section 9.1.2	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.	1.Obtain written informed consent from the subject as detailed in Section 7.5.

Section 9.1.2	Original text	Add" No. 11- The subject will be randomized to treatment group (CORI or Manual conventional instrumentation)."
Section 9.1.3	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 7. Instruct the subject on proper postoperative care/procedures, including any contraindicated treatments/medication(s).	1. Prior to surgery, 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. 7. Instruct the subject on proper postoperative care/procedures. Remove Randomization procedure into Pre-op, which is mentioned above.
Section 9.1.9	Where possible, a full Exit Visit should be completed for all subjects who discontinue the study early.	Where possible, the next scheduled study visit should be completed for all subjects who discontinue the study early.
Section 9.2.3	radiolucent lines, osteolysis & implant migration)	radiolucent lines, osteolysis & implant migration
Section 10.1	All statistical comparisons of data would describe the test statistic used as well as its distributional assumptions.	All statistical comparisons of data will describe the test statistic used as well as its distributional assumptions.
Section 10.2	Original Text	Newly Added "Randomized Population: This is defined as subjects randomized to either CORI or

		Conventional manual instrumentation groups."
Section 10.2	The ITT population is defined as subjects randomized to either CORI or conventional manual instrumentation groups who have at least one post-operative assessment on any of the effectiveness endpoints or health-related quality of life (HRQoL) endpoints. Data summarized on the ITT population will be based on the implant the subject was randomized to receive which may be different from device the subject actually received.	The ITT population is a subset of the randomized population which is defined as subjects randomized to either CORI or conventional manual instrumentation groups who have at least one post-operative assessment on any of the effectiveness endpoints or health-related quality of life (HRQoL) endpoints. Data summarized on the ITT population will be based on the intervention the subject was randomized to receive which may be different from the intervention the subject actually received.
Section 10.4.1	Original Text	New Added "For missing primary endpoint data, the Missing Value Treated as Failure (MVTF) missing value imputation method will be used. This is considered a conservative imputation method as all missing data on the primary endpoint will be considered as a failure, i.e. not attaining the pre-specified target alignment. More specific details of this imputation method will be included in the SAP."

Section 10.4.2	The transformed FJS-12 score (0-100) will be summarized at the preoperative and postoperative visits using continuous summary characteristics.	The transformed FJS-12 score (0-100) will be summarized at the postoperative visits using continuous summary characteristics.
Section 12.1.1 &12.1.2 &12.1.3 &12.1.4 &12.1.7 & 12.3	Original Text	Text Updated according to Protocol Template Rev D.
Section 13	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-Principal Investigator Obligations as well as applicable laws and regulations in China of this protocol.	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-Principal Investigator Obligations as well as all applicable local laws and regulations.
Section 14.4	Not Exist	New added section ”Interim Monitoring Visit-> Regular interim monitoring visits will be performed by the Sponsor or qualified person designated by the Sponsor.”

Section 18	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.	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 the local guidelines regarding compensation for injury resulting from participation in an industry-sponsored clinical trial.
Section 19	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.	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.
Section 20.2	S+N	Smith+Nephew

Section 22.1.1	The purpose to have the protocol amendment is to meet the requirements of the Hongkong site during the EC approval session. The protocol amendment for version 2.1 is minor.	The purpose to have the 1ST protocol amendment is to meet the requirements of the Hong Kong site during the EC approval session. The protocol amendment for version 2.1 is minor. The purpose to have the 2nd protocol amendment into version 3.0-Master is to update the protocol from Template B into Template D and also update the information within the protocol.
Section 22.1.2	The rationale to update the protocol is due to the protocol title inconsistency with other documents. Since the amendment is change that do not materially affect the study which is simply update the protocol title from "procedures" into "Procedure". Therefore, the amendment for version 2.1 is considered as minor.	The rationale to 1ST time protocol update is due to the protocol title inconsistency with other documents. Since the amendment is change that do not materially affect the study which is simply update the protocol title from "procedures" into "Procedure". Therefore, the amendment for version 2.1 is considered as minor. The rationale to 2nd time update the protocol is due to the protocol template updated from version B to version D. And also the information inside of the protocol need to be further updated.

Section 22.1.4	1ST Update from Version 2.0 to Version 2.1	2nd Update from Version 2.1 to Version 3.0-Master. This table added
Section 22.2	Not Exist	New section added "Sponsor Details"-> Smith & Nephew, Inc., 1450 E. Brooks Road, Memphis, TN 38116, United States
Section 22.4	Not applicable	Refer to Section 9.2 & 9.3 for Quality-of-Life measures.

3rd Update from Version 3.0-Master to Version 4.0-Master

Section	**Current Text** **Version 3.0-Master (03 MAR2021)**	**Revised Text** **Version 4.0-Master (07 Sep 2022)**
Throughout as applicable	Writing acronymns out in full at first use and tidying up use of the acronym vs full term. Making use of S+N, Smith+Nephew, and Smith&Nephew more consistent.	
ISO 14155 reference	ISO reference changed from ISO 14155:2011 to ISO14155:2020 throughout the study.	
Header	Version: 3.0-Master, 03 MAR2021	Version: 4.0-Master, Date 07 Sep 2022
Section 1.1&1.2	Protocol version and date: 3.0-Master, 03 MAR2021	Version: 4.0-Master, Date 07 Sep 2022
Cover Page	Protocol Author(s): Michelle Li, Associate Clinical Study Manager	Protocol Author(s): Michelle Li, Associate Clinical Study Manager

	Rahel Meister, Senior Clinical Study Manager Babajide Olayinka, Senior Biostatistician Sponsor Approval Kelli C. Armstrong, Clinical Strategy Director Robotics Alan Rossington, Director Biostatistics & Data Management	Rahel Meister, Senior Clinical Study Manager Manvendra Saxena, Clinical Study Manager Babajide Olayinka, Senior Biostatistician Sponsor Approval Julie Lankiewicz, Clinical Strategy Director Robotics Michael Robinson Independent Statistician
Section 1.2	Original Text- Coordinating Investigator Approval	Update the section into Clinical Institution Approval page
Section 1.3	Full internal sponsor approval	Only China operation head approval
Synopsis- Exclusion Criteria & Section 7.3	Original Text	a. Added "Targeted Global Region- Added South Korea b. Exclusion Criteria: Changed "point 3: Subject receives simultaneous bilateral UKA OR a unilateral UKA with contralateral TKA. c. Added exclusion criteria "point 4: Subject has one or more of the following arthroplasties that are not fully healed and well-

		functioning, as determined by the investigator: -Contralateral primary TKA or UKA, however, the subject can only have one knee enrolled in this study". And "point 6: Subject currently enrolled in another orthopedic d. Study Duration Timeline updated e. Study Schedule Screening i. Visit Duration changed from -28 to 0 day to-90 to 0 days. ii. Added subsection 1-pre-operative long leg X-rays (A/P) collected 6-months prior to the date of surgery is admissible. Study Duration Study period: 49 months Start enrollment: April 2022 Last subject first visit: Feb 2024 Last subject last visit: May 2026

Study Schedule & Table 9.1.1-9-1	Original Study Schedule Table	**Schedule of events**	**Pre-Operative Data** -90 to 0 days	**Operative Data & Discharge** Day 1 (+ up to 9 days)	**6 weeks** 42 ± 14 days	**6 months** 180 ± 14 days	**12 months** 365 ± 30 days
		Informed Consent	x				
		Demographics/ Medical History	x				
		Inclusion/Exclusion	x				

		Preoperative Examinations (eg. ECG, Blood Routine Examination, Biochemical Examination, Coagulation Examination) (1)	x				
		Pregnancy Test (2)	x				
		Concomitant Medication	x				
		Concomitant Medication Update		x	x	x	x
		Operative Data Collection		x			

		CORI Case Report (System time & cutting time)		x			
		Discharge Data Collection		x			
		Leg alignment long leg X-ray AP[3]	x	(x)[4]	x		(x)[5]
		Standard Lateral X-ray: Knee		(x)[4]	x		x
		Standard A/P X-ray: Knee					x
		KSS 2011					
		OKS	x		x	x	x
		FJS	x		x	x	x
		EQ-5D-5L			x	x	x
		Safety Assessment	x		x	x	x
		End of Study/Exit		x	x	x	x

		<table><tr><td></td><td></td><td></td><td>(x)[6]</td><td>(x)[6]</td><td>(x)</td></tr></table> 1. Applicable, at China sites only 2. Applicable, at China sites only. 3. Pre-operative long leg X-rays (A/P) collected 6-months prior to the date of surgery is admissible. 4. Post-operative standing weight bearing long leg X-rays (A/P) and standard lateral X-rays may be taken at discharge. 5. To be performed, only if standing weight bearing long leg A/P X-ray is taken as a standard of care at 12 and 24 months. 6. Exit form to be completed at the point of withdrawal if the study is not completed.
Region South Korea	Not exist	Added throughout the protocol where applicable.
Section 6.5 "Surgical Technique"	Original Text	All CORI study related procedures must be performed according to the User's Manual (Document ID: 500230 CORI for Knee Arthroplasty for Australia, Hong Kong, South Korea, and New Zealand, as well as Investigator's Brochure for China) and according to the according to the surgical technique

		and IFU of the specific Smith+Nephew Implant System. The primary endpoint of post-operative leg alignment is defined as the proportion of subjects achieving post-operative leg alignment 6 weeks after surgery within ± 3° from target. Because this assessment is comparing the target alignment vs measured alignment from 6 weeks postoperative imaging, the defined method of preoperatively planning alignment is left up to the individual investigator's discretion. Each investigator is to plan according to their own techniques. For the analysis of the primary endpoint, X-ray or CT may be utilized. The recommended CORI bone removal technique is a "burr all" technique per the user's manual (Document ID: 500230 CORI Knee Arthroplasty for Australia, Hong Kong, South Korea, and New Zealand, as well as Investigator's Brochure for China). However, a hybrid approach using "distal precision burring" may be used per surgeon's discretion. This will be

		captured in the eCRF along with a rationale of why this approach was chosen. Resurfacing of the patella will be left up to the discretion of each investigator. This will be captured in the eCRF. Surgeons selected to participate in this study will be familiar with CORI and have written evidence of training and expertise in the study procedure. The surgeons will conduct pre-study CORI cases, in order to establish the expertise of the individual surgeons. The exact number may be adjusted depending on the level of the individual experience of the surgeon, the subjects will not be randomized. CORI Case Report Forms of the non-randomized cases will be collected as proof of surgeons' experience and for inclusion in the safety analysis set (applicable only at sites in China).
7.1 "Subject Population"	Original Text "A total of 140 subjects will be enrolled in the study in up to 8 sites in Australia, Hong	Changed to At least 145 subjects will be enrolled into the study. At least 5 of these subjects will be treated with CORI

	Kong, New Zealand, and China Mainland".	directly to fulfil the learning needs of the surgeons prior to enrolling, a further 140 subjects who will be enrolled in the randomized stage of the study in up to 8 sites in Australia, China (Hong Kong), New Zealand, South Korea, and China mainland. Seventy (70) subjects will be enrolled for UKA with the use of the CORI and 70 subjects will be enrolled for UKA with the use of conventional manual instrumentation. Vulnerable subjects will not be enrolled in this study.
Section 7.3 "Exclusion Criteria"		Added exclusion Criteria Point 10 "Subject currently enrolled in another orthopedic clinical trial study
Section 7.4 "Screening"	Original Text "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	Changed To "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

	all inclusion and none of the exclusion criteria. 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".	meet all inclusion and none of the exclusion criteria. 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. In China sites, part of the screening process will include documentation of women's childbearing potential. If the woman is not of childbearing potential this should be documented in the medical history (e.g., surgically postmenopausal, postmenopausal [i.e., at least one year without menses]). For women of childbearing potential, their method of birth control should be documented in the source".
Section 7.5 "Informed Consent"	Original Text "Before conducting any study procedures or examinations, the purpose and nature of the study should be explained to	Changed To "Before conducting any study procedures or examinations, the purpose and nature of the study should be explained to the subject in their native language.

	the subject in their native language. The subject, or their legally authorized representative (if applicable), will then **read**, **sign**, and **personally date** the IRB/IEC-approved informed consent document(s) (see below for difficulties with reading and writing). Additionally, the individual who obtains consent from the subject will sign and date the informed consent document. A copy of the signed informed consent document will be provided to the subject, a copy will be placed in the subject's medical record, with the original filed in the ISF. If the subject is unable to read, the informed consent document and associated study information may be read aloud to the subject in the presence of an impartial witness. If possible, the subject shall sign and	The subject, or their legally authorized representative (if applicable), will then **read**, **sign**, and **personally date** the IRB/IEC-approved informed consent document(s) (see below for difficulties with reading and writing). Additionally, the individual who obtains consent from the subject will sign and date the informed consent document. A copy of the signed informed consent document will be provided to the subject, a copy will be placed in the subject's medical record, with the original filed in the ISF. If the subject is unable to read, the informed consent document and associated study information may be read aloud to the subject in the presence of an impartial witness. If possible, the subject shall sign and personally date the Informed Consent Form (ICF). Where this is not possible, due to difficulties in writing, the subject shall provide verbal consent to participate in the study. The witness shall then personally sign and date the informed consent form, attesting that the information was accurately explained and that the informed consent was freely given.

	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. ICFs will comply with Health Information Portability Accountability Act (HIPAA) regulations as well as and applicable laws and regulations in Australia (Privacy Act 1988), China, South Korea, and New Zealand (Privacy Act 1993)"	ICFs will comply with applicable laws and regulations in Australia (Privacy Act 1988), China, South Korea, and New Zealand (Privacy Act 1993). 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".
Section 7.8.2 "Withdrawal from Study"	Original Text	Added "Withdrawn subjects will not be replaced"

	Original Text	Changed To
Section 8.1 "Study Design"	"This study is a prospective, multi-center, randomized controlled, non-blinded follow-up study to evaluate the use of CORI in UKA procedure in achieving post-operative leg alignment. Up to 8 sites will participate within Australia, China (Hong Kong), New Zealand, and China Mainland. Subjects will be enrolled and randomized into one of two (2) groups, as shown in Table 8.1-8-1. All groups are treated with knee arthroplasty with a S+N Knee Implant System. (The implant system will be selected according to the registration status in each country)"	"This study is a prospective, multi-center, randomized controlled, non-blinded follow-up study to evaluate the use of CORI in UKA procedure in achieving post-operative leg alignment. Up to 8 sites will participate within Australia, Hong Kong, New Zealand, South Korea, and China Mainland. The pre-randomized stage of the study will comprise of at least 5 subjects enrolled and treated with CORI directly in order to fulfil the learning needs of the surgeons. Subjects who will comprise the randomized stage of the study will be enrolled and randomized into one of two (2) groups, as shown in Table 8.1-8-1. All groups are treated with knee arthroplasty with a S+N Knee Implant System. (The implant system will be selected according to the registration status in each country)"

Figure 8.1-8-3 Study Recruitment Timeline		
Section 10.2 "Analysis Population" Dot point "Randomized Population" and "Safety Population	Original Text "Randomized Population: This is defined as subjects randomized to either CORI or Conventional manual instrumentation groups. "Safety Population (SAF): This is defined as all subjects who completed a TKA with the use of the CORI or conventional manual instrumentation".	Changed To "Randomized population" changed to "Enrolled Population" "Enrolled Population: This is defined as subjects enrolled and/or randomized to either CORI or Conventional manual instrumentation groups. A total of 140 patients will be competitively enrolled and or/randomized in the study across all the sites including the sites in China". "Safety Population (SAF): This is defined as all subjects who completed a TKA (include non-randomized subjects in China as CORI is pre-market product in China) with the use of the CORI or conventional manual instrumentation"
Section 11 "Sample Size Justification"	Original Text	Added "To account for up to a 10% attrition rate in knees enrolled, 70 knees in each

		group (140 knees combined) will be enrolled into the randomized stage of the study. A minimum of an additional 5 subjects who will be treated with CORI directly to fulfil the learning needs of the surgeons will be enrolled at the pre-randomized study stage, thus leading to a minimum total study enrollment of 145 subjects".
Section 21.1 " Publication of Study Data"	Original Text	Deleted Reference to "Health Insurance Portability and Accountability Act of 1996"
Section 23.1.1 "General Purpose"	Original Text	Added "The Purpose of 3rd amendment is to expand the pre-operative data collection period, to increase the enrolment at all the sites and restrict the enrolment of patient who are either enrolled in the other study or were enrolled in the other study at least 1 year prior to screening during the EC approval session.
Section 23.6.1		Updated to ISO 14155:2020 guidelines.

"Principal Investigator Obligation according to ISO14155:2020"		

22.1.5 Approval/Notification

The version 2.0-master and 2.1-master of this protocol was not implemented as the study was still at design phase. The protocol v3.0-Master was implemented at all the sites following local EC approval. The protocol v4.0-Master will get implemented in each country following the local EC approval. China protocol v4.0-China, which incorporates the updates in the master, will be implemented at sites in China after local EC approval.

22.2 Sponsor Details

Smith & Nephew, Inc., 1450 E. Brooks Road, Memphis, TN 38116, United States

22.3 Instructions For Use & User Manuals

- CORI user's manual (Document ID: 500230, 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)

22.4 Equipment and Special Instructions

The following section provides a list of components of CORI (only UKA instruments will be used for this study):

Table 22.4-22-1 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 22.4-22-2 CORI Cart

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

Table 22.4-22-3 CORI Monitor

Article	Description
ROB10003	REAL INTELLIGENCE 24 in.Touch Screen

Table 22.4-22-4 CORI 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
ROB10013	REAL INTELLIGENCE Robotic Drill
ROB10014	REAL INTELLIGENCE Robotic Drill Tracker
ROB10015	REAL INTELLIGENCE Robotic Drill Attachment
ROB10016	REAL INTELLIGENCE Robotic Drill Guard

Article	Description
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 22.4-22-5 CORI 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 22.4-22-6 CORI Lids

Article	Description
ROB10087	Universal Base Tray Lid
ROB10088	Universal Insert Lid (A)
ROB10089	Universal Insert Lid (B)
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 22.4-22-7 CORI 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 22.4-22-8 CORI JOURNEY II UKA 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 22.4-22-9 CORI 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)

Article	Description
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 22.4-22-10 Total Knee Instruments

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

Article	Description
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 22.4-22-11 CORI 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 22.4-22-12 CORI 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
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

Article	Description
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 22.4-22-13 CORI 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 22.4-22-14 CORI 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 22.4-22-15 CORI 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

22.5 HEALTH ECONOMIC OUTCOME MEASURES/ QUALITY OF LIFE MEASURES

Refer to Section 9.2 & 9.3 for Quality of Life measures.

22.6 PRINCIPAL INVESTIGATOR OBLIGATIONS

22.6.1 Principal Investigator Obligation according to ISO14155:2020

1. General:
2. 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.
3. 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.
4. Qualification of the PI. The PI shall:
5. 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,

6. be experienced in the field of application and trained in the use of the investigational device under consideration,
7. disclose potential conflicts of interest, including financial, that interfere with the conduct of the clinical investigation or interpretation of results, and
8. be knowledgeable with the method of obtaining informed consent.
9. Qualification of investigation site. The PI shall be able to demonstrate that the proposed investigation site:
10. has the required number of eligible subjects needed within the agreed recruitment period, and;
11. 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,.
12. has adequate facilities.
13. Communication with the IEC. The PI shall:
14. provide the Sponsor with copies of any clinical-investigation-related communications between the PI and the IEC,
15. comply with the requirements described in 4.5 of ISO 14155.
16. 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.

17. 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.
18. Submit the following to the IEC if required by national regulations, the protocol or IEC, whichever is more stringent:
19. SAEs
20. 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.

21. Progress reports, including safety summary and deviations
22. Amendments to any documents already approved by the IEC.
23. If applicable, notifications of suspension or premature termination
24. If applicable, justification and request for resuming the clinical investigation after suspension.
25. Clinical investigation report or summary.
26. As a minimum, during the clinical investigation, the following information shall be obtained in writing from the IEC prior to implementation:
27. Approval/favorable opinion of amendments
28. Approval of the request for deviations that can affect the subject's rights, safety, and well-being or scientific integrity of the clinical investigation
29. Approval for resumption of a suspended clinical investigation if applicable.
30. 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,
31. 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.
32. Informed consent process. The PI shall:
33. General:
34. 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)

35. 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:
36. Ensure that the PI or his/her authorized designee conducts the informed consent process
37. Include all aspects of the clinical investigation that are relevant to the subject's decision to participate throughout the clinical investigation
38. Avoid any coercion or undue improper influence on, or inducement of, the subject to participate
39. Not waive or appear to waive the subject's legal rights
40. Use native non-technical language that is understandable to the subject
41. Provide ample time for the subject to read and understand the informed consent form and to consider participation in the clinical investigation
42. Include personally dated signatures and the PI or an authorized designee responsible for conducting the informed consent process
43. Show how informed consent will be obtained in special circumstances (see below) where the subject is unable to provide him or herself, and
44. Ensure important new information is provided to new and existing subjects throughout the clinical investigation.
45. Special circumstances for informed consent (the following provisions are subject to national regulations):
46. Subject needing legally authorized representatives: informed consent may be given by the legally authorized representative only if a subject is unable to make the decision to participate in a clinical investigation (e.g., infant, child, or

juvenile, seriously ill or unconscious subject, mentally ill person, mentally handicapped person). In such cases, the subject shall also be informed about the clinical investigation within his/her ability to understand.

47. Subject unable to read or write: informed consent shall be obtained through a supervised oral process if a subject or legally authorized representative is unable to read or write. An independent witness shall be present throughout the process. The written informed consent form and any other information shall be read aloud and explained to the prospective subject or his/her legally authorized representative and, whenever possible, either shall sign and personally date the informed consent form. The witness also signs and personally dates the informed consent for attesting that the information was accurately explained and that the informed consent was freely given.
48. Emergency treatments:
49. 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.
50. 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.
51. 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.
52. The subject shall be asked to provide informed consent for continued participation as soon as his/her medical condition allows.
53. The Principal Investigator may not enroll a subject without obtaining informed consent of the subject or his/her legally authorized representative only when the following conditions are fulfilled: the prospective subject fulfils the emergency

conditions and is obviously in a life-threatening situation; no sufficient clinical benefits are anticipated from the currently available treatment; there is a fair possibility that the life-threatening risk to the prospective subject can be avoided if the investigational device is used; anticipated risks are outweighed by the potential benefits of applying the investigational device ; the legally authorized representative cannot be promptly reached and informed.

54. 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):

55. Description and purpose
56. Potential benefits
57. Risks and inconveniences or the subject and, when applicable, for any embryo, fetus or nursing infant
58. Alternative procedures
59. Confidentiality
60. Compensation
61. Anticipated expenses, if any, to be borne by the subject for participating in the clinical investigation
62. Information on the role of Sponsor's representative in the clinical investigation
63. Contact persons
64. 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
65. 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
66. Statement indicating that a description of the clinical investigation has or shall be registered in a publicly accessible database
67. Termination procedures
68. Informed consent signature shall contain the following:
69. The voluntary agreement to participate in the clinical investigation and follow the investigator's instructions
70. 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;

71. A statement declaring that discontinuation/withdrawal and thereby revoking the informed consent at any time incurs no penalty for the subject;
72. A statement with regard to the possible consequences of withdrawal
73. 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
74. A statement confirming that the subject or his/her legally authorized representative agrees to the use of the subject's relevant personal data for the purpose of the clinical investigation
75. A statement confirming that the subject or his/her legally authorized representative agrees that Sponsor's representatives, regulatory authorities and IEC representatives will be granted direct access to the subject's medical records.
76. 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.
77. ensure compliance with the applicable regulatory requirements and ethical principles for the process of obtaining informed consent, and ensure and

document appropriate training if an authorized designee is appointed to conduct the informed consent process.

78. Compliance with the protocol. The Principal Investigator shall:
79. indicate his/her acceptance of the protocol in writing,
80. conduct the clinical investigation in compliance with the protocol,
81. 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,,
82. ensure that the investigational device is used solely by authorized users as specified in 7.2, and in accordance with the protocol and instructions for use,
83. propose to the Sponsor any appropriate modification(s) of the protocol or investigational device or of the use of the investigational device,
84. refrain from implementing any modifications to the protocol without agreement from the Sponsor, IEC and regulatory authorities, if required,
85. document and explain any deviation from the approved protocol that occurred during the course of the clinical investigation,
86. ensure that an adequate investigation site team and facilities exist and are maintained and documented during the clinical investigation,
87. ensure that maintenance and calibration of the equipment relevant for the assessment of the clinical investigation is appropriately performed and documented, where applicable,
88. ensure the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRF and in all required reports,
89. maintain the device accountability records,
90. 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.

91. allow and support the Sponsor to perform monitoring and auditing activities,
92. be accessible to the monitor and respond to questions during monitoring visits,
93. determine the cause and implement appropriate corrective and preventative actions to address significant noncompliance,
94. allow and support regulatory authorities and the IEC when performing auditing activities,
95. ensure that all clinical-investigation-related records are retained as required taking measures to prevent accidental or premature destruction, and
96. review and sign the clinical investigation report, as applicable.
97. Medical care of subjects. The Principal Investigator shall
98. provide adequate medical care to a subject during and after a subject's participation in a clinical investigation in the case of adverse events,
99. inform the subject of the nature and possible cause of any adverse events experienced,
100. 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,
101. inform the subject of any new significant findings occurring during the clinical investigation, including the need for additional medical care that may be required,
102. 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,

103. ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical investigation,

104. 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),

105. 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

106. 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.

107. Safety reporting. The Principal Investigator shall:

108. record every adverse event and observed device deficiency, together with an assessment,

109. 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,

110. 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,

111. 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

112. supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

113. 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:

114. 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.

115. 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.

116. 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.

117. 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.

118. 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.

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

120. Evaluate risks according to ISO 14971 before starting a trial,

121. Summarize benefit-risk analysis in trial documents,

122. Add residual risk and their nature, occurrence, severity, and outcome to the IB,

123. Include in CIP all anticipated adverse device effects and a rationale for the related benefit-risk ratio,

124. Include any anticipated adverse device effect in the consent form.

22.6.2 Principal Investigator Obligations according to GCP NMPA 2016

- Article 59 Before accepting clinical trial, clinical trial institutions shall evaluate relevant resources in accordance with the characteristics of investigational medical devices to decide whether to accept this clinical trial.
- Article 60 Clinical trial institutions shall properly keep clinical trial records and basic documents according to the agreement with the sponsor.
- Article 61 Investigators who are in charge of the clinical trial shall:
  - Have professional title and qualification above associate level, such as associate chief physician, associate professor and associate researcher in the clinical trial institutions;

  - Have professional knowledge and experience required for investigational medical devices and pass relevant trainings if necessary;
  - Be familiar with clinical trial requirements provided by sponsor, and the data and literatures related to clinical trial;
  - Be able to coordinate, allocate and assign personnel and devices of this trial, and to handle the adverse events and other correlating events related to investigational medical devices;
  - Be familiar with relevant national laws, regulations and this Provision.
- Article 62 Prior to a clinical trial, the medical device clinical trial administrative department of clinical trial institutions shall coordinate sponsor to file applications to the ethics committee and submit relevant documents in accordance with relevant provisions.
- Article 63 Investigators shall ensure that the staff member participating in the trial are familiar with the principles, indications, product performance, operating methods, installation requirements and technical specifications of investigational medical devices, understand preclinical research data and safety data of investigational medical devices, and master precautions and emergency treatment for possible risks in clinical trial.
- Article 64 Investigators shall ensure all participants of clinical trial fully understand the clinical trial protocol, relevant provisions, characteristics of investigational medical devices and relevant responsibilities of clinical trial, make sure that enough subjects meeting inclusion criteria in clinical trial protocol can be enrolled into clinical trial, ensure enough time in the agreed trial period, to implement and complete clinical trial safely according relevant regulations.
- Article 65 The investigator shall ensure that the investigational medical devices are only used for subjects of the clinical trial, and used for free.
- Article 66 Investigators shall strictly comply with clinical trial protocol. Without consent of sponsor and ethics committee or approval of China Food and Drug

Administration in accordance with regulations, investigators shall not deviate the protocol or substantially change the protocol. However, in case of an emergency that subjects face direct danger that needs to be eliminated immediately, it can be reported in writing afterwards.

- Article 67 Investigators shall be responsible for recruiting subjects and talking with subjects or their guardians. Investigators are responsible to specify the details relating to investigational medical devices and clinical trial for subjects, inform subjects of possible benefits and known and foreseeable risks, and obtain the signed and dated informed consent form from subjects and their guardians.
- Article 68 Investigators and other personnel participated in the trial shall not force or induce subjects in improper way to take part in the trial.
- Article 69 In case of finding unanticipated adverse events of investigational medical devices during clinical trial, investigators shall revise relevant content of informed consent form together with the sponsor. After being reviewed and approved by ethics committee in accordance with relevant working procedure, the affected subjects and their guardians shall resign the revised informed consent form for confirmation.
- Article 70 Investigators shall be responsible for making decisions relating to clinical trial. In case of adverse events relating to clinical trial, clinical trial institutions and investigators shall provide sufficient and timely treatment and management to subjects. In case subjects have complications and need treatment and management, investigators shall timely notify subjects.
- Article 71 In case of serious adverse events during clinical trial, investigators shall take proper treatment measures for subjects immediately, then report to medical device clinical trial administrative departments of clinical trial institutions where they belong to, and notify sponsor in writing through them. Clinical trial administrative departments of medical devices shall report to corresponding ethics committee and Food and Drug Administration of province,

autonomous region or municipality and the Health and Family Planning Commission where the clinical trial institution is located in written form within 24 hours. For lethal events, clinical trial institutions and investigators shall provide all necessary data to ethics committee and sponsor.

- Article 72 Investigators shall record all adverse events and device deficiency that occur during the process of clinical trial, analyze event cases together with sponsor, draft written analysis report, put forward opinions of continuing, suspending or terminating the trial, and report to ethics committee for review through medical device clinical trial administrative departments of clinical trial institutions.
- Article 73 Investigators shall ensure that clinical trial data are filled in case report forms accurately, completely, clearly and timely. Case report forms shall be signed by investigators. Any change of data shall be signed and dated by investigator, original records should be kept, clear and recognizable.
- Article 74 Clinical trial institutions and investigators shall ensure authenticity, accuracy, clarity and safety of data and documents generated in clinical trial.
- Article 75 Clinical trial institutions and investigators shall accept the monitoring and audit of sponsor as well as supervision of ethics committee, and provide all required records relating to the trial. In case Food and Drug Administration and Health and Family Planning Commission send inspectors to implement inspection, clinical trial institutions and investigators shall cooperate with them.
- Article 76 In case clinical trial institutions and investigators identify risks overweighting possible benefits, or have obtained the results that is sufficient to judge the safety and effectiveness of investigational medical devices, thus need to suspend or terminate clinical trial, it is required to notify subjects and ensure subjects to obtain proper treatment and follow-up, report in accordance with regulations and provide detailed written explanation at the same time. If necessary, report to the Food and Drug Administration of province, autonomous region or municipality where it locates.

- In case of receiving the notification of sponsor or ethics committee on the need of suspending or terminating clinical trial, investigators shall timely notify subjects and ensure subjects to obtain proper treatment and follow-up.
- Article 77 In case the sponsor violates relevant regulations or request to change the trial data and conclusion, clinical trial institutions and investigators shall report to Food and Drug Administration of province, autonomous region or municipality where the sponsor is located or report to the China Food and Drug Administration.
- Article 78 At the end of a clinical trial, the investigator shall ensure the completion of all records and reports. Meanwhile, the investigator shall ensure the quantity of received investigational medical devices is consistent with the used, discarded or returned devices, and ensure that the rest investigational medical devices are disposed properly and recorded for filing.
- Article 79 Investigators can authorize corresponding personnel to recruit subjects, continuously communicate with subjects, record the clinical trial data, and manage investigational medical devices in accordance with the needs of clinical trial. Investigators shall implement relevant training for the authorized personnel and document accordingly.