LONG TERM FOLLOW-UP OF INTEGRA® CADENCE™ TOTAL ANKLE SYSTEM IN PRIMARY ANKLE JOINT REPLACEMENT

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INVESTIGATOR SIGNATURE

Protocol Title: Long Term Follow-up of Integra® Cadence™ Total Ankle System in Primary Ankle Joint Replacement

Protocol Number: T-CTAS-002

Date: Version 1 / 27-Feb-2017

Superseded Version: N/A

I have read and understood the contents of this protocol, and agree to conduct the study as outlined herein. I will conduct the study in compliance with the principles described in the Declaration of Helsinki (version 2008, Seoul), the International Standard ISO14155:2011, the Good Clinical Practice and all applicable regulations.

In addition, I will provide copies of this protocol and all pertinent information to the study personnel under my supervision and will discuss this material with them to ensure they are fully informed regarding the study.

_____
Investigational Site Name (Hospital/Practice)

_____ Date: _____
Site Principal Investigator Signature

_____
Printed Name of Site Principal Investigator

STUDY SYNOPSIS

PROTOCOL TITLE:	Long Term Follow-up of Integra® Cadence™ Total Ankle System in Primary Ankle Joint Replacement
PROTOCOL NO.:	T-CTAS-002
PROTOCOL VERSION:	Version 1
PROTOCOL DATE:	27-Feb-2017
SPONSOR:	Integra LifeSciences Corporation 311 Enterprise Drive Plainsboro, NJ 08536, USA European Representative: Integra LifeSciences Services 97 Allée Alexandre Borodine 69800 Saint Priest, FRANCE
SPONSOR CONTACT:	Marilyne Blanc Clinical Research Manager Tel: +33 437 475 937 E-mail: marilyne.blanc@integralife.com
DEVICE:	Integra® Cadence™ Total Ankle System
DEVICE INDICATION:	The Integra® Cadence™ Total Ankle System (CTAS) is indicated for use to treat: • Primary arthritis (e.g. degenerative disease) • Secondary arthritis (e.g. post-traumatic, avascular necrosis, if minimally 2/3 of the talus is preserved) • Systemic arthritis of the ankle (e.g. rheumatoid arthritis, hemochromatosis) The CTAS is also indicated for revision surgeries following failed total ankle replacement (TAR) and non-union/mal-union of ankle arthrodesis, provided sufficient bone stock is present.
OBJECTIVE:	**Primary Objective:** To evaluate 2-year implant survivorship in subjects who receive CTAS when used for primary ankle arthroplasty. Implant survivorship is defined as absence of device removal or revision of one or more of the implant component(s). **NOTE:** Revision does not involve other joint-involving procedures that are termed reoperations such as gutter debridement and peri-prosthetic joint-involving surgeries that are considered additional procedures (such as subtalar joint arthrodesis, ligamentous release or plication, Achilles tendon lengthening, etc.).

	Secondary Objective: To evaluate 5-year and 10-year survivorship and relative changes in pain, functionality, patient satisfaction, radiographic performance, and quality of life scores at all visits as compared to pre-operative scores including: • PROMIS Physical Function – Mobility Item Bank v1.2 (PROMIS) • Foot and Ankle Ability Measure questionnaire (FAAM) (ADL Subscale only) • Ankle Visual Analog Scale (VAS) pain assessment • Short Form-36 Version 2 Health Survey (SF-36v2) • Total range of motion (degrees plantarflexion and dorsiflexion).
DESIGN:	Non-randomized, prospective, multi-center, international, open-label, single arm post approval clinical study using survivorship as the reference performance goal.
ENROLLMENT:	Up to seven centers (in Europe and Canada) will enroll and implant 60 patients in total. Maximum enrollment per center is 15 implanted patients. All patients will receive the CTAS.
INCLUSION CRITERIA:	Subjects will be included if he/she: 1. Is > 18 years of age. 2. Is skeletally mature. 3. Qualifies for primary Total Ankle Replacement (TAR) per the surgeon and has a diagnosis of one of the following: primary arthritis (e.g. degenerative disease), secondary arthritis (e.g. post-traumatic, avascular necrosis, if minimally 2/3 of the talus is preserved), or systemic arthritis of the ankle (e.g. rheumatoid arthritis, hemochromatosis). 4. Is suitable for TAR with Cadence™ Total Ankle System per the study surgeon based on the product indication and having considered deformity, stability, bone quality, soft-tissue envelope, and neurovascular status. 5. Is willing and able to cooperate in the required post-operative therapy. 6. Is willing and able to complete scheduled follow-up visits, evaluations and questionnaires as described in the Informed Consent (or Information Letter and Data Transfer Authorization Form, as applicable). 7. Reads, understands and signs the Ethical Committee (EC) approved Informed Consent (or Information Letter and Data Transfer Authorization Form, as applicable).

EXCLUSION CRITERIA:	Subjects will be excluded from the study if he/she: 1. Is morbidly obese (defined by a Body Mass Index (BMI) > 40 or BMI of 35 – 40 with significant medical problems caused by or made worse by their weight). 2. Is an active nicotine user (smoking, chewing, smokeless tobacco, patch) and unwilling to cease nicotine use within 1 month prior to surgery, and 2 months post-surgery. 3. Has one of the following conditions, which could compromise the affected limb: ankle arthrodesis with malleolar exeresis, severe neurological (Charcot's Arthropathy) or vascular disease, loss of musculature or neuromuscular compromise. 4. Has an active local/systemic infection that may affect the prosthetic joint or has a recent history of infection. 5. Continues on long-term medication, which may compromise bone stock (e.g. undergoing immunosuppressive therapy, long-term steroids) and is unable to cease medication usage from 3 weeks prior to surgery to 3 weeks post-surgery. 6. Has a condition that may impair proper wound healing (e.g., poor soft tissue envelope). 7. Had previous ankle surgery and/or injury that has adversely affected the anklebone stock. 8. Has had or is scheduled to have contralateral TAR. 9. Is pregnant or plans to become pregnant during the follow up period. 10. Has a metabolic disorder or disease that may compromise bone quality (e.g. arthrogryposis etc.), physiological or anatomical anomalies, and/or malignancy/local bone tumors. 11. Has severe avascular necrosis of the talus/tibia. 12. Has inadequate neuromuscular status (e.g., prior paralysis, severe neuropathy). 13. Has a known sensitivity or allergic reaction to one or more of the implanted materials. 14. Is a poor candidate for general anesthesia. 15. Is a prisoner, mentally incompetent or unable to understand what participation in this study entails, a known alcohol or drug abuser, or anticipated to be non-compliant.
INTRAOPERATIVE ELIGIBILITY CRITERIA:	Subjects will be included if he/she: 1. Receives the CTAS

STUDY DURATION:	Clinical and radiographic evaluations will occur at the following visit intervals: • Baseline/Screening • Surgery • 6 weeks (+/- 2 weeks) • 3 months (+/- 2 weeks) • 6 months (+/- 1 month) • 1 year (+/- 2 months) • 2 years (+/- 2 months) • 5 years (+/- 5 months) • 10 years (+/- 5 months)
DATA COLLECTION:	**Patient Data:** • Basic demographic data (e.g. sex, age, height, weight, nicotine use, work status); clinical presentation; diagnosis; systemic and musculoskeletal comorbidities; concomitant medication(s) **Procedural Data:** • Type of surgery; identification of joint operated; type of instrumentation; component sizes of CTAS used; additional procedures required, duration of surgery, duration of hospital stay • Intra-operative fluoroscopy • Postoperative physical therapy (PT) per surgeon's standard of care • Protocol deviations (PDs) at all visits. • Subsequent surgical interventions **Clinical Data:** • PROMIS • FAAM (ADL Subscale only) • Ankle VAS pain assessment • SF-36v2 • Implant survivorship • Clinical assessments (i.e., weight, nicotine use, work status, PT status, weight bearing (WB) status, and immobilization type). **Radiographic Assessment:** Evaluation of standard WB anteroposterior (AP) and neutral lateral: • Device migration • Device subsidence

	• Device tilting • Device condition • Radiolucency (10 lateral zones/ 10 AP zones) • Osteolysis • Heterotopic ossification • Adverse bony changes • Sclerosis • Additional observations Evaluation of standard WB maximum plantarflexion and dorsiflexion: • Ankle range of motion (ROM) **Safety Evaluation:** • Device and procedure related adverse events (AEs) and serious adverse events (SAEs) related to device and/or procedure or considered by the position as related to the study condition or the lower limbs
DATA EVALUATION:	**Primary Endpoint:** • Rate of implant survivorship at 2 years defined as absence of device removal or revision. **Secondary Endpoints:** • Relative change at all scheduled visits in the clinical and functional outcome measures over pre-surgery baseline values (PROMIS, ROM, FAAM ADL subscale, VAS, SF-36v2). • Implant survivorship at 5 and 10 years defined as absence of device removal or revision. • Radiographic success is defined as absence of implant radiolucency, subsidence, tilting, migration defined as no evidence of radiolucency >4 mm in more than 3 zones and of subsidence or tilting >4 degrees, or migration > 4mm. **Safety:** • Rate of all device and/or procedure related AEs, SAEs related to device and/or procedure or considered by the position as related to the study condition or the lower limbs and all subsequent surgical interventions.
STATISTICAL ANALYSIS:	Continuous variables will be analyzed using parametric or non-parametric methods, as applicable based on the distribution of the variable. Discrete variables will be analyzed using Fisher's exact test or Cochran-Mantel-Haenszel (CMH) test. All statistical tests will be 2-sided with an alpha level of 0.05 unless otherwise specified.

ABBREVIATIONS AND GLOSSARY

Abbreviations

ADL	Activities for Daily Living	ITT	Intent-to-Treat
AE	Adverse Event	NSAID	Non-Steroid Anti-Inflammatory Drug
AP	Anteroposterior	PP	Per Protocol
ANOVA	Analysis of Variance	PROMIS	Patient Reported Outcomes Measurement Information System
BMI	Body Mass Index	PT	Physical Therapy
BSI	British Standards Institution	REP	Radiographic Evaluation Protocol
CFR	Code of Federal Regulations	ROM	Range of Motion
CMH	Cochran-Mantel-Haenszel test	SAE	Serious Adverse Event
CRF	Case Report Form	SAP	Statistical Analysis Plan
CTAS	Cadence Total Ankle System	SF-36v2	Short Form-36 Version 2 Health Survey
CV	Curriculum Vitae	SOP	Standard Operating Procedures
EC	Ethical Committee	STAR	Scandinavian Total Ankle Replacement
EDC	Electronic Data Capture	TAR	Total Ankle Replacement
FAAM	Foot and Ankle Ability Measure	VAS	Visual Analog Scale
GCP	Good Clinical Practice	WB	Weight Bearing
ICF	Informed Consent Form	X-Rays	Radiographs
ICH E6 GCP	International Conference of Harmonization E6 Guideline on Good Clinical Practice		

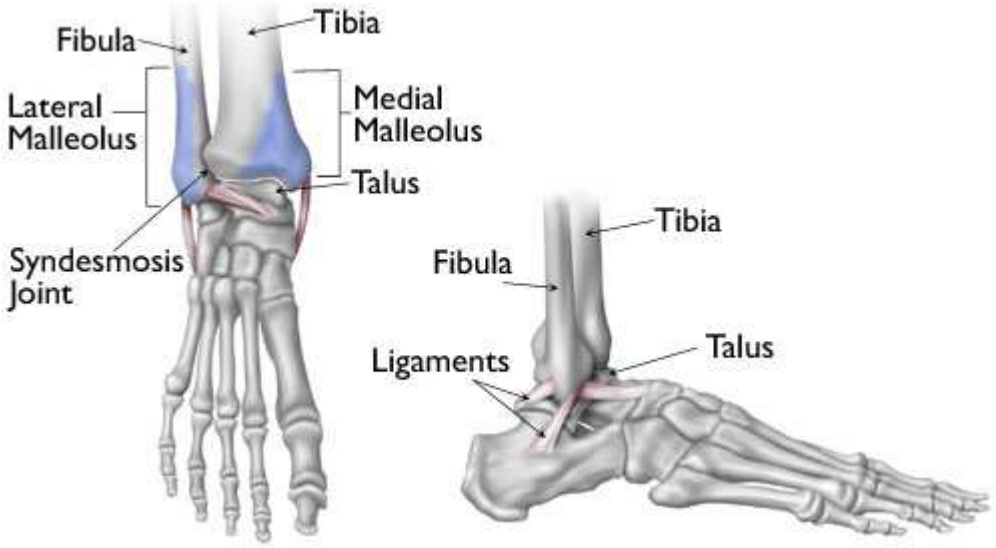
Glossary

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 (study) medical device. For users or other persons, this definition is restricted to events related to investigational (study) medical devices.
Adverse Device Effect	Any adverse event that based on appropriate medical judgment has a causal relationship with the device.
Avascular necrosis	A disease where there is cellular death of bone components due to interruption of the blood supply. Without blood, the bone tissue dies and the bone collapses. If avascular necrosis involves the bones of a joint, it often leads to destruction of the joint articular surfaces.
Complication	Any undesirable, unintended and direct result of an operation affecting the patient, which would not have occurred had the operation gone as well as could reasonably be hoped.
Dorsiflexion	Movement that flexes the foot in an upward direction
End-stage ankle osteoarthritis	The diagnosis of osteoarthritis has been confirmed based on radiological and clinical evidence (plain radiographs and unrelenting symptoms, respectively) and conservative management measures (such as painkillers and physiotherapy) have failed the previous 6 months.
Implant Survivorship	Implant survivorship is defined as absence of device removal or revision of one or more of the implant component(s). Revision does not involve other joint-involving procedures that are termed reoperations (such as gutter debridement and peri-prosthetic joint-involving surgeries that are considered additional procedures (such as subtalar joint arthrodesis, ligamentous release or plication, Achilles tendon lengthening, etc.).
Osteoarthritis	A clinical syndrome of joint pain accompanied by varying degrees of functional limitation and reduced quality of life. It is by far the most common form of arthritis and one of the leading causes of pain and disability worldwide.
Plantarflexion	Movement that flexes the foot in a downward direction.
Serious Adverse Device Effect	Any serious adverse events that based on appropriate medical judgment, are related to the device.
Serious Adverse Event	A serious adverse event (SAE) is any AE that: • results in death, • led to serious deterioration in the health of the subject, that either resulted in: 1. a life threatening illness or injury, 2. inpatient or prolongation of existing hospitalization,

	3. a permanent impairment of a body structure or a body function, 4. medical or surgical intervention to prevent a life-threatening illness or injury or permanent impairment to a body structure or a body function, • results in fetal distress, fetal death or congenital anomaly/birth defect. • is otherwise considered medically significant by the investigator.
Subsequent Surgical Intervention	Subsequent surgical interventions will be categorized according to the following definitions: • **Revision:** a procedure that modifies or removes part of the original implant configuration, (i.e. one or more of the component(s)). **NOTE:** Revision does not involve other joint-involving procedures that are termed reoperations (such as, gutter debridement and peri-prosthetic joint-involving surgeries that are considered additional procedures (such as subtalar joint arthrodesis, ligamentous release or plication, Achilles tendon lengthening, etc.). • **Removal:** a procedure where all of the original system configuration are removed with or without replacement. • **Re-operation:** any surgical procedure at the location of the index surgery site that does not remove, modify or add any component to the system. • **Supplemental fixation:** a procedure in which additional instrumentation not under study is implanted (e.g., supplemental placement of a rod/screw system or a plate/screw system). **NOTE:** Once a revision or removal occurs, no further study-related effectiveness endpoint assessments will be required as the results may invalidate the endpoints of the study or introduce extraneous factors into the results. All Subsequent Surgical Interventions are considered adverse events.
Unanticipated Adverse Device Effect	A serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the risk analysis report or protocol/clinical investigational plan or investigator brochure; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

1 INTRODUCTION

Total ankle replacement (TAR) is a procedure in which an injured ankle joint is replaced with a polyethylene and metal joint. Implant design has improved with a greater understanding of the complex biomechanics of the ankle joint. The ankle joint involves the articulation of the talus and the tibia, with the facets of the medial and lateral malleoli on the tibia parallel to the corresponding facets on the talus (Figure 1). The joint operates with a single degree of freedom and motion occurs in the sagittal, coronal, and transverse planes; the largest range of motion (ROM) occurs in the sagittal plane during dorsiflexion and plantar flexion, 13^0 to 33^0 and 23^0 to 56^0, respectively[1]. The ankle joint experiences loads of up to 5 times a person's body weight, most of which is transmitted over the superior portion of the talus[2].



Arthritic conditions in the ankle decrease the joint ROM, contributing to fewer steps per day, altering the normal gait, and affecting activities of daily living[2]. Ankle arthritis in its most severe state requires surgical intervention to support quality of life outcomes and pain reduction for patients[3]. Ankle fusion has been the traditional method of treating primary, secondary, and systemic arthritis in patients with loss of ankle function and increased pain refractory to conservative care (e.g., NSAIDS for pain and inflammation, limiting activity, wearing an ankle brace, shoe modifications, application of heat, and physical therapy (PT)).

[1] Bonasia DE, Dettoni F, Femino JE, Phisitkul P, Germano M, Amendola A. Total ankle replacement: why, when and how? Iowa Orthop J. 2010;30:119-30.
[2] Grunfeld R, Aydogan U, Juliano P. Ankle arthritis: review of diagnosis and operative management. Med Clin North Am. 2014 Mar;98(2):267-89.
[3] Terrell RD, Montgomery SR, Pannell WC, Sandlin MI, Inoue H, Wang JC, SooHoo NF. Comparison of practice patterns in total ankle replacement and ankle fusion in the United States. Foot Ankle Int. 2013 Nov;34(11):1486-92.

Early ankle replacement devices (first generation) were introduced in the 1970s and consisted of two components, a polyethylene tibial component and a metal talar component, and implants were available in both constrained and unconstrained models. These implants required cement for fixation and a large quantity of bone removal to position properly. Cementing techniques in the 1970s were not as advanced as today, and the large amount of bone resection contributed to high failure rates due to implant loosening[1]. In the 1980s, second generation TARs were introduced, including the Scandinavian Total Ankle Replacement (STAR) and the Agility Total Ankle System. Most of these TARs were semi-constrained and could be implanted cementless with less bone resection required than the first generation implants[1]. These later generation devices sought to improve implant survival by incorporating design changes, such as anatomic design, and biologic on-growth[4]. The most recent phase of implant design (third generation) were brought to market in the late 1990s, including the Salto, HINTEGRA, and Mobility, all unconstrained mobile-bearing systems[1]. A systematic review of intermediate and long-term outcomes found that results improved with the newer generation implants, with 82% of patients showing excellent or good results compared to 72% of patients undergoing ankle fusion[5].

Modern ankle prostheses consist of three components that include either a fixed or mobile polyethylene-bearing. Mobile-bearing implants work by providing two separate, fully conforming articular surfaces, one that is flat and one that is curved. Fixed-bearing ankle replacements have only one articulating, partially conforming interface. Commonalities among modern ankle replacement devices include porous-coating for bone ingrowth and material type. Most modern implants are composed of titanium alloy with cobalt chrome-polyethylene articulation[6].

Benefits of ankle arthroplasty over ankle arthrodesis include the preservation of motion, and anticipated improvement in pain and quality of life. Patients with degenerative changes in other joints may benefit from arthroplasty rather than arthrodesis since arthroplasty can support motion preservation, thereby limiting harmful loading on adjacent joints.

[4] Roukis TS, Prissel MA. Registry data trends of total ankle replacement use. J Foot Ankle Surg. 2013 Nov-Dec;52(6):728-35.

[5] Gougoulias NE, Khanna A, Maffulli N. History and evolution in total ankle arthroplasty. Br Med Bull. 2009;89:111-51.

[6] Cracchiolo A 3rd, Deorio JK. Design features of current total ankle replacements: implants and instrumentation. J Am Acad Orthop Surg. 2008 Sep;16(9):530-40.

2 DEVICE

2.1 Integra® Cadence™ Total Ankle System

The Integra® Cadence™ Total Ankle System (CTAS) is designed to treat ankle arthritis through replacement of the ankle joint with a prosthesis, thereby reducing pain, restoring alignment, and allowing for movement at the replaced joint. The prosthesis is composed of a tibial tray, a talar dome and an insert. Both the tibial tray and talar dome are secured to patient anatomy via bone cement; the insert is rigidly fixed to the tibial tray intra-operatively. When all three components are implanted, the insert acts as a bearing along the talar dome, enabling flexion and extension movement at the replaced joint. Each of the three components are available in a variety of sizes and design configurations intended for both primary surgery and revision surgery applications.

2.2 Indications for Use

The CTAS is designed to treat ankle arthritis through replacement of the ankle joint with a prosthesis, thereby reducing pain, restoring alignment, and allowing for movement at the replaced joint. The CTAS is indicated for use to treat:

- Systemic arthritis of the ankle (e.g. rheumatoid arthritis, hemochromatosis)
- Primary arthritis (e.g. degenerative disease)
- Secondary arthritis (e.g. post-traumatic, avascular necrosis, if minimally 2/3 of the talus is preserved).

The CTAS is also indicated for revision surgeries following failed TAR and non-union/mal-union of ankle arthrodesis, provided sufficient bone stock is present.

2.3 Regulatory Status

Integra® Cadence™ Total Ankle System (CTAS) is classified as a Class IIB Medical Devices in the European Union in accordance with Annex IX, according to Rule 8 in the Medical Device Directive 93/42/EEC. The product was CE marked on 21 March 2016.

3 CLINICAL STUDY OBJECTIVE

This study will evaluate the long term performance and safety data for the CTAS when used for primary arthroplasty in patients with primary arthritis (e.g. degenerative disease), secondary arthritis (e.g. post-traumatic, avascular necrosis, if minimally 2/3 of the talus is preserved), and systemic arthritis of the ankle (e.g. rheumatoid arthritis, hemochromatosis).

3.1 Primary Objective

To evaluate 2-year implant survivorship in subjects who receive the CTAS when used for primary ankle arthroplasty. Implant survivorship is defined as absence of device removal or revision of one or more of the implant component(s).

NOTE: Revision does not involve other joint-involving procedures that are termed reoperations (such as gutter debridement and peri-prosthetic joint-involving surgeries that are considered additional procedures (such as subtalar joint arthrodesis, ligamentous release or plication, Achilles tendon lengthening, etc.).

3.2 Secondary Objectives

To evaluate 5-year and 10-year survivorship, and relative changes in pain, functionality, patient satisfaction, radiographic performance, and quality of life scores at all visits as compared to pre-operative scores including:

- PROMIS Physical Function – Mobility Item Bank v1.2 (PROMIS)
- Foot and Ankle Ability Measure questionnaire (FAAM) (ADL Subscale only)
- Ankle Visual Analog Scale (VAS) pain assessment
- Short Form-36 Version 2 Health Survey (SF-36v2)
- Total ROM (degrees plantarflexion and dorsiflexion)

Imaging Objectives:

X-ray imaging will be used in this study to evaluate the radiographic performance of the device in support of a portion of the secondary endpoints of the study. Specifically, the following parameters will be evaluated, as further described in section 6.9:

Qualitative/Quantitative Evaluation

- Device migration
- Device subsidence
- Device tilting
- Device condition
- Radiolucency at 10 lateral and 10 AP zones
- Osteolysis
- Heterotopic ossification
- Adverse bony changes

- Sclerosis
- ROM

4 RISK/BENEFIT ANALYSIS

This study does not show any additional risk compared to the risks associated with a total ankle replacement surgery outside of this study, such as risks in the field of infection or resulting from anaesthesia. These risks relate to the surgical technique and are in no way related to the study. The study device is an legally marketed product, and the methodology of the study does not submit the patient to any additional procedures or exams outside the customary standard of care for total ankle replacement surgery and follow-up treatment.

Therefore, there is no additional risk for patients by being in the study. The study will collect data on the survivorship of a Total Ankle Prosthesis and the results will enable the medical community to assess the postoperative quality of life of future patients.

5 STUDY DESIGN

This is a post-market, prospective, non-randomized, multi-center, international, open-label clinical evaluation of the CTAS for use in primary ankle joint replacement. Data will be collected at specific time points and entered into case report forms (CRFs) based on the information contained in the patient medical records.

5.1 Study Endpoints

5.1.1 Primary Endpoint

Rate of survivorship of the CTAS as established by obtaining information on revision or implant removal over time. Survivorship success at 2 years is defined as absence of device removal or revision.

5.1.2 Secondary Efficacy Endpoints

Implant survivorship:

- Rate of the survivorship of the CTAS at the 5, and 10-year follow-up visit is defined as absence of device removal or revision.

Clinical Assessment:

- Relative change compared to pre-surgery (baseline) values for:
    - PROMIS
    - FAAM (ADL Subscale only)
    - VAS pain assessment
    - SF-36v2

Radiographic Assessment:

- Radiographic success is defined as absence of implant radiolucency, subsidence, tilting and/or migration defined as no evidence of radiolucency >4 mm in more than 3 zones and of subsidence or tilting >4 degrees, or migration > 4mm.

Safety Evaluation:

- Rate of all device and/or procedure related AEs, SAEs (related to device and/or procedure or considered by the position as related to the study condition or the lower limbs) and all subsequent surgical interventions.

5.2 Study Population

In order to participate in this investigation, study subjects will have to meet the criteria listed below including:

5.2.1 Inclusion Criteria

Subjects will be included if he/she:

1. Is > 18 years of age.
2. Is skeletally mature.
3. Qualifies for primary TAR per the surgeon and has a diagnosis of one of the following: primary arthritis (e.g. degenerative disease), secondary arthritis (e.g. post-traumatic, avascular necrosis, if minimally 2/3 of the talus is preserved), or systemic arthritis of the ankle (e.g. rheumatoid arthritis, hemochromatosis).
4. Is suitable for TAR with CTAS per the study surgeon based on the product indication and having considered deformity, stability, bone quality, soft- tissue envelope, and neurovascular status.
5. Is willing and able to cooperate in the required post-operative therapy.
6. Is willing and able to complete scheduled follow-up visits, evaluations, and questionnaires as described in the Informed Consent or Information Letter and Data Transfer Authorization Form, as applicable.
7. Reads, understands and signs the Ethical Committee approved Informed Consent or Information Letter and Data Transfer Authorization Form, as applicable.

5.2.2 Exclusion Criteria

Subjects will be excluded from the study if he/she:

1. Is Morbidly Obese (defined by BMI > 40 or BMI of 35 – 40 with significant medical problems caused by or made worse by their weight).
2. Is an active nicotine user (smoking, chewing, smokeless tobacco, patch) and unwilling to cease nicotine use within 1 month prior to surgery, and 2 months post-surgery.
3. Has one of the following conditions, which could compromise the affected limb: ankle arthrodesis with malleolar exeresis, severe neurological (Charcot's

Arthropathy) or vascular disease, loss of musculature or neuromuscular compromise.

4. Has an active local/systemic infection that may affect the prosthetic joint or has a recent history of infection.
5. Continues on long-term medication, which may compromise bone stock (e.g. undergoing immunosuppressive therapy, long-term steroids) and is unable to cease medication usage from 3 weeks prior to surgery to 3 weeks post-surgery.
6. Has a condition that may impair proper wound healing (e.g., poor soft tissue envelope).
7. Had previous ankle surgery and/or injury that has adversely affected the anklebone stock.
8. Has had or is scheduled to have contralateral TAR surgery.
9. Is pregnant or plans to become pregnant during the follow up period.
10. Has a metabolic disorder or disease that may compromise bone quality (e.g. arthrogryposis etc.), physiological or anatomical anomalies, and/or malignancy/local bone tumors.
11. Has severe avascular necrosis of the talus/tibia.
12. Has inadequate neuromuscular status (e.g., prior paralysis, severe neuropathy).
13. Has a known sensitivity or allergic reaction to one or more of the implanted materials.
14. Is a poor candidate for general anesthesia.
15. Is a prisoner, mentally incompetent or unable to understand what participation in this study entails, a known alcohol or drug abuser, or anticipated to be non-compliant.

5.2.3 Intraoperative Eligibility Criteria

Subjects will be included if he/she:

1. Receives the Cadence™ Total Ankle System

5.3 Patient Numbers and Study Involvement

Up to seven centers (in Europe and Canada) will enroll and implant 60 patients in total. Maximum enrollment per center is 15 implanted patients. All patients will receive the CTAS.

Investigators will have to enroll all the patients for whom all inclusion and exclusion criteria are satisfied consecutively.

The total study duration will be 12 years including:

- Period of patient enrollment estimated to last 2 years
- Period of follow-up for 10 years

6 STUDY PROCEDURES

6.1 Point of Enrollment

Consecutive patients will be evaluated for potential eligibility for entry into the study. Patients who potentially meet the study eligibility criteria based on their age and whether their medical condition appears to generally fit the characteristics specific to this study will be evaluated for study enrollment as follows:

- Patients who pass initial screening will be offered informed consent (or Information Letter and Data Transfer Authorization Form, as applicable).
- Patients who verbally agree to participate in the study will complete the informed consent process and be enrolled in the study by signing the informed consent form (or Information Letter and Data Transfer Authorization Form, as applicable). These subjects will then receive a unique subject identification number.
- Consented subjects will complete the study screening process to verify their eligibility and will be enrolled in the study once they fulfill the eligibility criteria and have signed the informed consent (or Information Letter and Data Transfer Authorization Form, as applicable). If they do not fulfill all of the eligibility criteria, the subject will be considered a screen failure. Inclusion/Exclusion and Study Completion/ Exit CRFs will be completed for all screen failures.
- Consented subjects that meet all eligibility Criteria other than the intraoperative eligibility criteria will be considered intraoperative screen failures. CRFs required to be completed for these subjects are the: Inclusion/Exclusion CRF, Operative Evaluation CRF, and Study Completion/Exit CRF.
- Consented and enrolled subjects implanted with the study device will be the only subjects counted towards the enrollment limits of 15 total enrolled subjects per site and 60 total subjects for the study. All applicable CRFs are required to be completed for these subjects.

Enrolled subjects that receive the CTAS will be included in all pertinent analyses regardless of their final disposition, unless the subjects are removed from the study per section 6.6.

If the patient decides not to participate in the study, s/he will continue to be treated as s/he as per the applicable standard of care. The choice of surgical treatment with the CTAS is independent of patient participation in the study, i.e. the patient may receive the CTAS regardless of their study participation.

6.2 Baseline Procedures

Once the subject is consented and enrolled, prior to surgery, obtain the following:

- Eligibility Criteria: confirmation the subject meets all the eligibility criteria.
- Baseline Demographics: sex, age, height, weight, nicotine use and work status.
- Medical history and diagnosis: previous surgical interventions, pre-operative medical conditions, diagnosis, joint affected, symptom duration and WB status.
- Patient Questionnaires: PROMIS, VAS Pain assessment, FAAM (ADL subscale only) and SF-36v2.

- Concomitant medications: record all condition related and pain medications taken at the time of screening to serve as a baseline in addition to any medications related to exclusion criteria #5, and confirm eligibility criteria. Documentation should include drug, dose, route and frequency, classification of drug, start dates and stop dates. At each follow-up visit, concomitant medications will be reviewed, updated and recorded on the Concomitant Medications CRF.
- X-rays: minimum study requirements are standard WB A/P, lateral, and maximum dorsiflexion and plantarflexion views per the Radiographic Evaluation Protocol (REP). Other imaging studies maybe required to complete the diagnosis.

6.3 Surgical Procedures

Subjects will undergo primary TAR using the CTAS. If during the study procedure, the investigator decides not to implant the CTAS in the subject for any reason, the subject is to be considered an intraoperative screen failure. The Inclusion/Exclusion CRF, Operative Evaluation CRF and Study Completion/Exit CRF should be completed for these subjects. All pertinent data for these subjects should be collected. Intraoperative screen fail subjects will not be included in any final data analyses and these subjects will not be counted as one of the maximum of 15 potential enrollments for the study at the site.

The surgical technique including the implantation of the ankle prosthesis will be performed according to the Surgical Technique for the CTAS and will be based on the surgeon's standard of care and the specific needs of the subject.

During the intraoperative procedure, immediately prior to inserting the device, a lateral fluoroscopy image of the ankle is to be collected and securely stored for possible future analyses.

Post-operative immobilization and PT will be prescribed at the discretion of the operating surgeon.

The following information about the surgical procedure will be collected:

- Type of surgery/procedure (i.e. joint replaced),
- Date of surgery,
- Total tourniquet time,
- Components and sizes of implants (i.e. tibial, talar and polyethylene insert), catalog numbers, lot numbers,
- Adjunctive procedures performed,
- Hospital stay (if applicable),
- Total operative time,
- Complications during surgery

6.4 Visit Schedule

Subjects are to be followed for 10 years post-surgery. Subjects are to return for follow-up visits at the following time points post-surgery:

- 6 weeks (+/- 2 weeks)
- 3 months (+/- 2 weeks)
- 6 months (+/- 1 month)
- 1 year (+/- 2 month)
- 2 years (+/- 2 months)
- 5 years (+/- 5 months)
- 10 years (+/- 5 months)

6.4.1 Data Collection

The following information will be collected during each follow-up visit:

- Clinical assessments i.e., weight, nicotine use, work status, PT status, WB status, immobilization type, and implant survivorship status.

NOTE: All attempts should be made to schedule and have a subject attend a follow-up visit in person. However, if in-person attendance is not possible, a phone visit consult is allowed to confirm with the subject the implant survivorship status at the time of the visit. This is the only study data permitted to be captured over the phone for this study, excluding routine subject information commonly collected over the phone such as information regarding AEs or medication changes.

- Patient Questionnaires: VAS pain assessment (**completed at all scheduled follow-up visits but at 6 weeks, only non-weight bearing VAS pain scale is required**)
- Patient Questionnaires: PROMIS, (FAAM) (ADL subscale only) and SF-36v2 (**completed at 3 and 6 months, and 1, 2, 5, and 10 year visits**).
- Concomitant medications: record all condition related and pain medications in addition to any medications related to exclusion criteria #5. Documentation should include drug, dose, route and frequency, classification of drug, start dates and stop dates. At each follow-up visit condition related and pain medications will be reviewed, updated and recorded on the Concomitant Medications CRF.
- Adverse Events: SAEs (related to device and/or procedure or considered by the position as related to the study condition or the lower limbs) are to be collected and only AEs that are possibly related, probably related or related to the device or study procedure (section 11).
- Protocol deviations (PDs): any deviation from the protocol is to be collected (section 9.2).
- Radiographic collection: standard WB A/P, lateral, and maximum dorsiflexion and plantarflexion views per the REP. Per the surgeon's discretion, WB radiographs may not be recommended at the 6-week visit and are therefore, not required per the protocol.

6.5 Visit Schedule

	Screen Baseline	Surgery	6-week (± 2-week)	3-month (± 2-week)	6-month (± 1-month)	1-year (± 2-months)	2-year (± 2-months)	5-year (± 5-months)	10-year (± 5-months)
Inclusion/Exclusion/Consent	X								
Baseline Demographics	X								
Medical History and Diagnosis	X								
Operative Evaluation		X							
Follow-up Visit			X	X	X	X	X	X	X
Ankle VAS Pain Assessment	X		X*	X	X	X	X	X	X
SF-36v2	X			X	X	X	X	X	X
FAAM (ADL subscale only)	X			X	X	X	X	X	X
PROMIS	X			X	X	X	X	X	X
Concomitant Medication	X		X	X	X	X	X	X	X
Protocol Deviations	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Study Completion/Exit		If required	If required	If required	If required	If required	If required	If required	X
Study required x-rays									
A/P	X		X**	X	X	X	X	X	X
Lateral Neutral	X		X**	X	X	X	X	X	X
Dorsiflexion (ROM)	X		X**	X	X	X	X	X	X
Plantarflexion (ROM)	X		X**	X	X	X	X	X	X
Intraoperative Fluoroscopy		X***							

* Non-weight bearing only

** Per Surgeon Discretion (Weight-bearing may not be recommended at this time)

*** Immediately prior to device insertion, a lateral fluoroscopy image of the ankle is required to be collected

6.6 Subject Completion and/or Exit Procedures

When a subject completes the study, voluntarily withdraws, is withdrawn by the investigator for any reason, the study is terminated, the investigator(s) is no longer able to locate the subject (lost to follow-up), or the subject is an intraoperative screen failure, a Study Completion/Exit CRF is required to be completed. The reason for the study exit will be reported along with any relevant information concerning the device, subject condition or death and autopsy (if applicable).

If a subject no longer meets study eligibility criteria after they have been enrolled in the study and have received the CTAS, the Investigator(s) must continue to obtain follow-up data for that subject just like every other subject in the trial.

All subjects withdrawn from the study due to an AE at study exit will be exited from the study and the AE status will be considered ongoing at study exit. While these subjects will no longer be participating in the study, the investigator is required to follow these subjects according to standard of care until the AE resolves, a resolution is no longer expected, or it returns to baseline.

For subjects requiring a removal or revision of the study device, as defined in section 11.6 of the protocol, all results from the time of baseline to the point of the removal or revision shall be included in the planned analyses.

After completing the 10-year visit requirements, the subject will be considered to have completed the study. If a subject withdraws from the study prematurely, all efforts should be made to confirm implant survivorship at the time of withdrawal as well as whether any ongoing AEs have been resolved. In all cases, the withdrawal, the reason for withdrawal, and its corresponding date will be documented. Before subjects are determined to be “lost to follow-up”, the site must document three (3) attempts to contact the subject (e.g. telephone, e-mail, certified letter) and allow two weeks after the third attempt for the subject to respond.

If a subject misses a visit and is unable to come to the visit in person for some reason, all efforts should be made to have the subject attend the visit in person (even if this visit is out of window). However, if the subject is unable to attend in person after multiple scheduling attempts, a phone call consult is allowed for a study visit in order to determine implant survivorship in the subject as well as routine medical information commonly collected over the phone such as any updates for AEs or medication changes. A phone visit is not ideal and should only be completed upon last resort.

6.7 Subject Pregnancy

In the event a subject suspects she is pregnant or becomes pregnant during the study, the subject is to immediately notify the study doctor and will be immediately suspended from imaging requirements. Imaging can recommence following pregnancy at the discretion of the study doctor.

6.8 Patient Reported Outcomes

Patient reported outcomes will be collected according to the study visit schedule and per the guidelines provided by the questionnaire developers. These include:

1. PROMIS (required at screening, 3m, 6m, 1y, 2y, 5y, and 10y visits)

2. VAS pain assessment (required at screening, 6w (Non WB only), 3m, 6m, 1y, 2y, 5y, and 10y visits)
3. FAAM (ADL subscale only) (required at screening, 3m, 6m, 1y, 2y, 5y, and 10y visits)
4. SF-36v2 (required at screening, 3m, 6m, 1y, 2y, 5y, and 10y visits)

6.8.1 PROMIS

The PROMIS Physical Function – Mobility item bank v1.2 was developed by the Patient-Reported Outcomes Measurement Information System (PROMIS). This item bank was developed by distilling relevant and psychometrically sound items from the full PROMIS physical function bank. PROMIS will be utilized at screening, 3m, 6m, 1y, 2y, 5y, and 10y visits. The research staff should not monitor the subject while they are completing the questionnaire, but should be available if the patient has questions.

6.8.2 VAS Pain Assessment

Patients will be asked to rate their ankle pain by placing a vertical mark through a 100mm scale at the level that most closely describes the pain they are experiencing at each follow-up visit. Separate scales will be used to assess pain while resting (Non WB) and during activity (Maximum WB). VAS will be measured at screening, 6w (Non WB only), 3m, 6m, 1y, 2y, 5y, and 10y visits. The research staff should not monitor the subject while they are completing the questionnaire, but should be available if the patient has questions.

6.8.3 FAAM (ADL Subscale Only)

Patients will be asked to complete the FAAM questionnaire (Activities of Daily Living Subscale only). FAAM has been validated and shown to be a responsive, valid measure of physical function for subjects with a broad range of musculoskeletal disorders of the lower leg, foot, and ankle. FAAM will be utilized at screening, 3m, 6m, 1y, 2y, 5y, and 10y visits. The research staff should not monitor the subject while they are completing the questionnaires, but should be available if the patient has questions.

6.8.4 SF-36v2

Patients will be asked to complete SF-36v2 at screening, 3m, 6m, 1y, 2y, 5y, and 10y visits. The research staff should not monitor the subject while they are completing the questionnaires, but should be available if the patient has questions.

6.9 Radiographic Assessment

AP, lateral, lateral dorsiflexion, and lateral plantarflexion radiographs will be performed preoperatively and at each follow-up visit per the REP. Immediately prior to device insertion during the implant surgery, a lateral fluoroscopy image is required to be collected. Per the surgeon's discretion, WB radiographs may not be recommended at the 6-week visit and are not required per the protocol. Radiographic analysis will be performed by independent radiologists, blinded towards patient. Radiographic assessments will include:

- Device migration

- Device subsidence
- Device tilting
- Device condition
- Radiolucency at 10 lateral and 10 AP zones
- Osteolysis
- Heterotopic ossification
- Adverse bony changes
- Sclerosis
- Additional observations

Evaluation of standard WB maximum plantarflexion and dorsiflexion:

- Ankle range of motion (ROM)

6.10 Monitoring Plan

Integra will determine the need and frequency of monitoring and site auditing visits based on the enrollment rate, the number of subject visits at each study site and Integra internal procedures. The investigator must allow the sponsors representatives (monitors) to contact and visit the study site and, upon request, give permission to inspect the various clinical trial records (i.e. CRFs, medical records and other pertinent data/information), as long as patient confidentiality is preserved, and that inspection is performed in accordance with local regulations.

The monitor will be responsible for the examination of CRFs at regular intervals, during the clinical trial period, to verify adherence to the protocol, ensure the integrity, accuracy, and consistency of the data as well as compliance with Good Clinical Practice (GCP).

The investigator agrees to cooperate with the monitor to assure that any corrections, clarifications, issues and/or problems detected during these visits are resolved in a timely manner.

6.10.1 Medical Record Requirements

The subject's medical record will be reviewed and includes but is not limited to:

- Progress notes of the physician or nurse
- Subject's hospital chart(s)
- Operative notes
- Anesthesia notes
- Discharge summaries
- Physical therapy notes
- Radiological evaluations

7 STATISTICAL CONSIDERATIONS

This section presents general information about statistical methodologies and concepts (e.g. statistical power, sample size) a brief analysis methodology, and some data conventions. Detailed descriptions of the statistical analysis methods and data conventions that will be used in this multi-center study will be provided as a separate document; i.e., the Statistical Analysis Plan (SAP).

7.1 Description of the Study Endpoints

7.1.1 Primary Objective

To evaluate 2-Year implant survivorship in subjects who receive the CTAS when used for primary ankle arthroplasty.

7.1.2 Secondary Objectives

To evaluate 5-year and 10-year survivorship, and relative changes in pain, functionality, patient satisfaction, radiographic performance, and quality of life scores at all visits as compared to pre-operative scores including:

- PROMIS
- FAAM (ADL Subscale only)
- VAS pain assessment
- SF-36v2
- Total ROM (degrees plantarflexion and dorsiflexion)

7.2 Sample Size Determination

This post-market descriptive study will include 60 patients in order to meet Notified Body (British Standards Institution (BSI)) regulatory requirements.

7.3 Statistical Methods

7.3.1 General Considerations

For categorical data, frequencies and percentages will be provided. For continuous data, descriptive statistics, including sample size, mean, median, standard deviation, and range of values (i.e., minimum and maximum values) will be provided.

Significance level of $\alpha=0.05$ will be used for all statistical tests and p-value ≤ 0.05 will be considered statistically significant unless otherwise specified. The 95% confidence intervals will be presented whenever appropriate.

Statistical analysis will be carried out using SAS software version 9.2 or higher.

An interim analysis will be conducted when subjects have completed the 2-year visit

7.3.2 Subject Disposition

The disposition of all subjects who sign an Informed Consent (or Information Letter and Data Transfer Authorization Form, as applicable) will be provided. The numbers of subjects screened, completed 2 year, 5 year, and 10 year and discontinued during the study, as well as the reasons for all discontinuations will be summarized for all centers. Disposition and reason for study discontinuation will also be provided as a by-subject listing.

7.3.3 Protocol Deviations

PDs will be identified and listed by centers.

7.3.4 Demographics and Baseline Characteristics

Demographic and baseline characteristics will be tabulated. Summarized demographic data will include numbers and percentages of males and females, mean, standard deviation, minimum and maximum age at surgery, BMI, weight and height for males and females separately; as well as analogous summary statistics for the baseline function, presenting diagnosis and other relevant patient characteristic factors.

7.3.5 Intent-To-Treat Population

The intent-to-treat (ITT) population is defined as all consented subjects with the CTAS implanted. The ITT population will be the primary population for the analysis of the primary and secondary endpoints.

7.3.6 Per-Protocol Population

The per protocol (PP) population is defined as all consented subjects with the CTAS implanted who are not associated with a major protocol deviation (i.e. eligibility criteria not met, subject enrolled without obtaining consent). This population will be clearly defined before the data analysis. The PP analysis will be considered supportive to the primary analysis.

7.3.7 Analysis of Primary Effectiveness Endpoint

The primary efficacy endpoint is defined as the survival rate at 2 years. The survival rate will be calculated along with two-sided 95% confidence interval.

7.3.8 Analysis of Secondary Effectiveness Outcomes

Implant survival rate at 5 year, 10 year and 95% confidence intervals will be calculated.

Other endpoints including PROMIS, FAAM ADL subscale, VAS, SF-36v2, total ROM (degrees plantarflexion and dorsiflexion) will be summarized by study visit. Change from baseline for the function evaluations will also be summarized by study visit.

Radiographic success will be summarized by numbers of success and percent of success at each of the evaluated intervals.

7.3.9 Analysis of Safety Outcomes

Safety summary will include numbers and percentages of AEs by relationship to study device, by type, and according to study interval in which they occurred. Listings of complications will include complication type, relation to study device, action taken, and clinical outcome.

Rate of device and/or procedure related AEs, SAEs (related to device and/or procedure or considered by the position as related to the study condition or the lower limbs) and all subsequent surgical Interventions will be provided.

Descriptive statistics will be provided for any severe device-related complication where relationship to the device is possible, probably related, or related. Summary and specific complications will also be tabulated.

7.3.10 Missing Data Analysis

The number and proportion of subjects eligible for and compliant with each follow-up examination will be presented. Subjects who withdraw from the study will be tabulated with reasons for withdrawal. The primary analysis on implant survivorship will be based on survival analysis with missing data treated as censored.

8 CLINICAL DATA MANAGEMENT

Integra will be responsible for the processing and quality control of the data. Data management will be carried out as described in the sponsor's SOPs for clinical studies.

The handling of data, including data quality control, will comply with regulatory guidelines (e.g. International Conference of Harmonization E6 Guideline on Good Clinical Practice ICH E6 GCP and local regulations where applicable) and the sponsor's SOPs as well as provisions of the study-specific Data Management Plan.

9 PROTOCOL

The study will not be started until approval has been obtained from the appropriate reviewing EC, if applicable. The approval should include study identification and the date of review.

If applicable, it is the responsibility of the Sponsor and/or the Investigator to keep the EC informed of any AEs/SAEs, PDs and/or amendments to the protocol as required by EC's guidelines and applicable regulations.

This study will be registered on the website http://clinicaltrials.gov/

9.1 Protocol Amendments

Once the final protocol has been issued and signed by the investigators, it must not be changed and/or altered. Protocol amendments are alterations to a legal document and have the same legal status and must pass through the appropriate steps before being implemented. Under no circumstances should an amendment to the study protocol be made without the written approval from the reviewing EC(s).

9.2 Protocol Deviations

A PD is defined as an event where the investigator and/or site personnel, or subject did not conduct or follow the study according to the protocol. All PDs regardless of whether medically justifiable, pre-approved by the sponsor or taken to protect a subject in an emergency, must be clearly documented on the protocol deviation CRF, identifying the deviation type and explanation of the circumstances for the deviation. It is the responsibility of the investigator to report PDs to the sponsor and reviewing EC, if applicable.

10 INFORMED CONSENT/ PATIENT INFORMATION AND DATA TRANSFER AUTHORIZATION

It is the responsibility of the investigator and/or a staff member appointed by the Investigator and trained for this responsibility to give each patient prior to inclusion in the study:

- Full and adequate verbal and written information regarding the objectives and steps of the study as well as any possible risks involved.
- Information regarding their right to withdraw from the study at any time.

Written subject information in the form of an Informed Consent Form (ICF or Patient Information and Data Transfer Authorization, as applicable) must be given to each subject before enrollment and adequate time must be allowed for the patient to review the information. Furthermore, once the patient has reviewed the information and been allowed to ask any questions, it is the responsibility of the investigator to obtain signed informed consent (or Patient Information and Data Transfer Authorization, as applicable) from all patients prior to their inclusion in the study.

The original signed ICF (or Patient Information and Data Transfer Authorization, as applicable) will be retained in the subject's study records, and a copy provided to the subject.

If the patient decides not to participate in the study, s/he will continue to be treated as s/he as per the applicable standard of care. The choice of surgical treatment with the CTAS is independent of patient participation in the study, i.e. the patient may receive the CTAS regardless of their study participation.

11 ADVERSE EVENT ASSESSMENT AND REPORTING

The definition of an AE to be used in this study is noted below and is based on GCP and international guidelines.

11.1 Adverse Event (AE) - Definition

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 (study) medical device.

For users or other persons, this definition is restricted to events related to investigational (study) medical devices.

11.2 Adverse Device Effect (ADE) - Definition

An ADE is any AE related to the use of the study device.

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

This definition includes any event resulting from an error or intentional misuse of the study device.

Refer to AE Relationship Section 11.7 below.

11.3 Serious Adverse Events (SAE)

An AE is serious when the subject outcome is:

- Death

  If it is suspect that the death was an outcome of the adverse event.

- Life-threatening

  If it is suspected that the subject was at substantial risk of dying at the time of the adverse event, or use or continued use of the device or other medical product might have resulted in the death of the subject.

- Hospitalization (initial or prolonged)

  If subject admission to the hospital or prolongation of hospitalization was a result of the adverse event.

  Emergency room visits that do not result in admission to the hospital should be evaluated for one of the other serious outcomes (e.g., life-threatening; required intervention to prevent permanent impairment or damage; other serious medically important event).

- Disability or Permanent Damage

  If the adverse event resulted in a substantial disruption of a person's ability to conduct normal life functions, i.e., the adverse event resulted in a significant,

persistent or permanent change, impairment, damage or disruption in the subject's body function/structure, physical activities and/or quality of life.

- Congenital Anomaly/Birth Defect

  If you suspect that exposure to a medical product prior to conception or during pregnancy may have resulted in an adverse outcome in the child.

- Required Intervention to Prevent Permanent Impairment or Damage (Devices)

  If you believe that medical or surgical intervention was necessary to preclude permanent impairment of a body function, or prevent permanent damage to a body structure, either situation suspected to be due to the use of a medical product.

- Other Serious (Important Medical Events)

  When the event does not fit the other outcomes, but the event may jeopardize the subject and may require medical or surgical intervention (treatment) to prevent one of the other outcomes. Examples include allergic bronchospasm (a serious problem with breathing) requiring treatment in an emergency room, serious blood dyscrasias (blood disorders) or seizures/convulsions that do not result in hospitalization. The development of drug dependence or drug abuse would also be examples of important medical events.

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the Clinical Protocol, without serious deterioration in health, are not considered reportable SAEs.

11.4 Serious Adverse Device Effect (SADE) - Definition

A SADE is any SAE that based on appropriate medical judgment, is related to the device. Refer to AE Relationship Section 11.7 below.

11.5 Unanticipated Serious Adverse Device Effect (USADE)

A SADE which by its nature, incidence, severity or outcome has not been identified in the risk analysis report or protocol; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the risk analysis report or protocol, or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

11.6 Subsequent Surgical Interventions - Definitions

Subjects requiring a CTAS device removal or revision subsequent secondary surgical intervention shall be followed from the point of the subsequent secondary surgical intervention until the original AE is resolved, a resolution is no longer expected or the AE returns to baseline. Subjects requiring a CTAS device re-operation or supplemental fixation should be followed through completion of the study similar to any other subject

Subsequent surgical interventions will be categorized according to the following definitions:

- **Revision:** a procedure that modifies or removes part of the original implant configuration, i.e., one or more of the component(s).

  NOTE: Revision does not involve other joint-involving procedures that are termed reoperations such as, gutter debridement and peri-prosthetic joint-involving surgeries that are considered additional procedures (such as subtalar joint arthrodesis, ligamentous release or plication, Achilles tendon lengthening, etc.).

- **Removal:** a procedure where all of the original system configuration are removed with or without replacement.

- **Re-operation:** any surgical procedure at the location of the index surgery site that does not remove, modify or add any component to the system.

- **Supplemental fixation:** a procedure in which additional instrumentation not under study is implanted (e.g., supplemental placement or of a rod/screw system or a plate/screw system).

  NOTE: From the point of the revision or removal occurs, no further study-related effectiveness endpoint assessments will be required as the results may invalidate the endpoints of the study or introduce extraneous factors into the results. All subsequent surgical Interventions are considered AEs.

11.7 Adverse Event Relationship - Definitions

The relationship of AEs to the investigational device will be categorized according to the following definitions:

- **Not related:** the AE is due to an underlying or concurrent illness or the effect of another device, drug, intervention, environment, etc., and is definitely not related to the study device and/or study procedure i.e. determined with certainty to have no relationship to the study device and/or study procedure.

- **Possibly related:** the Adverse Event onset has a temporal relationship to the study device and/or study procedure, but an alternative cause and/or etiology (e.g. other drugs, products, chemicals, underlying disease, environment, etc.), is equally or more likely compared to the potential relationship to the study device and/or study procedure, which makes a causal relationship possible.

- **Probably related:** the Adverse Event onset has a temporal relationship to the study device and/or study procedure and another cause and/or etiology (e.g. other drugs, products, chemicals, underlying disease, environment, etc.), is unlikely or significantly less likely compared to the potential relationship to the study device and/or study procedure, which makes a causal relationship probable.

- **Related:** strong evidence exists that the study device and/or study procedure caused the AE. There is a causal and temporal relationship between the event onset and the study device and/or study procedure. There is strong therapeutic/mechanistic evidence that the event was caused by the study device and/or study procedure. The patient's clinical state and concomitant therapies have been ruled out as a cause.

11.8 Adverse Event Recording

For the purposes of this study, AEs spontaneously reported by the subject and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures need to be recorded when in the physician's opinion the AE is either:

1. An AE possibly related, probably related, or related to the CTAS or CTAS study procedure.

OR

2. SAE possibly related, probably related, or related to the CTAS (i.e. SADE), or CTAS study procedure

OR

3. SAE considered by the position as related to the study condition or the lower limbs

The study procedure is defined as the CTAS surgery to replace the ankle joint, and for AE recording purposes includes any post-surgical complications attributable to the surgery (e.g. surgical site infection, failure of wound closure, etc.).

The point at which adverse events are to be collected is when the subject is officially enrolled and receives the CTAS device. No AEs are to be collected for screen fails.

When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Each recordable AE must be described as follows:

- AE term: a medically defined diagnosis/symptom
- AE description: explain the circumstance of becoming aware of the event, how the subject explained the circumstances surrounding the onset of the event, the underlying cause (the diagnosis), coexisting disease, or other condition or complaint involving the event
- AE duration: document by entering the date of onset (start date) and date of resolution (stop date)
- AE severity: document as serious or not serious (if not serious, AE must be possibly related, probably, or related to the device or study procedure in order to be reported)
- AE frequency: document as a single episode, intermittent or continuous
- AE intensity: document as
    1. mild (transient and easily tolerated by the subject),
    2. moderate (discomfort and interrupts normal activities), or
    3. severe (incapacitating with inability to work or do usual activity).
- Device Relationship: document as not-related, possibly-related, probably-related, related (see definitions in section 11.7). If not related to the device or study procedure, the AE must be an SAE considered by the position as related to the study condition or the lower limbs in order to be recorded.

- Treatment: document as none, medication, hospitalization, surgical or other. Any prescribed medication should be noted in the subject's medical records and if required transcribed onto the appropriate CRF.
- Outcome: document as recovered without sequelae, recovered with sequelae, ongoing, death or other. AEs will be followed until a resolution has occurred, until a resolution is no longer expected, the AE returns to baseline or the subject exits the study.

Any subject withdrawn from the study due to an AE should be followed as specified in section 6.6. The investigator should prepare a complete written summary of the event and its outcome, in addition to recording the event on the appropriate CRF.

11.9 Adverse Event Reporting

All recordable defined SAEs, whether or not considered causally related to the study device and/or study procedure must be reported by the investigator to the attention of the sponsor, within five working days from the point in time when the Investigator or site personnel becomes aware of the SAE and to the reviewing EC as required per their guidelines (if applicable). The information reported will include a minimum of the following: subject number, a narrative description of the event and an assessment by the investigator as to the intensity of the event and relatedness to study device. Follow-up information on the recordable SAE may be requested by the sponsor.

As the product is CE-marked and used per its intended purpose, the Medical Device vigilance system applies: The Investigator should report incidents with the Medical Device to the manufacturer or to the National Competent Authority, as per national laws.

12 INVESTIGATOR RESPONSIBILITIES

The investigator is responsible for ensuring that the study is conducted according to this approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as described by the ICH E6 GCP, the International Standard ISO14155:2011, as well as that informed consent (or Information Letter and Data Transfer Authorization Form, as applicable) is obtained from the subjects prior to their enrollment in the study.

It is the Investigator's responsibility to ensure that all staff assisting with the study have appropriate qualifications, are fully instructed on the study procedures and will conduct the study in compliance with the European Directive 95/46/EC and applicable regulation in terms of data protection.

12.1 Subject Data Protection

Subjects will be identified in the CRF with a unique subject number and initials.

The investigator should keep a subject identification list. The subject should be informed that the data will be stored and analyzed by computer, that identification of individual subject data will only be possible for the Investigator and the monitor. Furthermore, the Investigator should inform the subject that the records relevant to the study may be inspected by the study Sponsor, designated Sponsor Representative, or other persons as required by law.

The personal data of the patients will be collected and processed in compliance with the European Directive 95/46/EC on the protection of individuals with regard to the processing of personal data and on the free movement of such data and in compliance with its implementation in local laws. The data process was authorized by the French data protection authority CNIL (Commission Nationale Informatique et Libertés), recognized by other European countries under the European Directive 95/46/EC.

Integra LifeSciences Corporation subscribes to the “Privacy Shield” principles.

12.2 Investigator Records

The investigator shall maintain the following accurate, complete, and current records relating to the investigators participation in the study.

1. All correspondence with another Investigator, the EC, the Sponsor, the designated Sponsor Representative, the National Competent Authority, including required reports.
2. Names of all subjects who received the CTAS in the study
3. Records of each subject’s case history and exposure to the device. Case histories include the CRFs and supporting data including signed and dated ICFs (if required) and medical records such as physician progress notes, hospital chart(s), and nurses progress notes. Such records shall include:
    - Documents evidencing informed consent (or Information Letter and Data Transfer Authorization Form, as applicable).
    - All relevant observations, including records concerning AEs (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
    - A record of the exposure of each subject to the device including the date and time of each use and any other therapy.
4. The protocol with documents showing the dates of and reasons for each deviation from the protocol.
5. Any other records required to be maintained by regulation.

12.3 Recording and Collection of Data

The site is responsible for secure storage of all source documents for all data collected for this study. All source documents and CRFs must be completed as soon as possible after the subject's visit. Corrections to data on the CRFs will be documented in an electronic audit trail in the EDC, which is 21 CFR Part 11 compliant. The Investigator will review and sign CRFs to indicate that, to his/her knowledge, forms are complete and accurate. If further changes are made after the Investigator original review, the investigator will need to again sign the CRFs electronically. Designated source documents will be signed and dated by appropriate study personnel. The investigator must agree to complete and maintain source documents and CRFs for each subject participating in the study.

12.4 Investigator Reports

The Investigators will be responsible for the accurate and timely reporting of any study annual or final reports to the EC, if applicable, and must also provide copies of these reports to the sponsor.

12.5 Investigator Summary

A study summary will contain the results of all data analysis performed and the conclusion thereof and will further reflect the investigator's overall experience with the device in the study.

12.6 Investigator Documents

Current Curriculum Vitae (CV) will be collected from all investigators and sub-investigators participating in the study. The CV should contain information regarding name, title, occupation, education, research experience, former positions held and a list of publications. The CV must be signed and dated and should be updated every 2 years.

13 ARCHIVING

All study documentation at the investigator site and sponsor site will be archived in accordance with ICH E6 GCP and the Sponsor's quality standards and SOPs.

Study records must be retained by the investigator and sponsor for 15 years following the conclusion/ termination of the study. Study records should not be destroyed without prior written agreement between the sponsor and the study investigator. At the completion of the study, details of the archival process must be provided to the sponsor. Study records are subject to inspection by applicable health and regulatory agencies at any time.

Records to be retained by the investigator include, but are not restricted to:

- Source data and the primary records upon which they are based (e.g. subject's progress notes, adverse event data, test results, and any other diagnostic procedures required to evaluate the progress of the study).
- Signed protocols and protocol amendments
- Delegation of authority log
- Site visit logs
- Correspondence to and from the sponsor, designee, EC and Competent Authority (if applicable)
- Investigator and sub-investigator CVs
- Signed ICF (or Information Letter and Data Transfer Authorization Form, as applicable)
- SAE reports, if applicable
- Ethical Committee approval letter (if applicable)
- Other documents pertaining to the conduct of the study

These documents must be maintained and kept on file by the investigator so that the conduct of the study can be fully documented and monitored.

14 PUBLICATION POLICY

The intention of this study is to publish all results after review and analysis of the short-term (e.g. 2-year), mid-term (e.g. 5-year), and the long-term (e.g. 10-year) data after all subjects have completed each study time-point. For each publication using data from this study, the sponsor will develop a publication plan that will be shared and discussed with the investigators prior to being finalized. All publication requirements will be explained in detail in the study agreements.

APPENDIX A: PATIENT QUESTIONNAIRES

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Note: The Patient Questionnaires attached in this appendix are for information purposes only. Patient Questionnaires for use in the study will be provided by the sponsor (in the appropriate languages required in the different countries).