



## **INFINITY™ Total Ankle Replacement Follow-up (ITAR)**

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## ABBREVIATIONS/TERMINOLOGY

**Arthroplasty** is a surgical procedure to restore the integrity and function of a joint. A joint can be restored by resurfacing the bones; an artificial joint (prosthesis) may also be used. Osteoarthritis (OA) or degenerative joint disease is a loss of the cartilage or cushion in a joint, and is the most common reason for arthroplasty

**COFAS** - Canadian Orthopaedic Foot & Ankle Society

**Good Manufacturing Practice (GMP)** - regulations set forth by the United States Department of Health and Human Services by the Food and Drug Administration (FDA) under the regulations 21 CFR Parts 808, 812, 820.

**ICH** - The International Conference on Harmonization

**ICH E6** Good Clinical Practice (GCP)

**Good Clinical Practice (GCP)** is an international ethical and scientific quality standard for designing, conducting, recording, and reporting trials that involve human subjects. Compliance with GCP assures that the rights, safety, and well-being of trial subjects are protected and that the clinical trial data are credible. This International Conference on Harmonization (ICH) guidance provides a unified standard for the European Union, Japan, and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in those jurisdictions.

**IRB/EC/REC** - is an Institutional Review Board, Ethical Review Committee, Research Ethical Committee - a committee established to review and approve research involving human subjects. The purpose of the IRB/EC/REC is to ensure that all human subject research be conducted in accordance with all federal, institutional, and ethical guidelines

**ISO 14155:2011** addresses good clinical practice for the design, conduct, recording and reporting of clinical investigations carried out in human subjects to assess the safety or performance of medical devices for regulatory purposes. The principles set forth in ISO 14155:2011 also apply to all other clinical investigations and should be followed as far as possible, depending on the nature of the clinical investigation and the requirements of national regulations.

**ISO 14155:2011** also specifies general requirements intended to protect the rights, safety and well-being of human subjects, ensure the scientific conduct of the clinical investigation and the credibility of the results, define the responsibilities of the sponsor and principal investigator, and assist sponsors, investigators, ethics committees, regulatory authorities and other bodies involved in the conformity assessment of medical devices.

**Osteolysis** - pathological destruction or disappearance of bone tissue.

**Subsidence** - sinking or settling in bone, as of a prosthetic component of a total joint implant.

## PROTOCOL SYNOPSIS

<b>Study Title</b>	The INFINITY™ Total Ankle Replacement Follow-up (ITAR)
<b>Study Design</b>	Prospective, multi-site, multi-year post-market clinical follow-up study
<b>Study Group</b>	Primary/Unilateral and/or bilateral Total Ankle Arthroplasty subjects implanted with INFINITY™ Total Ankle System
<b>N Subjects</b>	200 with 10 sites
<b>Follow-Up Schedule</b>	Subject enrollment will consist of a Pre-operative, Operative, 6 months, 1 yr., 2 yr., 5yr., 7 yr., 10 yr., and an unscheduled visit as needed.
<b>Primary Objective</b>	Evaluate the long-term survivorship of the INFINITY™ implant over 10 years
<b>Secondary Objective(s)</b>	<p>Secondary objectives assessed will be to:</p> <ul style="list-style-type: none"> <li>• Identify and assess the implant for component loosening and/or subsidence, any osteolysis and/or cyst formation through radiographic evaluation early and throughout the lifetime of the implant.</li> <li>• Compare the improvements in self-reported physical, mental, and social health measures from pre-op through 10 years post operatively; assessed by PROMIS® Global Health.</li> <li>• Compare pain and functional improvement in the Ankle Osteoarthritis Score (AOS), which is a visual analogue scale specifically designed as a modification of the Foot Function Index.</li> <li>• Compare the improvement in patient/physician reported function scores from pre-op through 10 years post-operatively, assessed by the FAOS questionnaire.</li> <li>• Compare satisfaction of total ankle replacement post operatively utilizing a four point scale</li> <li>• Identify and report the safety of the implant in terms of complications and adverse events.</li> </ul>
<b>Inclusion Criteria</b>	<p>Subjects to be included in the study must meet all of the following criteria:</p> <ul style="list-style-type: none"> <li>• Be 21 years of age or older at the time of surgery;</li> <li>• Diagnosed with unilateral and/or bilateral ankle joint disease;</li> <li>• Diagnosed with ankle joint damage from rheumatoid arthritis, post-traumatic, or degenerative arthritis;</li> <li>• Willing and able to consent to participate (written, informed consent);</li> <li>• Willing and able to attend the requested follow-up visits;</li> <li>• A clinical decision has been made to use INFINITY™ Total Ankle System replacement prior to enrollment in the research.</li> </ul>
<b>Exclusion Criteria</b>	<p>Subjects will be excluded from the study if they meet any of the following criteria:</p> <ul style="list-style-type: none"> <li>• Subjects with an ankle condition, as determined by the investigator, to be an inappropriate candidate for a total ankle replacement;</li> <li>• Subjects requiring revision total ankle replacement of the ankle being considered for study</li> </ul>

**SCHEDULE of EVENTS**

<b>Procedures</b>	<b>Pre-op</b>	<b>Op.</b>	<b>6 mo +/-30 days</b>	<b>1 yr +/-60 days</b>	<b>2 yr +/-60 days</b>	<b>5 yr +/-60 days</b>	<b>7 yr +/-60 days</b>	<b>10 yr +/-60 days</b>	<b>Study Close</b>
Informed Consent	X								
Inclusion/Exclusion Criteria	X								
Medical History/Demographics	X								
Operative (Surgical) procedure/device		X							
PROMIS Global Health	X		X	X	X	X	X	X	
Ankle Osteoarthritis Score (AOS)	X		X	X	X	X	X	X	
FAOS Questionnaire	X		X	X	X	X	X	X	
Total Ankle Replacement Satisfaction			X	X	X	X	X	X	
Radiographic Assessment (Investigator requirement)	X		X	X	X	X	X	X	
Adverse Event Assessment			X	X	X	X	X	X	
End of Study									X
Surgical Intervention <sup>1</sup>									
*Sponsor-approved Unscheduled Visit <sup>2</sup>									

<sup>1</sup>&<sup>2</sup> These are not scheduled time point events but will be observed for throughout study participation.

## INTRODUCTION

Wright Medical introduced the INFINITY™, total ankle system, for use in total ankle arthroplasty replacement (TAR) in the United States in 2013 and in Canada and Europe in 2014. The INFINITY™ Total Ankle System is a fixed-bearing, bone-sparing total ankle prosthesis that restores mobility to a failing ankle joint. It encompasses three components (i.e., tibial tray, tibial insert, and talar dome).

The INFINITY™ Total Ankle System is indicated in patients with ankle joints damaged by severe rheumatoid, post-traumatic, or degenerative arthritis, as well as for patients with a failed previous ankle surgery. Its intended use is to give patients limited mobility by reducing pain, restoring alignment and replacing the flexion and extension in the ankle joint.

The technological features of the INFINITY™ Total Ankle System are similar to the predicate devices (INBONE® Total Ankle System, DePuy Agility™, INBONE® II Total Ankle System), which have all been cleared through the 510K process with the FDA, with regard to design and materials. The goal of the design was to limit the amount of bone resection and soft tissue dissection required for ankle arthroplasty; hence the overall profile of the INFINITY™ Total Ankle System was significantly reduced along with the incision length required to perform the surgical procedure.

Currently, there has been little data published characterizing the use of the INFINITY™ Total Ankle System. This study's data collection will begin early in the utilization and implantation of the product and the data will allow for the filling of this gap in knowledge, support the long-term data collection, as well as the product's use and performance.

## STUDY OVERVIEW

### *Study Rationale*

The primary outcome measure of this post-market clinical observational study is to collect data relating to the INFINITY™ Total Ankle System survivorship at 10 years. The secondary outcome measures are to characterize the improvements after implantation over a 10 year period using patient reported outcome measures related to quality of life, pain and functional improvements, safety of the implants, as well as radiographic assessments (X-Rays)

The outcome measures collected in this study will be analyzed and reported as required for local, regional, and country requirements (i.e., regulatory authorities and notified bodies).

### *Part Numbers and Brief Descriptions of Configurations*

All configurations and sizes listed in the table below can be included in the study. These products are manufactured according to ICH GCP in accordance with applicable Good Manufacturing Practice (GMP) and with the ISO 14155:2011: through relevant manufacturing and related validation processes.

Part No.	Description	Part No.	Description
<b>INFINITY™ Poly Insert</b>		<b>INFINITY™ Tibial Component</b>	
33651106	POLY INSERT, SZ1/1+ 6MM	33650001	Tibial tray SZ1 STD
33651108	POLY INSERT, SZ1/1+ 8MM	33650002	Tibial tray SZ2 STD
33651110	POLY INSERT, SZ1/1+ 10MM	33650003	Tibial tray SZ3 STD
33651112	POLY INSERT, SZ1/1+ 12MM	33650004	Tibial tray SZ4 STD
33652206	POLY INSERT, SZ2 6MM	33650005	Tibial tray SZ5 STD
33652208	POLY INSERT, SZ2 8MM	33650013	Tibial tray SZ3 Long
33652210	POLY INSERT, SZ2 10MM	33650014	Tibial tray SZ4 Long
33652212	POLY INSERT, SZ2 12MM	33650015	Tibial tray SZ5 Long
33653206	POLY INSERT, SZ2 +6MM	<b>INFINITY™ Talar Component</b>	
33653208	POLY INSERT, SZ2 +8MM	33630021	Talar Dome SZ 1
33653210	POLY INSERT, SZ2 +10MM	33630022	Talar Dome SZ 2
33653212	POLY INSERT, SZ2 +12MM	33630023	Talar Dome SZ 3
33653306	POLY INSERT, SZ3 6MM	33630024	Talar Dome SZ 4
33653308	POLY INSERT, SZ3 8MM	33630025	Talar Dome SZ 5
33653310	POLY INSERT, SZ3 10MM	<b>INBONE® II Talar Component</b>	
33653312	POLY INSERT, SZ3 12MM	220220901	Talar Dome SZ 1 SULCUS
33654307	POLY INSERT, SZ3 + 7MM	220220902	Talar Dome SZ 2 SULCUS
33654309	POLY INSERT, SZ3 + 9MM	220220903	Talar Dome SZ 3 SULCUS
33654311	POLY INSERT, SZ3 11MM	220220904	Talar Dome SZ 4 SULCUS
33654313	POLY INSERT, SZ3 13MM	220220905	Talar Dome SZ 5 SULCUS
33654406	POLY INSERT, SZ4 6MM	<b>INBONE® II Talar Stem</b>	
33654408	POLY INSERT, SZ4 8MM	200347901	TALAR STEM 10MM
33654410	POLY INSERT, SZ4 10MM	200347902	TALAR STEM 14MM
33654412	POLY INSERT, SZ4 12MM		
33655407	POLY INSERT, SZ4 +7MM		
33655409	POLY INSERT, SZ4 +9MM		
33655411	POLY INSERT, SZ4 +11MM		
33655413	POLY INSERT, SZ4 +13MM		
33655506	POLY INSERT, SZ5 6MM		
33655508	POLY INSERT, SZ5 8MM		
33655510	POLY INSERT, SZ5 10MM		
33655512	POLY INSERT, SZ5 12MM		

### ***Indications for Use (IFU)***

Indications for use in patients with ankle joints damaged by:

- Severe rheumatoid arthritis;
- Post-traumatic, or;



- Degenerative arthritis;
- Additionally, for patients with a failed previous ankle surgery

### ***Risks and Benefits***

#### ***Benefits***

The clinical benefit to the INFINITY™ Total Ankle System is to give a patient improvement in mobility by reducing pain, restoring alignment and replacing the flexion and extension in the ankle joint.

#### ***Risks***

There are no additional risks anticipated, specific to participating in this study. The study is not examining any experimental procedures and participation in the study is not predicted to affect the medical treatment received by enrolled subjects. The INFINITY™ Total Ankle does not pose additional risks compared to other standard total ankle systems when used for the same clinical application. The risks of ankle replacement include intra-operative complications such as peri-prosthetic fracture, neurovascular damage and tendon injury. Early post-operative problems include infection, wound healing problems, deep vein thrombosis, and peri-prosthetic fracture. Late complications include infection, peri-prosthetic fracture, loosening, implant failure, ongoing pain. These risks are comparable to those in alternative implants and alternative surgical procedures.

## **STUDY DESIGN**

The selected design is a multi-center, non-randomized, prospective study of 200 subjects in the US with ten investigational sites and a potential for more as needed to meet the enrollment requirements. The study subjects included are those with ankle joints damaged by severe rheumatoid arthritis, post-traumatic disease, and degenerative arthritis and implanted with the INFINITY™ Total Ankle System.

### ***Primary and Secondary Endpoints***

The primary endpoint is a survivorship rate at 10 years as defined with a Kaplan Meier survivorship analysis. Secondary endpoints identify, assess and compare functional improvements or deviations collected through investigator observation and patient self-reporting, and include:

- Identification and assessment of the implant through radiographic assessment for component loosening and/or subsidence, any osteolysis and/or cyst formation early and throughout the lifetime of the implant.

- Comparison of improvements in self-reported physical, mental, and social health measures from pre-op through 10 years post operatively; assessed by PROMIS®.
- Comparison of pain and functional improvement from pre-op through 10 years in the AOS which is a visual analogue scale specifically designed as a modification of the Foot function Index.
- Comparison of the improvements in patient/physician reported function scores from pre-op through 10 years post-operatively, assessed by FAOS scores.
- Compare satisfaction of total ankle replacement post operatively utilizing a four point scale
- Identification and reporting on the safety of the implant in terms of complications and adverse events.

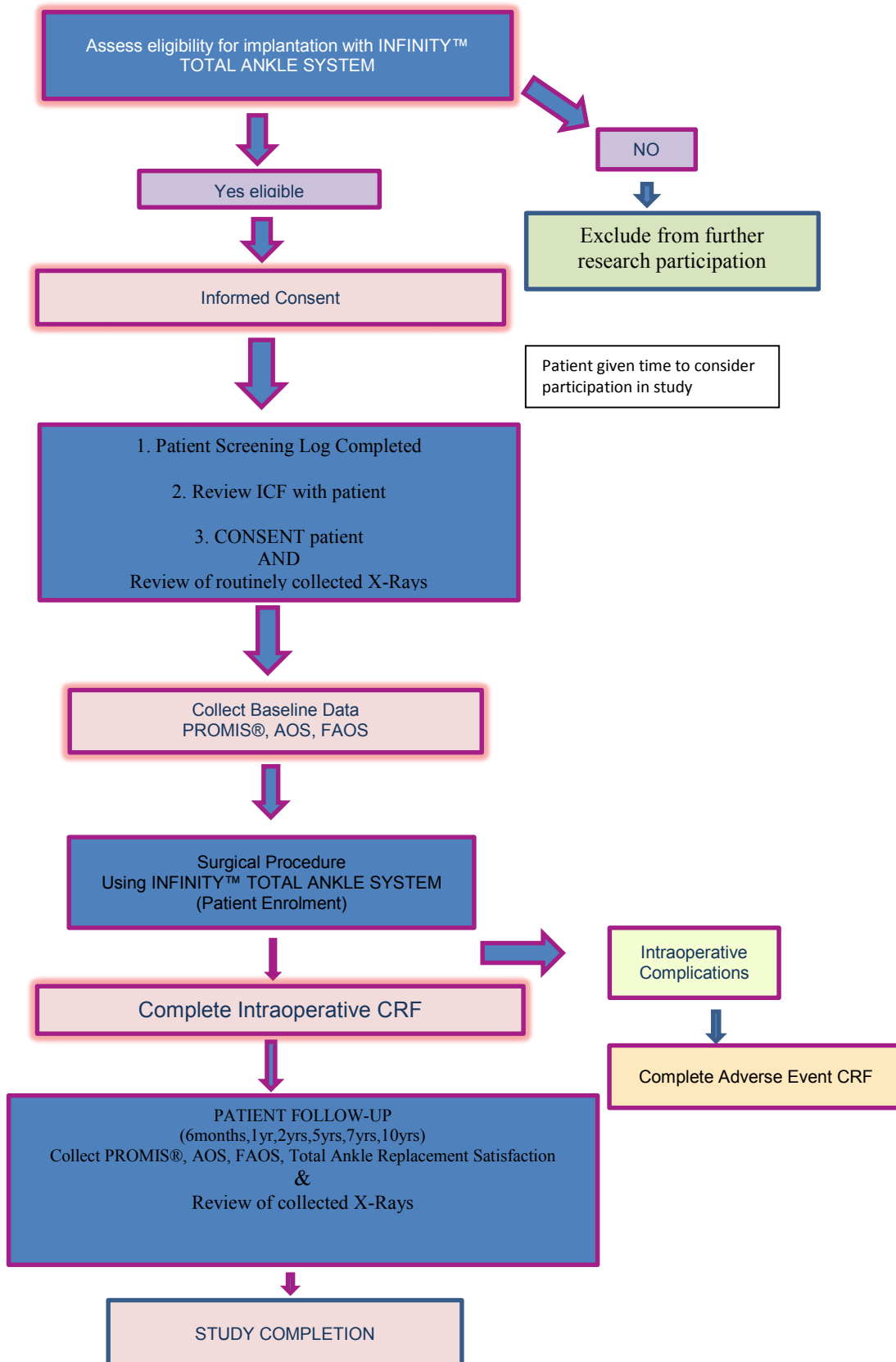
#### ***Planned visits and Follow-Up Time Points***

Subjects will be seen prospectively at the following intervals Pre-Op, Operative, 6 months, 1, 2, 5, 7, and 10 years.

If there are special circumstances where the subjects require a visit outside the windows of the established visits, the investigator may seek approval from Wright Medical for an acceptance of an “unscheduled visit” and it will be determined if the data will be included and analyzed.

### **SITE/SUBJECT SELECTION**

Clinical Research Sites will be identified to participate in the study based on current experience, and training in the use of the INFINITY™ Total Ankle System and according to ICH GCP guidelines and ISO 14155: 2011 which states; qualified by education, training and experience to perform his or her respective task(s). It is the expectation the surgeon will adhere to and follow the INFINITY™ Surgical Technique and have knowledge of the contraindications as provided in the Instructions for Use (IFU). (See Appendix A).

*Study Design Summary*

### ***Informed Consent***

Prior to any conducting any protocol required data collection, including evaluations and questionnaires, written informed consent must be obtained from the subject in compliance with 21 CFR Part 50.

Subjects will be recruited based on interest in participating in the study. All subjects will be consented by an appropriately trained clinician or research nurse using the IRB/EC/REC approved consent form in order to participate in the study and prior to any data collection, or any study procedure. The study clinician or research nurse will assess whether the patient can give informed consent or not during the consent process. The potential participant must be allowed ample time to review the informed consent and should be allowed to take the time to read, review, ask questions, and receive answers as well as being fully informed of all aspects of the study before a decision is made to participate. The source documentation will include a statement of the consent process and include details of the person taking consent for study participation.

### ***Screening***

Subjects with interest in participating in the study, after signing the informed consent document, will then be invited to participate if they meet the Inclusion Criteria.

### ***Point of Enrollment***

Subjects will be considered enrolled in the study when they have:

- Been informed of all aspects of the study and have signed Informed Consent document
- Acknowledged the appropriate patient data release information (included in the Informed Consent document)
- Satisfied the Inclusion/Exclusion Criteria
- Implanted with the Device

Investigators should document subject enrollment by completing the screening and enrollment logs located within the trial master file. The Source documentation should clearly state that all inclusion and exclusion criteria have been met and the patient data release and informed consent documents have been signed and appropriately dated prior to any study related activity,

The investigative sites will be assigned three digit a site code \*\*\*, and at enrollment the subject will be assigned a sequential subject identification number corresponding to the order the subject was enrolled (i.e. the first subject enrolled at each site will be site number \*\*\* followed by subject identifier 001). The assigned codes will be used to identify the subject on all case report forms. All investigative sites will be provided protocol training of the during the site initiation visits. Investigative sites will be provided paper case report forms/booklets, which may be used as source documentation, these must signed by the individual completing the form; i.e., coordinator, patient, or investigator.

***Study Duration, Subject Participation and Estimated Enrollment Period***

The total study duration from , first patient, first visit, (FPFV) to last patient, last visit (LPLV) is expected to be 12 years, with a recruitment period of 24 months The investigator/investigative site must make every reasonable attempt to contact the patients to complete all scheduled post-operative visits within the visit window. In instances where the individual cannot be reached, the investigator/investigative site will document at least two attempts to contact the patient via phone/mail and one certified letter for each time point. Due to the length of this study and the risk of lost to follow-up potential, if a subject has an inability to and, for some unforeseen reason cannot be seen on the hospital site, patient reported outcome measure case report forms may be completed remotely by post or telephone and returned to the investigative site/investigator for review and submission. If this process is applied it must documented and reported to Wright accordingly.

***Subject Withdrawal or Discontinuation***

Subjects maintain the right to discontinue their participation in the study at any point without penalty or loss of benefit to which the subject is otherwise entitled per ICH E6 4.8.10(m) guidelines. Although, a subject is not obliged to give his or her reason(s) for withdrawing prematurely from this study, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights per ICH E6 4.3.4 guidelines.

***Device Failure***

Subjects will be considered a treatment failure, and will be withdrawn from the study if any sections of the device (tibial or talar metal components) have been removed at any time during their participation. This should be reported onto the adverse event form. In addition, any surgical intervention during study participation that relates to their total ankle replacement will be reported on the surgical intervention case report form.

***Procedures and Case Report Forms***

Subject medical history and demographic information will be collected and recorded onto the demographic case report form. The following information will be collected on these forms:

- Date of birth
- Gender
- Height
- Weight
- BMI calculation
- Smoking status
- Status of other joints that affect ambulation ( i.e., knee replacement, contralateral arthritis and/or ankle replacement)
- Concomitant health conditions (diabetes and other medical conditions, etc.)

***Operative Procedure Information***

The information related to the subject's operation will be collected and recorded according to the Operative Information Case Report Forms. The following operative information related to the primary TAR procedure will be documented on these forms:

- Primary diagnosis
- Any previous surgery to index joint
- Date of operation
- Site location

- Surgical approach
  - Instrumentation type (standard) or (additional approved INFINITY™ instrumentation)
  - List concomitant operative procedures such as tendon/deltoid lengthening or other reconstructive process required to make final implantation correct
- Cement use
- Intraoperative complications (to be collected on the Adverse Event Case Report Form)
- Product description and eight-digit product code for all components implanted

### ***Patient Reported Outcome Measures (PROMS)***

***The standard care pathway for patients undergoing Total Ankle Replacement includes the collection of Patient Reported Outcome Measures (PROMS), in some institutions. The study aims to use this data, wherever possible, to fulfill the secondary outcome measures of the study and avoid duplication of data collection. As there is some variance nationally regarding the questionnaires which are used for PROMS data collection, participants may be required to supplement one or more of the following questionnaires for the purposes of the research study:***

*PROMIS® (Patient-Reported Outcomes Measurement Information System)* is a set of person-centered measures that evaluates and monitors physical, mental, and social health in adults and children. It can be used with the general population and with individuals living with chronic conditions.

- PROMIS Scale v1.2 - Global Health

*The Foot and Ankle Outcome Score (FAOS)* is a self-report measure that evaluates symptoms and functional limitations in individuals with generalized foot and ankle disorders. Items for the Foot and Ankle Outcome Score were adapted from the Knee Injury and Osteoarthritis Outcome Score. The FAOS is composed of the following 5 subscales: pain (9 items), other symptoms (7 items), activities of daily living (7 items), sports and recreational activities (5 items), and foot and ankle-related quality of life (4 items).

*Ankle Osteoarthritis Score (AOS)* is a reliable, validated, visual analog based, disease specific self-administered instrument designed specifically to measure disability and pain from ankle osteoarthritis. Both Pain and Disability components are used to calculate the total score. The score is from zero to one hundred with a lower score indicating more normal function. The minimally important difference for the AOS score is not known.

*Total Ankle Replacement Satisfaction*, this study will be evaluating the patient's satisfaction with their total ankle replacement post operatively (6months,1yr,2yrs,5yrs,7yrs,10yrs) utilizing a four point scale.

### ***Surgeon-completed Radiographic Report***

This report includes usual standard of care pre-operative radiographs will include a standing AP and lateral film of the ankle. Arthritis can be assessed by CT if available but, not required for this study.

Coronal plane deformity should be measured in degrees as the angle between a line perpendicular to the anatomical axis of the tibia and a line drawn along the top of the talar dome see (see figure) and recorded as either varus or valgus.



The Canadian Orthopaedic Foot and Ankle Society (COFAS) end-stage arthritis classification should be identified and recorded as:

Type 1: Isolated ankle arthritis

Type 2: Ankle arthritis with intra-articular varus or valgus deformity or a tight heel cord, or both

- intra-articular ankle varus or valgus alignment\* was defined as the angle of the proximal talar surface (talar tilt) to the lateral border of
- the tibia in the distal diaphysis and metaphyseal region more than 10 degrees on the AP weightbearing ankle views

Type 3: Ankle arthritis with hindfoot deformity, tibial malunion, midfoot abductus or adductus, supinated midfoot, plantar flexed first ray, etc.

- hindfoot deformity defined as the angle between the lateral border of the calcaneus and the long axis of the tibia on the AP view of the ankle (varus more than 5 degrees, valgus more than 10 degrees)
- Tibial deformity defined as an angulation between the lateral border of the tibia more than 10 degrees on the AP view of the ankle\*\*

Type 4: Types 1, 2, and 3 plus subtalar, calcaneocuboid, or talonavicular arthritis\*\*\*

The post-operative radiographic evaluations will be to assess, record, and report migration, loosening, subsidence of the device, any osteolysis and cyst formation.

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\* Greater than 10 degrees (defined as the angle between a line perpendicular to the anatomical axis of the tibia and a line drawn along the top of the talar dome see (see figure) and recorded as either varus or valgus)

\*\* If the patient has required staged surgical correction of deformity as part of the management of ankle arthritis (within 18 months of TAR), this should be considered a type 3. However, if the patient has undergone historic corrective surgery then the current foot position should be used for the purpose of COFAS grading (ie if fully corrected then can be Grade 1).

\*\*\* this would include patients with prior arthrodesis of the subtalar, calcaneocuboid, or talonavicular joints

## STATISTICAL CONSIDERATION

### *Sample Size*

The total sample size is 200 subjects. The sample size was not calculated using statistical methods. A non-parametric statistical analysis for survivorship using the Kaplan-Meier will be applied to determine the implant survivorship.

Mechanical survivorship for total hip and knee replacement is currently thought to be approximately 10 years. This benchmark for long-term data collection is not only relevant to the safety and survivorship of the implant but, also to provide assurances that for the introduction of new implants, a data collection plan is in place for ongoing evaluations and reporting.

The information gained from this data collection will be analyzed at times based on potential publication periods around 2, 5, and 7 years with a final analysis after all subjects have completed all follow-up requirements at the 10 year final visit. In addition, at time points determined by the investigators and/or Wright Medical will be evaluated as needed or required for additional analysis of data for reporting and/or publication purposes will be done throughout the study.

### *Demographics*

Descriptive statistics will be applied for the demographic data of all subjects. Pre to post-operative comparisons will be made for all outcome measures at the specific data collection time points. Summary statistics for continuous variables may include subject count, mean, standard deviation, minimum and maximum values.

## ADVERSE EVENTS

*Unanticipated Adverse Device Effect (UADE),  
Serious Adverse Events (SAE's) & ADVERSE EVENTS (AE's)*

### *Overview*

Procedural and device related events will be described and collected on the AE form. It is the responsibility of the operating surgeon/s to be aware and note the adverse effects from the package insert/instructions for use by the manufacturer/sponsor. (See appendix A) The number of subjects experiencing each adverse event percentage or proportion of the total number of subjects experiencing each adverse event will also be reported. All adverse events shall be reported in an interim and/or final report of the clinical investigation. All device deficiencies related to the identity, quality, durability, reliability, safety or performance of the investigational medical device shall be documented throughout the clinical investigation and appropriately managed by the sponsor.

Potential intraoperative and early postoperative complications, related to all total ankle replacements may include:

- pain;
- sudden drop in blood pressure intra-operatively due to the use of bone cement;
- damage to blood vessels;



- temporary or permanent nerve damage resulting in pain or numbness of the affected limb;
- cardiovascular disorders including venous thrombosis, pulmonary embolism, or myocardial infarction.
- hematoma;
- delayed wound healing; and
- deep wound infection (early or late) which may necessitate removal of the prosthesis.
- rarely an arthrodesis of the involved joint or amputation of the limb may be required.

Potential, late postoperative complications can include:

- pain;
- bone fracture by trauma or excessive loading, particularly in the presence of poor bone stock;
- peri-articular calcification or ossification, with or without impediment to joint mobility; and
- inadequate range of motion due to improper selection or positioning of components or peri-articular calcification.

### ***Adverse Event Data Collection and Reporting***

The following definitions from 21 CFR.

#### ***Adverse Event (AE)***

Adverse event means any untoward medical occurrence associated with the use of an intervention in humans, whether or not considered intervention-related

#### ***Serious Adverse Event (SAE)***

An adverse event (AE) or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- death, or
- a life-threatening adverse event, or
- inpatient hospitalization or prolongation of existing hospitalization, or
- a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

#### ***Adverse Event Status Updates (AE)***

The Investigator will follow up subjects who experience an AE until it is either resolved, determined to be chronic, stable, or, until the subject's participation in the study ends.

Prior to completion of the study, the Investigator will complete the Adverse Event Status Update Case Report Form to document any AE's previously reported as ongoing.

## ***Recording and Reporting Adverse Events – Investigator & Sponsor Responsibilities***

### *Recording and Reporting Adverse Events - Investigator Responsibilities*

The Investigator will:

- Record protocol required AE's together with an assessment as recorded in the Adverse Event Case Report Forms;
- Supply Wright Medical, upon their request, with any additional information related to the safety reporting of a particular AE

### *Recording and Reporting Adverse Events - Wright Medical Responsibilities*

Wright Medical is responsible for the classification of AEs and ongoing safety evaluation of the study and will:

- review the Investigator's assessment of all AEs; determine and document, in writing, the seriousness of the adverse event and relationship of the adverse event to the implanted components.

In case of disagreement between Wright Medical and the Investigator, Wright Medical shall:

- communicate both opinions to concerned parties; and
- as required, ensure that the IRB/EC/REC and regulatory authorities are informed or significant new information involving the product during the study.

### *Recording and Reporting Serious Adverse Events (SAE's) – (Immediately Reportable) Investigator Responsibilities*

- The investigator must report the following events to the Sponsor within 24 hours after learning of the event, regardless of relationship to study, using the appropriate SAE reporting form and guidelines;
- The investigator must report new significant follow-up information for these events to the Sponsor within 24 hours after becoming aware of the information. New significant information includes the following:
  - New signs or symptoms or a change in the diagnosis.
  - Significant new diagnostic test results.
  - Change in causality based on new information.
  - Change in the event/s outcome, including recovery.
  - Additional narrative information on the clinical course of the event.

### *Recording and Reporting Serious Adverse Events (SAE's) – Wright Medical Sponsor Responsibilities*

- SAEs must be summarized on the annual report to the IRB/EC/REC

### *Recording and Reporting Unanticipated Adverse Device Effect (UADE)– Wright Medical Sponsor Responsibilities*

Definition - An adverse reaction that is both unexpected (not consistent with the applicable product information) and also meets the definition of a Serious Adverse Event/Reaction

- UADEs must be reported to the IRB/EC/REC in accordance with GCP guidelines i.e. 7 or 15 days

## ***DATA MANAGEMENT***

### ***Overview***

All information will be collected according to the protocol and defined case report forms. Investigator subject records (e.g. medical records, imaging reports, surgical notes or, paper case report form booklets) will be considered source documents for the study. This information will be entered by the site through a website provided by Wright Medical. Data will be received by Wright Medical through the electronic data capture system. The Investigator must allow Wright Medical or its representative's access to the subject files. This access includes inspection of records.

In order to facilitate potential site monitoring visits, the investigator is required to keep records, including the identity of all participating subjects, all original signed Informed Consent Documents, and source documents. These records must be retained by the Investigating site according to local regulations as specified in the Clinical Trial Agreement.

If the Investigator relocates, retires, or for any reason withdraws from the study, Wright Medical should be notified ahead of time. The study records must then be transferred to an acceptable designee (another investigator, institution, or Wright Medical). The investigator must obtain Wright Medical's written permission before disposing of any records.

### ***Participant Confidentiality***

The study team will ensure that the participants' anonymity is maintained. The participants will be identified only by study number on the electronic CRF. All documents will be stored securely and only accessible by study staff and authorized personnel. To ensure confidentiality, none of the data stored or transferred electronically will contain personal identifiers.

### ***Monitoring Plan***

There is a need for on-site monitoring before, during, and after the clinical study. The sponsor may determine that remote monitoring (without visiting the site), in conjunction with procedures such as investigator's documented training, meetings, and extensive written guidance or telephone communication, can assure appropriate conduct of the clinical study. With the study data being provided to Wright via the remote electronic data capture system, there is an opportunity to review data in a real time manner at Wright Medical and not only reviewed during an on-site visit. The study will be monitored by Wright Medical or its authorized representatives in accordance with the internal procedures of Wright Medical. The frequency of the visits will be determined by Wright and scheduled early on with at least a minimum of each quarter based on enrollment and the number of active follow-up visits at each site. This may vary based on the enrollment and data collected at the sites, any compliance concerns and need for additional training and oversight.

Prior to study initiation, each clinical study site will be inspected by Wright Medical or its authorized representative. Additionally, each site will have an initiation visit to ensure Investigator(s) and study personnel:

- have the appropriate knowledge, experience, and equipment necessary to comply with the study requirements
- fully understand all aspects of the study including the study protocol and data collection methods
- Fully understand the procedures related to subject selection

Upon study commencement, regular monitoring visits will be conducted to ensure:

- ongoing compliance with the study protocol;
- ongoing compliance with any conditions of approval of the reviewing IRB/EC/REC;
- maintenance of complete study and regulatory records
- continued acceptability of the site's facilities

Source documents and Investigator site files will be reviewed during the monitoring visits, including, but is not limited to:

- reviewing case report forms for accuracy and completeness;
- verifying timely and accurate data collection (in comparison with the source documentation);
- reviewing and resolving missing or inconsistent study data;
- verifying the investigational site maintains all required source documents, supporting medical records, and signed Informed Consent Documents; and
- verifying the investigational site maintains documentation and reports for any AEs

Monitors will evaluate and summarize the results of each visit in a written report that identifies any repeated data problems and providing specific recommendations for the resolution of noted deficiencies.

### ***Amendments to Study Protocol***

Amendments cannot be made to the study protocol without the written consent of Wright Medical. Additionally, amendments to the study protocol must be approved by the IRB/EC/REC prior to their implementation.

### ***Deviations from Study Protocol***

Investigators should not deviate from the study protocol except to deliver emergency care or to eliminate an immediate hazard to the subject. Deviations should be reported by completing the Protocol Deviation Case Report Form. Investigators must report all deviations from the study protocol to Wright Medical or its designated representatives. Additionally, any deviations found during monitoring visits must also be reported to Wright Medical or its designated representatives. All deviations with the potential to affect subject safety, rights, or well-being will also be reported to the IRB/EC/REC as soon as possible; based on the IRB/EC/REC requirements within the jurisdiction with each site.

## **STUDY ETHICS**

### ***Institutional Review Board/Ethical Review Committee***

It is the responsibility of the principal investigator at each participating site to obtain prospective approval of the study protocol, protocol amendments, patient information sheets, Informed Consent documents, and any other

relevant documents, if applicable, from the IRB/EC/REC. All correspondence with the IRB/EC/REC should be retained in the Investigator Master site File. Copies of IRB/EC/REC approvals must be forwarded to Wright Medical or its designated representative prior to enrolling subjects. The Investigator must immediately report to Wright Medical or its designated representative if the IRB/EC/REC withdraws its approval of the study for any reason.

### ***Statements of Compliance***

This study will be conducted in accordance with 21 CFR Part 11, 50, 54, 56, and the ethical principles originating from the Declaration of Helsinki, GCPs, and in compliance with local regulatory requirements. This study will be registered with ClinicalTrials.gov.

### ***Financial Disclosures***

All Investigators must complete, sign and date the Financial Disclosure form prior to their participation in the clinical study. Each Investigator must notify Wright Medical or its designated representative if any relevant changes occur during the course of the study and for one year following the completion of the study. Copies of the Financial Disclosure form for each Investigator will be maintained in the sponsor's investigational files.

### ***Sponsor Discontinuation Criteria***

Wright Medical reserves the right to terminate a non-performing site. Reasons for considering early termination or suspension of an individual site may include, but are not limited to:

- Site non-compliance with study protocol or failure to comply with government or local regulations
- Failure to submit data in a timely manner
- Failure to comply with or act upon findings
- Failure to maintain pace to complete enrollment

Wright Medical reserves the right to discontinue the study at any time and will notify each investigator immediately at the time of such a decision. Formal documentation will be provided to the investigators to notify their IRB/EC/REC, research institutions. After such a decision, the Investigator must contact all participating subjects to notify them of this decision and its impact on their follow-up.

## **STUDY COMPLETION**

### ***Subject Enrollment Completion***

Individual subject enrollment will be considered complete once the subject has completed all of their clinical visits and outcome measurements required by the study protocol. The investigator should then complete the Study Completion Case Report Form.

### ***Study Closeout Activities***

The study will be considered complete once the last subject at the last active site has completed their clinical visits and all outcome measurements required by the study protocol. Additionally, the following activities must be completed at each site before the study is considered complete:

- All essential documents are complete and up to date
- The Investigator has completed and submitted all required case report forms

- Arrangements are made for archiving and record retention

All IRB's/EC/REC's have been notified of the conclusion of the study

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## **APPENDIX**

### ***Instructions for Use (IFU), INFINITY™ Surgical Technique***



*Case Report Forms*