A Retrospective Study of the Navio◊ Robotic-assisted Surgical System

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Study Product Name:	Navio◊ Robotic-assisted Surgical System
Sponsor:	Smith & Nephew, Inc. 1450 E. Brooks Road Memphis, TN 38116 US

Nondisclosure Statement

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ABBREVIATIONS & DEFINITIONS

AE	Adverse Event
ADE	Adverse Device Effect
BMI	Body Mass Index
CAPA	Corrective and Preventive Action
CFR	Code of Federal Regulations
CRF	Case Report Form
CRO	Contract Research Organization
CSR	Clinical Study Report
CV	Curriculum Vitae
DevD	Device Deficiency
EC	Ethics Committee
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
ID	Identification
ISO	International Organization for Standardization
IRB	Institutional Review Board
KSS	Knee Society Score
PI	Principal Investigator
PP	Per Protocol
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System, SAS® Institute, Cary, NC
TKA	Total Knee Arthroplasty
UKR	Unicondylar Knee Replacement
USADE	Unanticipated Serious Adverse Device Effect

Protocol Synopsis:

Title of Study:	A Retrospective Study of the Navio◊ Robotic-assisted Surgical System
Study Type:	Post-market
Study Device:	Navio◊ Robotic-assisted Surgical System
Indications	Navio System-assisted Unicondylar Knee Replacements (UKR) are indicated for restoring either compartment of a knee that has been affected by: • Non-inflammatory degenerative joint disease including osteoarthritis, traumatic arthritis, or avascular necrosis • Correction of functional deformity • Treatment of fractures that are unmanageable using other techniques
Study design:	A retrospective, multi-center, cohort study with prospective follow-up and comparison to historical control
Primary Endpoint:	Navio System assisted Unicondylar Knee Replacement (UKR) revision rate 2 years postoperative
Secondary Endpoints:	Given the retrospective-prospective study design, secondary endpoint data will be collected to the extent that it is available and will include: • Change in Knee Society Score (KSS) from baseline to 2 years (-3months) or greater postoperative • Change in VR12 from baseline to 2 years (-3months) or greater postoperative • Anterior/Posterior and lateral radiographic assessments
Safety Assessment:	Study device and procedure-related adverse events (AE) incidence and frequency
Length of Study:	Up to 1 year: includes enrollment phase and collection of a minimum of 2-year postoperative follow-up data
Study Visits:	Retrospective pre-operative, operative and any available postoperative follow-up; Prospective 2-year or greater postoperative follow-up
Number of Sites:	Up to 10 sites in the United States and Europe
Sample Size:	One hundred twenty-eight (128) subjects, including 10% inflation to allow for attrition
Inclusion Criteria:	1. Male or female subjects ≥ 18 years old (at the time of surgery) who have undergone Navio System-assisted UKR prior to IRB/EC site approval. This includes UKR procedures with all Unicondylar Knee cemented implant designs. 2. Subject had a primary diagnosis of unicompartmental, non-inflammatory degenerative joint disease including osteoarthritis, traumatic arthritis, or avascular necrosis, required correction of functional deformity, or required treatment of fractures that were unmanageable using other techniques.
Exclusion Criteria:	1. Subject received the Navio System-assisted UKR on the index joint as a revision for a previously failed UKR.

	2. Subject, in the opinion of the Investigator, had advanced osteoarthritis or joint disease at the time of surgery and was better suited for Total Knee Arthroplasty (TKA). 3. Subject, in the opinion of the Investigator, had a neuromuscular disorder that prohibited control of the index joint. 4. Subject, in the opinion of the Investigator, was morbidly obese. 5. Subject, in the opinion of the Investigator, was contraindicated for UKR. 6. Subject (prospective subjects only), in the opinion of the Investigator, has an emotional or neurological condition including mental illness, mental retardation, drug or alcohol abuse. 7. Subject (prospective subjects only) is a prisoner.

1. Background and Study Rationale

1.1. Background

Total Knee Arthroplasty (TKA) has become an effective and reliable treatment for arthritis of the knee (1). TKA is associated with low morbidity and mortality, and its effectiveness in reducing joint pain and improving range of motion is well established. In 2014, over 750,000 knee replacements were performed in the United States (2); it is estimated that 8-12% of these are Unicondylar Knee Replacements (UKR) (3).

UKR was first used in the 1970's and can be beneficial, as the UKR surgery preserves bone and ligaments, unlike many TKA systems. Recovery and rehabilitation are typically shorter (4). Initial revision rates as high as 30% over 6 years (5) led to proposed guidelines for patient selection (6). Resulting changes in the patient population, along with improvements in surgical technique have led to better outcomes and lower revision rates. A meta-analysis of 31 cohort studies published between 2000 and 2016 (7) reported annual revision rates[1] by subgroup: males, 1.43%; females, 1.52%; age ≥ 60year, 1.45%; age < 60year, 2.16%; Body Mass Index (BMI) < 30, 0.79%; BMI ≥ 30, 0.91%.

A significant innovation in knee arthroplasty has been the introduction of computer navigation and robotic-assisted surgery (8). These technologies have improved the accuracy of bone preparation, implant positioning, and soft tissue balance in UKR and it is estimated that 15-20% of UKR surgeries in the United States are performed with robotic assistance (9). The Navio◊ Robotic-assisted Surgical 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. This system has been used in over 1000 UKR surgeries to date. The clinical effectiveness of the Navio System continues to be evaluated in the literature, and clinical studies are warranted to further evaluate the system.

This study is to be conducted according to US and international standards of Good Clinical Practice (GCP) including International Conference on Harmonisation (ICH) E6, the Code of Federal Regulation (CFR) and other applicable government regulations and institutional research policies and procedures.

2. Study Objectives

This clinical study will evaluate the 2-year safety and effectiveness of the Navio System in UKR in subjects ≥ 18years of age, as demonstrated by revision rate, changes in clinical, functional, and quality of life outcomes over time, radiographic assessments and Adverse Event (AE) incidence and frequency.

2.1. Primary Endpoint

Navio System assisted UKR revision rate 2 years postoperatively.

[1] $Annual\ Revision\ Rate\ (\%) = \frac{Failures}{Observed\ component\ years} \times 100$

$Observed\ component\ years = Total\ observed\ knees \times Mean\ follow-up\ (years)$

2.2. Secondary Endpoints

Given the retrospective-prospective study design, secondary endpoint data will be collected to the extent that it is available and will include:

- Change in Knee Society Score (KSS) from baseline to 2 years (-3months) or greater postoperative
- Change in VR12 from baseline to 2 years (-3months) or greater postoperative
- Anterior/Posterior and lateral radiographic assessments:
    - Radiographic findings
    - Component orientation
    - Radiolucencies
    - Migration
    - Osteolysis
    - Stress shielding
    - Subsidence

3. Study Design

This is a retrospective, multi-center, cohort study with prospective follow-up and comparison to historical control to collect 2-year safety and effectiveness data on 128 subjects, at up to 10 sites in the United States and Europe, who have undergone Navio System-assisted UKR.

Subject data will be retrospectively evaluated at the pre-operative, operative, and any available postoperative follow-up visits as well as prospectively evaluated at the 2-year (-3months) or greater postoperative follow-up visit.

4. Study Device

The Smith & Nephew Navio Robotic-assisted Surgical System aids the surgeon in planning and executing a procedure involving bone preparation for prosthesis implantation. The system is comprised of computer-assisted surgical instrument control, a commercially available surgical drill, image-free navigation, and planning software with standard navigation technology.

The Navio System uses data gathered during the beginning of the surgical procedure (planning phase) to generate a computer model of the knee surface to be remodeled in preparation for the implant. The software uses data collected during the planning phase along with pre-loaded data describing the implant geometry to guide the surgeon in shaping the knee for the selected implant. The Navio system software then allows the surgeon to evaluate the range of motion and fit of the implant prior to finalizing the procedure.

The Navio system software consists of a patient and user management module, a surgical planner, and an intraoperative cutting module. The surgeon uses patient data collected at the surgical site to align the implant and shape the target surface of the bone to accept the intended implant. The Navio system also uses the tracked position of the surgical bur to control its cutting engagement to the bone that is to receive the implant. This cutting control is based on the bur's proximity to the planned target surface of the bone.

The cutting control is achieved in two ways:

- Exposure control adjusts the bur's exposure with respect to a guard. If the surgeon encroaches on a portion of bone that is not to be cut, the Navio system retracts the spinning bur behind the guard, disabling cutting. The Navio system software also adjusts the depth of the cut by adjusting the exposure of the bur outside of the bur guard.
- Speed control regulates the signal transmitted to the drill motor. This limits the speed of the spinning bur or disables bur motion entirely if the target surface has been reached. Bur motion is also disabled if the bur is moved outside of expected cutting boundaries.

The surgeon can alternate between these two cutting control modes. The surgeon can also disable both cutting control modes and operate the Navio system as a standard navigated drill.

The Navio system incorporates a detailed user interface that provides procedure setup, tracking status, visual indicators, and real-time cutting progress during the procedure.

The Navio System is shown below:

Description	Part Number
Tracking Camera and Stand	110001
Navio System Cart	NPFS-02000, -02010, -02020, -02070
Anspach Drill Foot Control	120041
Navio System Foot Control	100460
Navio System Handpiece	110137
Anspach Drill	101209

The function of each component is as follows:

- Tracking Camera and Stand - The mobile infrared tracking camera is used to determine the position of the point probe and the surgical bur tip and track their movement by scanning the position of reflective trackers relative to the position of trackers mounted on the patient's femur and tibia.
- Navio System Cart - The mobile cart contains the electronic control system, electrical system integration unit, computer, and uninterruptible power supply (UPS). Navio system carts are available in 120 VAC and 220-240 VAC versions. The cart provides storage for the power cord, Anspach◊ drill foot control, and the Navio system foot control. The touchscreen monitor is the primary user interface for the Navio system.
- Anspach◊ Drill Foot Control - The Anspach drill foot control is used to control the Anspach drill during surgery. The surgeon must press the foot control to activate the bur. The speed of the bur is controlled by the Navio system software in speed control mode.
- Navio System Foot Control - The Navio system foot control is used as an alternative to the touchscreen monitor when data points are being collected to define landmarks, shape bone, and position the implant prior to surgery.
- Navio System Handpiece - The Navio system handpiece controls the position of the Anspach Drill and bur relative to the position of the guard and the desired profile of the bone being cut. In exposure mode, as the bur nears the target surface of the bone intended to accept the implant, the Anspach drill and bur retracts into the guard to prevent further cutting of bone.

The Navio system is intended to assist the surgeon in providing software-defined spatial boundaries for orientation and reference information to anatomical structures during orthopedic procedures. The system 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 UKR and patellofemoral arthroplasty. The Navio System is indicated for use with cemented implants only (refer to User Manuals for more detail).

4.1. Surgical Technique

The operative visit of this study is retrospective. The use of the Navio System was performed per standard of care at the participating study sites. The Navio System is indicated for all cemented Unicondylar Knee implants, therefore, all Unicondylar Knee cemented implant designs will be included in this study.

5. STUDY POPULATION

5.1. Subject Screening and Enrollment

To eliminate the potential for selection bias, Investigators will consecutively screen subjects by date of surgery, starting with their first Navio-assisted UKR subject. For screening, only information in the medical records will be reviewed. Subjects meeting all eligibility criteria will be listed on a Screening and Enrollment log.

Once a subject has completed the informed consent process, if required by the IRB/EC, the subject will be considered enrolled and assigned a consecutive Subject Identification (ID) number that identifies a single study knee. The subject ID number will be listed on the Screening and Enrollment Log. In the event that a subject has bilateral Navio assisted UKR, only the first treated knee will be enrolled and assigned a Subject ID. The Screening and Enrollment Log is the source in which records all screening and enrollment details are recorded.

5.2. Informed Consent

Study sites will obtain IRB/EC approval for this study.

An IRB/EC waiver of informed consent for study participation should be requested for those subjects who meet eligibility criteria and have retrospectively completed a 2-year postoperative visit, are deceased, or are lost to follow-up, per IRB/EC policy. If allowed, a retrospective data set will be collected on these subjects. A copy of the waiver of informed consent will be placed in the subject file.

Subjects who meet eligibility criteria, are alive, and have not completed a 2-year postoperative visit, will be contacted and asked to provide Informed Consent prior to any retrospective or prospective data collection. These subjects may consent for participation only in the retrospective phase of the study or may consent for participation in both the retrospective and prospective phases of the study. The informed consent process will be documented in the subject's medical record and on the study Case Report Forms (CRFs). The informed consent form (ICF) will be placed in the subject file and a copy will be provided to the subject.

If a subject refuses participation, no further information will be collected. Reason for exclusion should be noted on the Screening and Enrollment Log.

5.3. Subject Inclusion Criteria

Subjects must meet the following inclusion criteria to be included in the study:

1. Male or female subjects ≥ 18 years old (at the time of surgery) who have undergone Navio System-assisted UKR prior to the date of IRB/EC approval of the study site. This includes UKR procedures with all Unicondylar Knee cemented implant designs.
2. Subject had a primary diagnosis of unicompartmental, non-inflammatory degenerative joint disease, including osteoarthritis, traumatic arthritis, or avascular necrosis, required correction of functional deformity, or required treatment of fractures that were unmanageable using other techniques.

5.4. Subject Exclusion Criteria

Subjects will be excluded from the study if they meet any of the following exclusion criteria:

1. Subject received the Navio System-assisted UKR on the index joint as a revision for a previously failed UKR.
2. Subject, in the opinion of the Investigator, had advanced osteoarthritis or joint disease at the time of surgery and was better suited for TKA.
3. Subject, in the opinion of the Investigator, had a neuromuscular disorder that prohibited control of the index joint.
4. Subject, in the opinion of the Investigator, was morbidly obese.
5. Subject, in the opinion of the Investigator, was contraindicated for UKR.
6. Subject (prospective subjects only), in the opinion of the Investigator, has an emotional or neurological condition including mental illness, mental retardation, drug or alcohol abuse.
7. Subject (prospective subjects only) is a prisoner.

6. STUDY PROCEDURES

6.1. Study Schematic

The intervals and schedule of events are provided in Table 1.

	Retrospective Data Collection[1]				Prospective Data Collection[2]
	Screening and Enrollment	Pre-operative	Operative / Discharge	Follow-up	2-year (-3months)or greater postoperative follow-up
Informed Consent	√[3]				
Inclusion/Exclusion	√				
Demographics/ Medical History		√			
Operative and Discharge Data Collection			√		
Implant Status[4]				√	√
Knee Society Score (KSS)		√		√	√
VR-12		√		√	√
Radiographic Assessment		√	√	√	√
Adverse Event Assessment			√	√	√
End of Study/Exit				√*	√

[1]Given the retrospective-prospective study design, data will be collected to the extent it is available.
[2]Visit may occur in an office or remotely. If completed remotely (e.g. telephone call, mailing of subject questionnaires and/or any other means), secondary endpoint data will be collected to the extent possible.
[3]Informed consent/waiver of informed consent from the IRB/EC must be obtained prior to retrospective and prospective data collection.
[4]Subjects who have undergone a revision procedure of the study knee will be considered terminated from the study from the date of the revision. Study related data will not be collected following the date of the revision.
*if applicable

6.2. Retrospective Data Collection

- Verify subject meets inclusion/exclusion criteria
- Obtain Informed Consent, as required by the IRB/EC, on an IRB/EC approved ICF or a waiver of informed consent
- Assign a Subject ID
- Collect the following retrospective data, to the extent it is available in the subject's medical records, per CRF completion guidelines:
  - Demographic and medical history information
  - Operative and Discharge data
  - Implant Status

- KSS – pre-operative and any available postoperative follow-up
- VR-12 – pre-operative and any available postoperative follow-up
- Pre-Operative anterior/posterior and lateral radiographic assessments:
    - Radiographic findings
    - Osteolysis
- Post-Operative anterior/posterior and lateral radiographic assessments that are available:
    - Radiographic findings
    - Component orientation
    - Radiolucencies
    - Migration
    - Osteolysis
    - Stress shielding
    - Subsidence
- Revision CRF, if applicable
- End of Study CRF, if applicable
- Study Device and Procedure-Related Adverse Events

6.3. Prospective Data Collection: 2-Year (-3 months) or Greater Postoperative Follow-up

Collect the following prospective data for subjects who have not retrospectively completed a 2-year (-3months) or greater postoperative visit and consent to participate in the prospective phase of the study:

- Implant Status
- KSS
- VR-12
- Anterior/Posterior and lateral radiographs and assessments:
    - Radiographic findings
    - Component orientation
    - Radiolucencies
    - Migration
    - Osteolysis
    - Stress shielding
    - Subsidence
- Revision CRF, if applicable
- End of Study CRF
- Study Device and Procedure-Related Adverse Events

The prospective follow-up visit may occur in an office or remotely. If completed remotely (e.g. telephone call, mailing of subject questionnaires and/or any other means), secondary endpoint data will be collected to the extent possible.

If the subject already completed the 2-year visit at the time of enrollment, 2-year visit data will be collected retrospectively as defined in section 6.2.

7. SUBJECT COMPLETION AND DISPOSITION

7.1. Conditions for Study Termination

All reasonable efforts should be made to collect 2-year postoperative data on all subjects enrolled in this study. There are multiple reasons a subject may be terminated from the study. For each case, information will be obtained on the End of Study CRF, detailing circumstances leading to the withdrawal.

A. Voluntary Withdrawal

Study participation is voluntary and subjects may withdraw from the study without giving reason for doing so.

B. Lost to Follow-Up

During the course of this study, it may not be possible to locate a subject for informed consent and participation prospectively. Study personnel must make a reasonable effort to contact the subject and document the contact attempts according to the site's policies prior to declaring a subject to be lost to follow-up. Copies of all attempts to reach the subjects by regular mail, email and/or any other means should be documented in the subject's medical record.

C. Study Termination by Investigator/Sponsor

The Investigator **should** withdraw subjects from the study:

- if the study knee was revised during the follow-up phase of the study
- if the Investigator or the Sponsor stops the study for any reason

D. Pregnancy

In the unlikely event that a subject becomes pregnant from the time point of signing the Informed Consent until the end of the study, study procedures that are contraindicated during pregnancy and/or lactation (e.g. x-rays) will not be obtained. However, the subject will continue to be followed and information will be collected regarding the outcome of the pregnancy.

E. Study Site Discontinuation

A specific study site in this multicenter study may also warrant termination under the following conditions:

- non-compliance to GCP or protocol
- failure to enroll subjects
- major protocol deviations
- inaccurate or incomplete data
- unsafe or unethical practices
- safety or performance considerations
- investigator involuntarily discontinues participation in study

F. Revisions

Subjects who have undergone a revision procedure of the study knee will be considered terminated from the study from the date of the revision. Study-related data will not be collected following the date of the revision. The appropriate CRFs will be completed for these subjects to document the details of study termination and revision.

8. Safety Reporting

Adverse Events (AE) related to the study device (Navio), the unicondylar implant, or procedure including Adverse Device Effects (ADE), Serious Adverse Device Effects (SADE), Unanticipated Serious Adverse Device Effect (USADE), and Device Deficiencies (DevD) occurring from the time of the study procedure until revision or study completion must be recorded on the appropriate CRF and reported. If the event is known to have been previously reported to Smith & Nephew, this must be noted on the CRF. After consent, in addition to all events related to Navio, the unicondylar implant or the procedure, all serious adverse events (SAE), regardless of causality, must be recorded on the appropriate CRF and reported to sponsor and IRB if necessary. Events leading to a revision should be reported at all times regardless of causality.

Adverse Device Effects (ADE) occurring after study completion will be handled as product complaints reportable by the Sponsor and will not be entered into the study database.

8.1. Definitions for Safety Reporting

A. Adverse Event

An 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 (10).

For the purpose of this study, this definition includes:

- events related to either Navio or the unicondylar implant
- events related to the procedures involved
- during the prospective data collection period, a worsening of any conditions previously recorded as part of the medical history assessment that meets serious adverse event criteria

B. Serious Adverse Event (SAE)

An SAE is an AE that (10):

- led to death,
- led to serious deterioration in the health of the subject, that either resulted in:
    1) a life-threatening illness or injury, or
    2) a permanent impairment of a body structure or a body function, 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
- led to fetal distress, fetal death or a congenital abnormality or birth defect

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

C. Adverse Device Effect (ADE)

An ADE is an AE related to the use of an investigational medical device (10).

This definition includes:

- AEs resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device
- Any event resulting from use error or from intentional misuse of the investigational medical device.
- For the purposes of this study, any event related to a Smith & Nephew unicondylar implant will be classified as an adverse device event

D. Serious Adverse Device Effect (SADE)

An SADE is an ADE that has resulted in any of the consequences characteristic of an SAE (10).

E. Unanticipated Serious Adverse Device Effect (USADE)

An USADE is an SADE which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report or the clinical investigation plan (10, 11).

F. Device Deficiency (DevD)

A DevD is an inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety, or performance. DevD include malfunctions, use errors, and inadequate labeling.

For this study, DevD should be reported when they concern any component of the Navio system as well as its packaging and tools that need to be used during surgery according to the User Manual.

G. Revisions

A specially designed Revision CRF will be used in addition to the AE CRF, to document in detail revisions of any study knee. Please note that at all phases of the study, all revisions should be reported, regardless of whether or not it is related to Navio, the unicondylar knee or the study procedure.

8.2. Safety: Investigator's Responsibilities

Reporting of adverse events during the retrospective data collection portion of the study:
Investigators are responsible for documenting ADE, SADE, U(S)ADE and DevD identified during the medical record review. This includes events related to the study device (Navio), the unicondylar implant, or procedure. Investigators will record ADE, SADE, U(S)ADE and observed DevD, together with an assessment in the subject's source data. Investigators are responsible for documenting ADE, SADE, U(S)ADE and DevD on the appropriate CRF and submitting them to the Sponsor according to the timelines described.

Reporting of adverse events during the prospective data collection portion of the study:
At each prospective contact with the subject, the Investigator must seek information on previous events and current events that could be deemed serious by specific questioning and, as appropriate, by assessment of the subject. All study device (Navio), unicondylar implant, and procedure related adverse events and all serious adverse events (SAE) regardless of causality, must be recorded on the appropriate CRF and reported to sponsor and IRB. Unresolved AE should be followed by the Investigator until the events are resolved or through to the end of the study, whichever occurs first. Unresolved AEs at the end of the subject's participation should be monitored by the Investigator as part of the site's normal standard of care.

All events must be recorded in standard English medical terminology.

The Investigator will categorize AE as mild, moderate or severe based on the following definitions:

- Mild: the subject is aware of the sign or symptom, but finds it easily tolerated. The event is of little concern to the subject and/or little clinical significance. The event is not expected to have any effect on the subject's overall health or well-being.
- Moderate: the subject has discomfort enough to cause interference with or change in usual activities. The event is of some concern to the subject's health or wellbeing and may require medical intervention and/or close follow-up.
- Severe: the adverse event interferes considerably with the subject's usual activities. The event is of definite concern to the subject and/or poses a substantial risk to the subject's health or wellbeing. The event is likely to require medical intervention and/or close follow-up and may be incapacitating or life threatening. Hospitalization and treatment may be required.

The Investigator is responsible for describing the relationship of the AE to the study device/procedure based on the following definitions:

- Unrelated: the event is clearly not related to the study device or procedure
- Possible: the event may or may not be related to the study device or procedure. A relationship cannot be ruled out.
- Definite: the event is clearly related to the study device or procedure.

8.3. Timelines for Submission of Safety Information:

The timelines begin when the Investigator becomes aware of the event (i.e. during review of the medical records for the retrospective phase of the study or during the prospective phase of the study).

The Investigator will report to the Sponsor:

- As soon as possible, but no greater than **24 hours upon identifying the event, SADE, U(S)ADE and DevD that could have led to a SADE**:
    - if suitable action had not been taken
    - if intervention had not been made, or
    - if circumstances had been less fortunate
- During the prospective portion of the study, SAEs must be reported to the sponsor as soon as possible, but no greater than 24 hours of the investigator's awareness that the event meets SAE criteria.
- **Revisions**, **within 24 hours upon identifying the event.**

* Retrospective SADE do not require reporting within 24 hours, but should be reported promptly, if a product complaint was not previously submitted to Smith & nephew Product Complaints

Investigators may also be asked to supply the Sponsor, upon Sponsor's request, with any additional information related to the safety reporting of a particular event.

The Principal Investigator (PI) will be responsible for reporting applicable adverse events to the IRB/EC of the study site per their institutional requirements, and to the regulatory authorities as required by the national regulations.

8.4. Safety Reporting: Sponsor's Responsibilities

The Sponsor will provide progress reports on safety events to the Investigator to report to the IRB/EC as required.

In the case of multicenter studies, the Sponsor will inform all Investigators in writing of all SADE that were reported by all sites throughout the clinical investigation and based on perceived risk.

The Sponsor will also, in case of SADE and device deficiencies that could have led to SADE, determine whether the risk analysis needs to be updated and assess whether corrective or preventive action is required.

9. Statistical Procedures

Smith & Nephew Global Biostatistics Department will conduct statistical analysis. Unless otherwise stated, all significance tests and hypothesis testing will be two-sided, performed at the 5% significance level.

Where data summaries are specified, categorical and ordinal variables will be summarized using frequency distributions which will detail the number and percentage of subjects which fall into each category. Continuous variables will be summarized using the following summary statistics: mean, median, standard deviation, minimum and maximum values, and number of observations.

In formal analyses, resulting P-values will be quoted and 95% two-sided confidence intervals generated where appropriate. All analyses will be performed in SAS v9.4 (or later).

No formal interim analysis is planned.

9.1. Sample Size Calculation

This study will screen and consent patients until a total of 128 subjects, from up to 10 sites, treated with the study device have been enrolled in the study.

The study is intended to test for non-inferiority in the percentage of revision-free survival at 2 years recorded during the study compared to existing literature. The Australian Orthopaedic Association National Joint Replacement Registry 2015 Annual Report (13) records the revision-free survival for at 2-years as 95.7%.

Using a non-inferiority margin of 7%, a sample size of 115 subjects will provide at least 80% power at the 5% significance level using exact binomial methods. To allow for a 10% attrition and drop-out rate, a total of 128 subjects will be enrolled.

9.2. Missing Data

A complete accountability report, along with the explanation for lost-to-follow-up, death, revision, and withdrawn subjects is to be provided in the Clinical Study Report (CSR). The methods used to handle missing or incomplete data for the efficacy and safety measures will be detailed in the Statistical Analysis Plan (SAP).

9.3. Evaluability

All subjects that receive a study device are considered study participants. The following study populations and analysis sets will be defined:

- Safety Population: This will include all subjects that received the study device.
- Full Analysis Set (FAS): This will include all subjects that received the study device.
- Per Protocol Population (PP): This will include all subjects that received the study device, meet the inclusion/exclusion criteria, attend the follow-up assessments, and have no significant protocol deviations. Subjects that are required to be withdrawn from the study under the protocol (e.g. due to revision) will be included regardless of attendance of follow-up visits unless they are deemed to have significant protocol deviations or failed to meet the inclusion/exclusion criteria.

Statistical analysis will be performed using each of the patient populations as follows: analysis of the primary, secondary efficacy objectives will be performed separately using both the FAS and the PP Population. All safety analyses will utilize the Safety Population.

9.4. Analyses

A formal SAP will be written and finalized prior to database lock. The SAP will detail the summaries and analyses to be performed.

- Primary endpoint:

  The primary endpoint of the study is the Navio System assisted UKR revision rate at 2 years postoperatively. A one-sided 95% confidence interval for the revision [free] rate of the Navio System assisted UKR will be calculated using exact binomial methods. Non-inferiority, using a 7% non-inferiority margin will be declared if the lower bound of the confidence interval is >88.7%. Time to occurrence of revision will also be analyzed using Kaplan-Meier survival analysis. Where appropriate, statistical modeling will be considered with prognostic and baseline factors adjusted for.

- Secondary endpoints:

  Where appropriate, the secondary endpoints will be analyzed using either an ANOVA or Repeated Measures analysis, depending on whether a comparison between two time points or multiple time points is conducted. In each case, prognostic and baseline factors will be adjusted for. For endpoints where further analysis is not warranted, or not considered appropriate, tabulations detailing frequency distributions and/or summary statistics will be produced.

- Safety:

  Numbers and types of AE, along with rates of AE types; with 95% confidence intervals for the rates (constructed using either exact binomial or asymptotic methods where appropriate) will be tabulated.

10. ETHICAL CONSIDERATIONS

10.1. Ethical Approval

In accordance with the Declaration of Helsinki and local regulations of the participating countries, sites must gain written IRB/EC approval prior to enrolling research participants in the study.

10.2. Protocol Amendments

Neither the Investigator nor the Sponsor will modify this protocol without mutual agreement. After agreement to initiate the modification, in the form of a protocol amendment, the Investigator agrees not to implement this modification until instructed to do so by the Sponsor. It will be necessary to obtain IRB/EC approval prior to implementation of any change in the protocol that may affect the scientific soundness or the rights, safety, or welfare of the subjects involved. Notification shall be submitted to the IRB/EC of the study site by the Investigator.

10.3. Informed Consent

Investigators must apply for the appropriate IRB/EC approvals on this study.

An IRB/EC waiver of informed consent for study participation should be requested for those subjects who meet eligibility criteria and have retrospectively completed a 2-year postoperative visit, are deceased, or are lost to follow-up/cannot be contacted, as per IRB/EC policy. If allowed, the informed consent waiver from the IRB/EC will allow for retrospective data collection from all subjects who have undergone Navio System assisted UKR, thereby eliminating selection bias. A copy of the waiver of informed consent will be placed in the subject file.

Subjects who meet eligibility criteria, are alive and have not completed a 2-year postoperative visit must sign an IRB/EC approved ICF according to ISO14155 guidelines, GCP guidelines and all applicable national regulations prior to any retrospective or prospective data collection. These subjects must be informed of the purpose of the study and the potential risks and benefits known or that can be reasonably predicted or expected as described in the written consent form. The subject shall have sufficient opportunity to consider participation in each phase of the study; a subject cannot be led to believe that they are waiving their rights as a subject or the liability of the Sponsor or Investigator. Subjects are then invited to sign and date the consent form, indicating their consent for participation in the retrospective and/or prospective phases of the study. The Investigator will retain the original copy of the signed consent form in the study files. A duplicate copy shall be provided to the subject.

10.4. Risk – Benefit Analysis

A. Study-Related Risks

Possible risks that may occur as a result of study procedures are:

- Subjects completing the prospective phase of the study will be asked to complete questionnaires, however, these are not interventional procedures and are not expected to add significant time.
- The prospective phase of the study involves the use of x-ray evaluation. X-ray exposure is cumulative over a lifetime and total exposure should be kept to a minimum. However, since the x-ray exposure when participating in the study is equivalent to the exposure the subject would receive if they chose not to participate in the study, there is no additional risk associated with this study.

- As a result of enrollment in the study, there could be a risk of loss of protected subject information confidentiality. All applicable confidentiality standards and data protection and privacy laws will be followed by the Sponsor to ensure that data collected is handled in confidence. Data will be coded and handled only by appropriately qualified and authorized personnel.

Risks related to the general surgical procedures are not considered here because these could be present regardless of participation into the study.

B. Study-Related Benefits

Because the surgery and all the follow-up visits are the same as if the subject would not participate in this study, there are no additional medical benefits associated with participating in this study. The information gained from this study may help improve the treatment of people that need to undergo UKR.

11. MONITORING PROCEDURES

11.1. Source Documentation

Investigators are responsible for obtaining and maintaining complete subject health information in the medical record for each subject (source documents). Examples of source documents are hospital records, clinic and office charts, memoranda, dispensing records, subject questionnaires, clinic evaluation transcriptions, operative notes, x-rays, radiology reports, blood collection reports and shipment records, and research subject files. Members of the Investigator study site team will abstract data from source documents into study specific paper CRFs developed by the Sponsor.

As a minimum entry in the medical records, the PI shall ensure that clinical records are clearly marked to indicate that the subject is enrolled in a particular clinical study and if they completed per protocol or discontinued early and the reason.

11.2. Direct Access

This study may be monitored by the Sponsor or a qualified person designated by the Sponsor. This qualified person could be an employee of the Sponsor or of a Contract Research Organization (CRO - Sponsor's agent).

The Investigator will provide the Sponsor, Sponsor's agents, IRB/EC and regulatory agencies with direct access to all source data/documents to permit study-related monitoring, audits, IRB/EC review, and regulatory inspections.

11.3. Site Qualification Visit

A site qualification visit may be performed by the Sponsor or designee 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.

11.4. Prior to Study Initiation

The Investigator must ensure the activities below are completed prior to the initiation of the study and provide supporting documentation to the Sponsor:

- **Clinical Study Agreement**: must be fully executed with the site and the Sponsor and any other appropriate party.
- **Documentation of Qualifications:** a current, signed and dated Curriculum Vitae (CV) for the Investigator and for all key members of investigator study site team listed on the Delegation of Authority Log must be submitted to the Sponsor prior to the study and updated as applicable to staff changes and confirmed at close out visit.
- **Conflict of Interest:** all participating Investigators are required by International Organization for Standardization (ISO) 14155 to provide details of conflict of interest (including financial, if applicable) according to local regulations. This information must be updated promptly by the Investigator and submitted to the Sponsor if any changes occur through the duration of the study and for one year following completion of the study.

11.5. 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 designee following execution of the Clinical Study Agreement and documented IRB/EC approval.

11.6. Interim Monitoring Visits

A clinical monitor, whether an employee of the Sponsor or its designee, has the obligation to follow this study closely. In doing so, the monitor will, in addition to maintaining necessary contact with the study site, visit the study sites at periodic intervals according to a schedule determined by the Sponsor. During these visits, the monitor will:

- verify informed consent process
- perform source data verification according to the Clinical Monitoring Plan
- verify that source documentation is complete and available
- ensure compliance with the protocol
- ensure all required study documentation is complete and available in Investigator Site File

11.7. 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.

11.8. Closeout 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/EC reporting requirements.

11.9. Documentation of Monitoring Visits

Activities associated with a monitoring visit will be documented by the monitor. This includes:

- monitor visit log on site

- a follow-up letter to the Investigator following each monitor visit summarizing the visit and detailing any site deficiencies and action items to clarify or address issues noted

11.10. Data Handling and Record Keeping Requirements

CRF will be supplied by the Sponsor. Subjects will be identified by a subject ID and subject code. Only the Investigator site will have the key to identify individual subjects.

The Investigator is responsible for the timely and accurate completion of CRF. All documents related to the study must be securely archived at the study site or in a central archive.

Data required according to this protocol are to be recorded on the CRF at the time of medical record review. Once a subject is enrolled, completed CRF should be sent to the Sponsor, either by fax or by e-mail, as soon as possible, and no later than 10 working days upon completion of the CRF.

11.11. Data Recording and Record Retention

Clinical research records shall be stored in a manner that ensures privacy, confidentiality, security and accessibility of the records both during and after the conduct of the study. The Investigator/Institution will take measures to prevent accidental or premature destruction of those documents. The Investigator must retain essential study documents for at least 2 years after the latest of the following: the date the study is terminated or completed or the date the documents are no longer needed to support a premarket approval application. If the Investigator needs to dispose of the documents, the Sponsor should be contacted for approval prior to disposal or destruction. For discontinued product, the essential documents will be retained until at least 2 years have elapsed since the formal discontinuation (via notification of the Food and Drug Administration [FDA] or other regulatory agency) of clinical development of the investigational product. The Investigator will retain these documents for a longer period if required by the applicable local laws.

If the responsible Investigator retires, relocates, or withdraws from responsibility of keeping the study records, custody must be transferred to a person who will accept the responsibility. The Sponsor must be notified in writing of the name and address of the new custodian. Under no circumstance shall the Investigator relocate or dispose of any study documents before having obtained written approval from the Sponsor.

12. DEVIATIONS FROM PROTOCOL

A protocol deviation is an instance of failure, intentionally or unintentionally, to follow the requirements of the protocol. Protocol deviations include but are not limited to: deviations from inclusion/exclusion criteria, endpoint variable criteria, study visits outside the window, and GCP guidelines.

12.1. Protocol Deviation Reporting Requirements

Deviations must be reported to the Sponsor through the specially designed Protocol Deviation Log as soon as reasonably possible.

When protocol deviations affect the scientific soundness of the study or the rights, safety or welfare of the study subjects, the Investigator must also report protocol deviations to the IRB/EC of the study site. It is the responsibility of the Principal Investigator (PI) to inform the IRB/EC of the study site of the incident, per local requirements. The local IRB/EC should be consulted on protocol deviation reporting requirements.

Investigators and all study staff (staff at the site and at Sponsor) are responsible for ensuring adherence to study protocol. During the monitoring visits, the Sponsor representative will review all deviations with the Investigator. If a deviation is discovered outside of a monitoring visit, it should be evaluated via phone, email or letter. Appropriate measures to address the occurrence, additional monitoring visits, or audit of the study should be taken, which may include defining and implementing a Corrective and Preventive Action (CAPA).

13. Publication Policy

The preparation and submission for publication of manuscripts containing the study results shall be in accordance with a process determined by the Clinical Trial Agreements between the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to the Health Insurance Portability and Accountability Act of 1996.

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