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Revo-M Study

Prospective, feasibility study to evaluate performance, patient benefits, and acceptance of a new energy storage and return prosthetic foot

REVISION RECORD		
Date	Version	Description
22-Jan-2020	1.0	Initial release

Sponsor

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Investigator's Acknowledgement of Revo-M Study

Name	Revo-M Study
Version	1.0
Investigational Site	

I acknowledge the study protocol indicated above and agree to conduct the study in accordance with it.

Acknowledged by:

Printed Name	**Signature**	**Date**

Sponsor Approvals of Revo-M Study

Sponsor	Otto Bock HealthCare LP
Name & Document Number	Revo-M Study
Version	1.0

I acknowledge the study protocol indicated above and agree to oversee the conduct of this study in accordance with it.

Acknowledged by:

		Signature	Date
Sponsor	Russ Lundstrom		
	Director of Clinical and Field Clinical Services – North America		

Table of Contents

Clinical Study Summary

Title	Prospective, feasibility study to evaluate performance, patient benefits, and acceptance of a new energy storage and return prosthetic foot
Purpose	To characterize differences in performance and patient reported outcomes between the Taleo, Proflex XC, and the new Revo prosthetic foot.
Design	A prospective, interventional, multicenter pilot study
Co-Sponsors	Ottobock SE & Co. KGaA (Germany) Otto Bock HealthCare LP (United States)
Control	Current Energy Storing and Return prosthetic foot
Study Devices	Revo-M, Taleo, and ProFlex XC prosthetic feet
Enrollment	Up to 30 K3 subjects; at least 12 transtibial and 12 transfemoral
Clinical Sites	Up to 5 sites in the United States
Primary Safety Objective	To characterize all device-related adverse events, stumbles, and falls experienced by subjects in the study by frequency and severity.
Primary Efficacy Objectives	1. To characterize perception of mobility as measured by the PLUS-M while wearing the Revo-M compared to the everyday feet. 2. To characterize the level of activity restrictions as measured by the Trinity Amputation and Prosthesis Experience Scales Activity Restrictions subscale (TAPES-AR) while wearing the Revo-M compared to the everyday feet.
Secondary Efficacy Objectives	1. To characterize the level of walking endurance as measured by the distance walked in the six minute walk test and the perceived exertion measured by Borg CR100 while wearing the Revo-M compared to the everyday feet. 2. To characterize the perception of balance confidence as measured by the extended Activities-specific Balance Confidence (ABC) Scale while wearing the Revo-M compared to the everyday feet. 3. To characterize the level of functional satisfaction as measured by the TAPES Functional Satisfaction (TAPES-FUN) subscale while wearing the Revo-M compared to the everyday feet.

Exploratory Objective	1. To characterize the outcome measures described in the primary and secondary objectives while wearing the Revo-M compared to the comparative feet (Taleo/ProFlex XC). 2. To characterize perception of quality of life as measured by the EQ-5D-5L while wearing the Revo-M compared to the everyday feet and the comparative feet. 3. To characterize the level of fatigue as measured by the PROMIS Fatigue Short Form 7a while wearing the Revo-M compared to the everyday feet and the comparative feet. 4. To characterize activity level as measured by steps per day and cadence recorded by a StepWatch™ activity monitor while wearing the Revo-M compared to the everyday feet and the comparative feet. 5. To characterize the Physiologic Cost Index of walking as measured during the 6-minute Walk Test while wearing the Revo-M compared to the everyday feet and the comparative feet. 6. To characterize the perception of pain interference as measured by the PROMIS Pain Interference short form 4a collected from the patient journal while wearing the Revo-M compared to the everyday feet and the comparative feet.	
Estimated Timeline	Estimated study start/first subject in	February 2020
	Period II start/fitting with 1st study foot	April 2020
	Period III start/cross-over to 2nd study foot	June 2020
	Period IV start/cross-over to control foot	August 2020
	Last patient out	December 2020

List of Abbreviations and Definition of Terms

AE	Adverse Event
ABC	Activity-based Balance Confidence
CPO	Certified Prosthetist Orthotist
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
K3	K-level 3 or Medicare Functional Classification Level 3. Has the ability or potential for ambulation with variable cadence. Typical of the community ambulator who has the ability to traverse most environmental barriers and may have vocational, therapeutic, or exercise activity that demands prosthetic utilization beyond simple locomotion.
KD	Knee Disarticulation
IRB	Ethics Committee or Institutional Review Board

MFCL	Medicare Functional Classification Level
PCI	Physiological Cost Index
PLUS-M	Prosthetic Limb User Survey of Mobility
PROMIS	Patient Reported Outcomes Measurement Information System
SAE	Serious Adverse Event
Sponsor	The institution funding and responsible for the total clinical investigation, in this case Otto Bock HealthCare LP (US)
TAPES-AR	Activity Restriction domain of the Trinity Amputation and Prosthesis Experiences Scales
TAPES-FUN	Functional subscale in the Satisfaction domain of the Trinity Amputation and Prosthesis Experiences Scales
TT	Transtibial
TF	Transfemoral

Background and Rationale

Prosthetic feet are modular components that are designed to replace the function of the ankle-foot complex after losing a part of the lower limb. An individualized selection of the prosthetic foot is of utmost importance with regard to the successful prosthetic treatment of an amputee. Ideally, the design and function of the prosthetic leg leads to the lowest level of joint overload regardless of amputation level in order to prevent long-term damage. The selection of the prosthetic foot is decisive for both the static and dynamic behavior of a prosthesis. Depending on the condition and mobility of the patient, there are a large number of prosthetic feet that are suitable for certain activities.

Prosthetic energy-storage-and-release (ESR) feet are designed to store energy during early stance phase and then release a portion of that energy late in stance phase. To date, they are state of the art for lower limb amputees. This is especially true for higher mobility grade amputees [Baumgartner, 2009]. Nevertheless, these feet also provide many benefits for lower mobility patients [Kraft, 2015].

The prosthetic heel is the primary area of impact loading in the prosthesis. As the foot contacts the ground, the heel is loaded in compression and unloaded slowly as the amputee moves into mid-stance and keel loading begins (Figure 1). Some ESR feet have a heel that consists of a compressible foam material and this simulates controlled plantarflexion as it compresses and brings the forefoot into contact with the ground. The foam heel uses a viscoelastic material that dissipates energy as it compresses and expands. Other types of ESR feet utilize a heel spring that is typically made from carbon fiber or a similar material. This spring acts like the compressible foam with regards to simulated plantarflexion during loading of the limb, but with much greater energy-storage and energy-return capability. The heel initially compresses and then releases energy as the foot moves into mid-stance. Thus, for this design, the heel is an important energy-storage and energy-return part of the prosthesis. As the stiffness of the heel increases, the extent of the impact absorption decreases and less energy is dissipated. However, in ESR feet with a flexible keel, the keel begins to

deflect as the person moves into midstance and energy is stored as the foot dorsiflexes. As this tibial advancement occurs, the keel spring is deflected and energy is stored until the amputee nears the end of stance phase and begins unloading the prosthesis. As the foot is unloaded in terminal stance, the keel spring returns a portion of the stored energy and assists in propelling the limb forward into pre-swing (Figure 1). [Hafner, 2002]

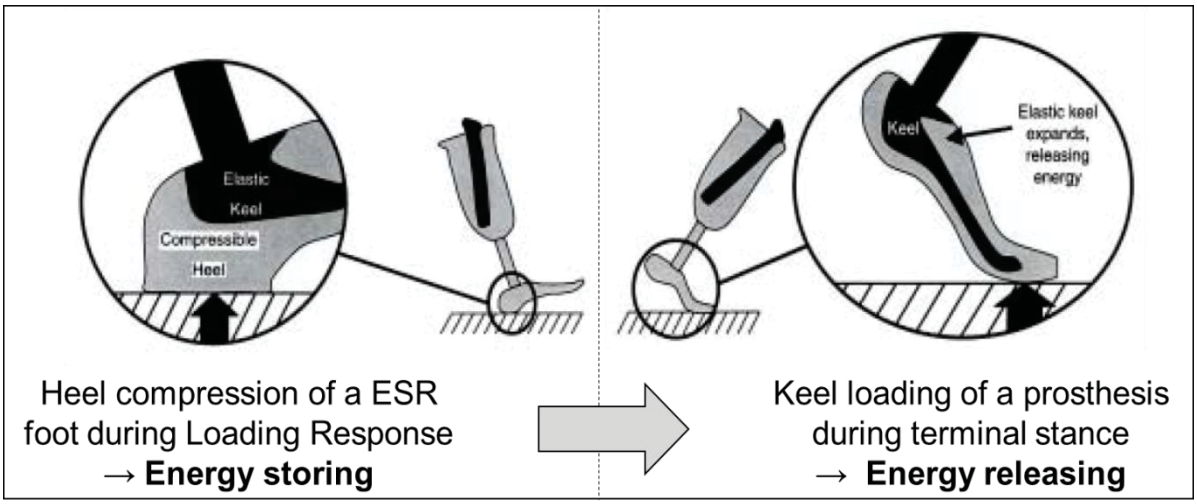

Figure 1 Principles of ESR feet, modified from Hafner et al. [Hafner, 2002]

The elastic behavior of ESR feet may negatively influence the stability and comfort of standing and walking. In addition, it is important that the energy is returned at the right moment; otherwise, it will disrupt rather than support locomotion. Therefore, a high number of parameters have to be considered during the development of an ESR foot. Many of them can be determined with computer simulations, but not all. It is possible that the user will reject a prosthetic foot that perfectly meets their criteria according to the simulation. Therefore, it is necessary during development to evaluate these feet under close to daily-use conditions.

Ottobock is currently developing a new prosthetic foot, the Revo-M, which should be better adapted to the needs of the moderately active users. In particular, it should provide better energy management by optimizing the timing and amount of energy returned. It should also adapt to varying ground conditions.

Study Devices

Ottobock Investigational Study Device (Revo-M)

Manufacturer

Ottobock SE & Co. KGaA

Max-Näder-Straße 15, 37115 Duderstadt

Model number, Version

Product Name	Version
Revo-M	FM2.0

Intended Use

The Revo-M foot is intended for exoskeletal fitting of lower limb amputees. It is intended for moderate to high-activity level amputees (MFCL grade 2, 3 or 4).

Technical Description

The Revo-M prosthetic foot belongs to the group of energy-storage-and-release (abbrev: ESR) feet. It utilizes carbon springs and polyurethane-foam bumpers as elastic elements. These elastic elements allow for a harmonic rollover during stance phase. The proximal connection to other prosthetic components is provided by the aluminum upper part, which contains a pyramid adaptor for this purpose. Furthermore, there is a pivoting joint at the center of the foot within the aluminum upper part that combines with a tension element in the heel region to form a connection to the elastic elements of the foot.

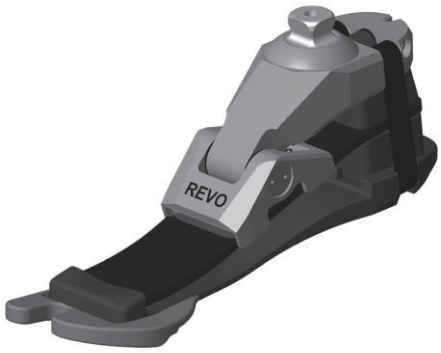

Figure 2 CAD-rendered image of Revo-M without foot shell

Comparative Study Devices (Taleo and ProFlex XC)

Two commercially available comparative study devices will also be assessed in the study, the Taleo and the ProFlex XC. The comparative foot for transfemoral subjects will be the Taleo manufactured by Ottobock. The comparative foot for transtibial subjects will be the ProFlex XC manufactured by Össur.

Figure 3 Comparative Study Devices, Taleo (left) and ProFlex XC (right)

Study Device Technical Specifications

Table 1 Technical Specifications for the Three Study Devices

Specification	Revo-M (Investigational)	ProFlex XC (Comparative TT)	Taleo (Comparative TF)
Activity Levels	K2, K3 and K4	K3 and K4	K3
Max Body Weight	Size 26: 275 lbs (125 kg) Size 24: 220 lbs (100 kg)	365 lbs (165 kg)	330 lbs (150 kg)
Heel Height	Size 26: 10 mm Size 24: 20 mm	10 mm	Normal footshell (N) 10 +/- 5mm, Slim footshell (S) 15 +/- 5 mm
Footshell shape	Size 26: Normal Size 24: Slim	Normal	Normal (N), Slim (S)
Min. Clearance Height	Size 26: 112.5 mm (4 7/16") Size 24: 110 mm (4 1/3")	155 mm (6 1/8 “)	158 mm (6 1/4")
Sizes	24, 26 cm	22-24, 25-27, 28-30 cm	22 - 30 cm

Regulatory Classification

All study devices are Class I devices

FDA Registration under Device Listing Regulation number 890.3420 product code ISH.

Purpose

The purpose of the Revo-M Study is to characterize differences in performance and patient reported outcomes between the Revo investigational prosthetic foot and a comparative prosthetic foot (Taleo or Proflex XC) when compared to the control foot which is the subject’s currently used energy storage and return (ESR) prosthetic foot. The data obtained from this study may also serve to evaluate the long-term performance of Revo.

Protocol

Study Summary

Period I

The study is planned to be divided into four periods as illustrated in Figure 4. The only clinical measures to occur from the beginning of Period I are the StepWatch, Patient Journal, and Socket Comfort Score. After enrollment, the subject will spend 8 weeks (+/-2 weeks) using their own energy storage and return foot. Informed consent, demographic information, general health information, and adverse events will be collected during this period. After enrollment, the subject will be randomized to Revo, Taleo (if a transfemoral amputee), or the Proflex XC (if a transtibial amputee).

Period II – Period IV

Baseline measures are taken just prior to Period II. After the first 8 week follow up, the subject will crossover to the second comparator. After the second 8 week follow up, the subject will crossover to control. During Period IV, assessments will be repeated as in baseline. Table 2 summarizes the assessments and order of events.

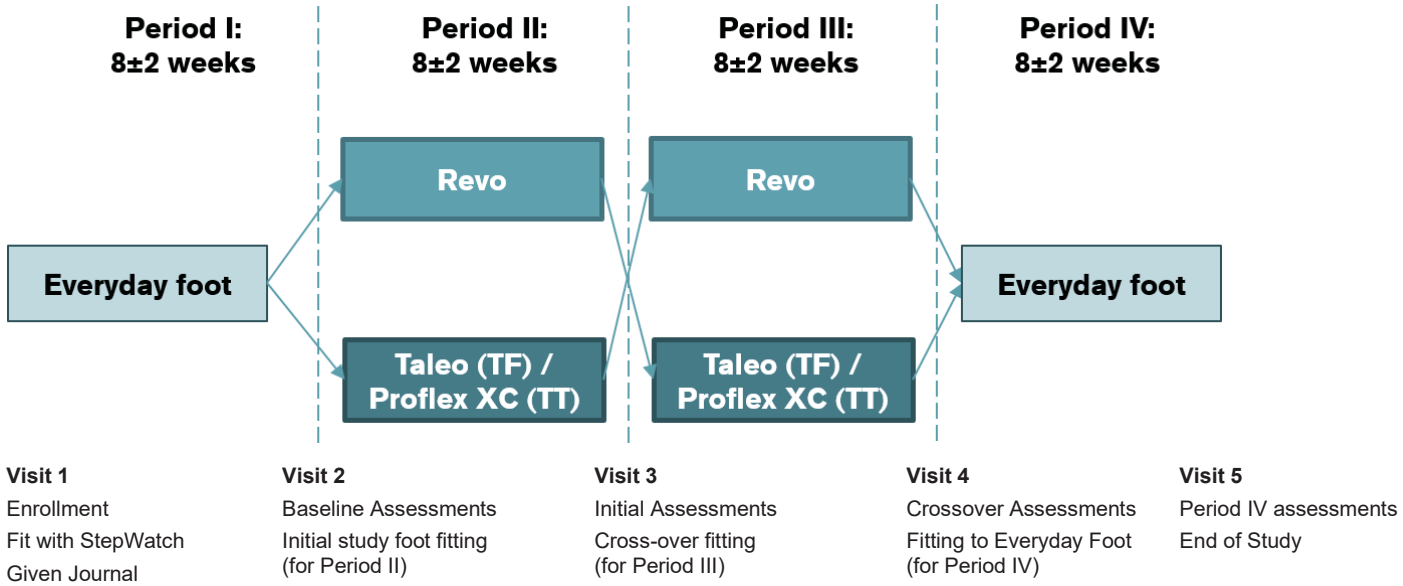

Figure 4 Study Periods and Visits

Table 2 Assessments by Period and Study Visit

Period I (Control)			Period II (Revo/ Comparative)	Period III (Revo/ Comparative)	Period IV (Control)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Measurement	**Enrollment**	**Baseline 8 ± 2 weeks**	**Period II Follow up 8 ± 2 weeks**	**Period III Follow up 8 ± 2 weeks**	**Period IV Follo 8 ± 2 weeks**
Demographics / General Health	X				
SCS	X	X	X	X	X
ABC (extended)		X	X	X	X
PLUS-M		X	X	X	X
PROMIS-F (7a)		X	X	X	X
TAPES-FUN + TAPES-AR		X	X	X	X
EQ-5D-5L		X	X	X	X
6 Minute Walk Test (incl. BORG RPE and continuous HR)		X	X	X	X
Foot Preference Questionnaire					X
Patient Journal (incl. Pain Interference)	X	X	X	X	X
Step Count*	X	X	X	X	X
Adverse Events	X	X	X	X	X
Fitting with prosthetic foot for subsequent Period		X	X	X	

* Subject is fitted with StepWatch at previous visit so that the data may be collected prior to the following visit, this process starts at enrollment

Objectives

Safety

Safety Objectives

1. To characterize all device-related adverse events, stumbles, and falls experienced by subjects in the study by frequency and severity.

Effectiveness

Primary Efficacy Objectives

1. To characterize perception of mobility as measured by the PLUS-M while wearing the Revo-M compared to the everyday feet.
2. To characterize the level of activity restrictions as measured by the Trinity Amputation and Prosthesis Experience Scales Activity Restrictions subscale (TAPES-AR) while wearing the Revo-M compared to the everyday feet.

Secondary Efficacy Objectives

1. To characterize the level of walking endurance as measured by the distance walked in the six minute walk test and the perceived exertion measured by Borg CR100 while wearing the Revo-M compared to the everyday feet.
2. To characterize the perception of balance confidence as measured by the extended Activities-specific Balance Confidence (ABC) Scale while wearing the Revo-M compared to the everyday feet.
3. To characterize the level of functional satisfaction as measured by the TAPES Functional Satisfaction (TAPES-FUN) subscale while wearing the Revo-M compared to the everyday feet.

Exploratory Objectives

1. To characterize the outcome measures described in the primary and secondary objectives while wearing the Revo-M compared to the comparative feet (Taleo/ProFlex XC).
2. To characterize perception of quality of life as measured by the EQ-5D-5L while wearing the Revo-M compared to the everyday feet and the comparative feet.
3. To characterize the level of fatigue as measured by the PROMIS Fatigue Short Form 7a while wearing the Revo-M compared to the everyday feet and the comparative feet.
4. To characterize activity level as measured by steps per day and cadence recorded by a StepWatch™ activity monitor while wearing the Revo-M compared to the everyday feet and the comparative feet.
5. To characterize the Physiologic Cost Index of walking as measured during the 6-minute Walk Test while wearing the Revo-M compared to the everyday feet and the comparative feet.

6. To characterize the perception of pain interference as measured by the PROMIS Pain Interference short form 4a collected from the patient journal while wearing the Revo-M compared to the everyday feet and the comparative feet.

Eligibility Criteria

Patients must meet all of the below mentioned inclusion criteria and none of the exclusion criteria to be eligible to participate in the study.

Inclusion criteria

1. Person is 18 years or older.
2. Currently uses an energy storage and return foot.
3. Person has been a unilateral transfemoral (TF), or transtibial (TT) amputee using a prosthesis for at least 1 year.
4. For TF amputees, the person must be wearing an Ottobock Microprocessor-controlled Knee (MPK) with a compatible prosthetic foot
5. Person weighs ≤ 275 lbs (125 kg) size 26-27cm or ≤ 220 lbs (100 kg) size 24-25cm
6. Person is a K3 ambulator based on Medicare Functional Classification Level (MFCL).
7. Prosthetic foot size is 24 to 27 centimeters.
8. Socket Comfort Score of at least 7
9. Ability to read and understand English
10. A person is able and willing to give consent

Exclusion criteria

1. Current prosthetic foot is too old or worn out as assessed by the CPO.
2. TT subject with currently fit with a Proflex XC or TF subject currently fit with a Taleo.
3. Patient is pregnant or planning to become pregnant.
4. Person who has a life-threatening medical condition (i.e. terminal cancer, severe heart disease).
5. Person has conditions that would prevent participation and pose increased risk (e.g. unstable cardiovascular conditions that preclude physical activity such as walking, problems with vestibular system, etc.).
6. Ulceration or skin breakdown of the residual limb.
7. Person currently has residual limb issues that significantly reduce their ability to load the prosthesis.

Patient Population

Up to 30 existing prosthetic foot users will be enrolled in the study. At least 12 of the subjects will be transfemoral (TF) or knee disarticulation (KD) amputees and at least 12 will be transtibial amputees (TT). There is no exclusion with regards to the cause of amputation (e.g. whether traumatic, cancer or dysvascular).

Vulnerable Subjects

Only adults between the ages of 18 and 75 will be enrolled in the study. No minors may take part in this study. Women of childbearing age who are currently pregnant or who are planning to become pregnant during the time of the study, may not be enrolled in this study.

Study Procedures

Informed Consent

The Investigator is responsible for ensuring that data collection does not take place before the patient and/or legal guardian has given informed consent. Written consent must be given by the patient after the receipt of detailed information. The verbal explanation will cover all the elements specified in the written information provided for the patient.

The Investigator will inform the patient of the aims and methods of the study. The patient must be given every opportunity to clarify any points he/she does not understand and if necessary, ask for more information. At the end of the interview the patient may be given time to reflect if this is required, or more time for discussion with family, caregivers or their own General Practitioner. Patients and/or legal guardians will be required to sign and date the informed consent form. After completion, informed consent forms will be kept and archived by the Investigator in the Study File, and a copy given to the patient.

Prior to the beginning of the study, the Investigator will provide the Sponsor with a copy of the sample informed consent form approved by the IRB and evidence that the IRB has approved the study. The Sponsor must approve any changes to the informed consent form template.

It should be emphasized that the patient is at liberty to withdraw their consent to participate at any time, without penalty, loss of benefits or normal medical care to which the patient is otherwise entitled. Patients who refuse to give, or withdraw written informed consent will not be included or continue in this study.

Data collection

Data will be collected and entered by the Investigator in the form of electronic Case Report Forms (eCRFs) into an Electronic Data Capture (EDC) system by means of prospective data collection.

The following eCRFs are planned to be used for prospective data collection at participating sites:

1. Enrollment
2. Baseline
3. Follow-up
4. Patient Journal

5. Adverse Event
6. Study Termination

Enrollment

After a patient has signed the written Informed Consent Form and meets the inclusion-exclusion criteria, the patient will be considered enrolled in the study. At this point, demographic data, medical history (including fall history) will be collected.

Alignment Assessment

All subjects will undergo an assessment of alignment by the CPO with their current ESR foot. Minor changes to the alignment may be done if the CPO deems it necessary.

Baseline Testing

Baseline testing with the patient's current ESR foot will be conducted at the end of Period I and will include four questionnaires, the PLUS-M, EQ-5D-5L, PROMIS Pain Interference short form, and the extended Activity-specific Balance Confidence Scale. One performance measure will be conducted, the six-minute walk test (see Clinical Tests & Measuresfor test descriptions).

Randomization

The fittings during Period II and Period III are determined at random and according to amputation level. Subjects will be randomized to start with either the Revo (regardless of amputation level) or the comparative foot: Taleo if TF or KD, Proflex XC if TT. After completing Period II with the assigned foot, subjects will cross over to be fit with either the Revo, if starting with the comparative foot or the comparative foot if starting with the Revo.

Fitting process for the Revo-M investigational foot

The Revo prosthetic foot has several components which have different mechanical characteristics to allow the foot to be tailored to the patient. Subjects will complete several walking trials to determine the optimal configuration.

Fitting process for the comparative feet: Taleo and ProFlex XC

The Taleo is customizable with heel wedges that come in three different stiffnesses (soft, medium and hard). The CPO may give the subjects the opportunity to try each wedge to determine which is best.

ProFlex XC does not have any customizable components, so no configuration process is required.

Home-use Periods

Subjects will have four home-use periods during the study approximately 8 weeks in duration as shown in Figure 4 above. Prior to each home-use period, subjects will be fitted with the assigned foot and be given a Patient Journal and a StepWatch activity monitor. The Patient Journals will be completed weekly for the duration of the home-use period. The StepWatch will be worn for approximately one month and then mailed back to the clinical site. At the end of the home-use period, subjects will return to the site for a follow-up visit for assessments (see Clinical Tests & Measures for test descriptions).

Clinical Tests & Measures

Data collection for the following clinical functional assessments will be collected on eCRFs. Several questionnaires and two performance based measures will be used in the study.

For an overview of the assessments required by visit, see Table 2.

Activity monitoring (daily step counts)

The StepWatch will be used for activity monitoring to collect daily step counts during the first month of each home-use period.

Six-minute walk test (6minWT)

The six-minute walk test is performed as an objective evaluation of functional exercise capacity. The six-minute walk test is easy to administer, well tolerated, and typically reflective of activities of daily living. The test measures the distance that the patient can walk on a flat, hard surface, indoors, in a period of six minutes. The walk test is patient self-paced and assesses the level of functional capacity. Patients are allowed to stop and rest during the test, however, the timer does not stop. If the patient is unable to complete the time, the time stopped is noted and the reason for stopping prematurely is recorded. When administering the six-minute walk test, the recommendations of the American Thoracic Society will be followed (ATS Statement, 2002), which requires systolic blood pressure to be below 180 mm Hg and heart rate to be below 120 bpm prior to the test.

Before and immediately after the test, the Borg Rating of Perceived Exertion (RPE) using the CR100 (centiMax) scale (Borg 2002) will be measured.

Prior to the test, all subjects will wear a heart rate strap, and after the test the recorded heart rate will be collected.

Trinity Amputation and Prosthesis Experience Scales (TAPES)

The TAPES is a quality of life measure with nine subscales that broadly fall into three domains: Psychosocial, Activity Restriction, and Satisfaction with the prosthesis (Gallagher et al, 2010). The three subscales of the Activity Restriction domain are referred to as TAPES-AR and the functional subscale of the Satisfaction domain is referred to as TAPES-FUN. Only the TAPES-AR domain and TAPES-FUN subscale are used in this protocol.

PROMIS Fatigue Short Form 7a

PROMIS item banks and their short forms are a reliable and precise measurements of patient reported outcome measures (Cella, 2005-2008). The PROMIS Fatigue item banks assess a range of self-reported symptoms, from mild subjective feelings of tiredness to an overwhelming, debilitating, and sustained sense of exhaustion that likely decreases one's ability to execute daily activities and function normally in family or social roles. Fatigue is divided into the experience of fatigue (frequency, duration, and intensity) and the impact of fatigue on physical, mental, and social activities. The fatigue short forms are universal rather than disease-specific. All assess fatigue over the past seven days.

The original adult short form (7a) was constructed by the domain team with a focus on representing the range of the trait and also representing the content of the item bank. Domain experts reviewed short forms to give input on the relevance of each item. Each domain group worked independently

and the original short forms are 6-10 items long depending on the domain. Psychometric properties and clinical input were both used and likely varied in importance across domains.

Extended Activities-Specific Balance Confidence (ABC) Scale

The ABC Scale (Lajoie 2004) is a self-administered questionnaire that asks the patient to rate his or her confidence in performing various ambulatory activities on a scale from 0% (no confidence) to 100% (complete confidence) without losing balance or becoming unsteady. Scores for each of the 16 items will be collected and an average percentage calculated, with scores <67 indicating an increased risk of falling (Miller et al., 2003/2004).

5 items of interest were added to gauge the impact of the reported increase in proprioception in earlier models of the Revo-M on balance confidence.

This test was selected since it measures patient perceived balance confidence, and is expected to help assess the impact of the new foot.

Prosthetic Limb Users Survey-M (PLUS-M)

The PLUS-M is a valid and reliable self-reported measure for the mobility of adults with lower limb amputations. PLUS-M asks about the subject's ability to perform simple and complex tasks. This questionnaire asks about the current timeframe for the patient. High PLUS-M scores correspond with greater mobility (Hafner et al., 2016).

EQ-5D-5L

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol group, applicable to a wide range of health conditions and treatments. It has widespread currency outside the profession. It is often referred to as a quality of life questionnaire.

The EQ-5D-5L, is a very simple measure which subjects complete at the start and end of treatment. Its name means 'EuroQol – 5 Dimensions – 5 Levels' and comprises five dimensions of health: mobility, ability to self-care, ability to undertake usual activities, pain and discomfort, and anxiety and depression. There are five options (levels) under each domain. Index scores will be computed whereby higher scores indicate higher quality of life.

PROMIS Pain Interference

The PROMIS Pain Interference – Short Form 4a has been incorporated into the patient journal. The patient will be asked six questions related to how pain may have interfered with certain activities in the last 7 days, and rate them on a 1-5 scale, with '1' being 'not at all' and '5' being 'very much.'

Study-specific Questionnaires

Subject Study-specific Questionnaire (Subject SSQ)

Questions have been developed to assess the end users' preferences regarding the three prosthetic feet.

Patient Journal

Subjects will be provided with a 'journal' to answer a questionnaire once per week during the accommodation period while wearing the current ESR foot and during home use while wearing the study devices. The weekly questionnaire in the journal will including questions about satisfaction with the prosthesis, positive and negative observations about prosthetic performance, medical issues, the use of pain medication and the PROMIS Pain Interference short form. The journals will be completed online using links that will be provided to subjects. In the case that a subject does not have easy access to the internet, paper journals will be provided. The journals will be reviewed together with the Investigator during in-person visits. In addition, subjects will also record in the journal any falls and resulting injuries. If any of the journal entries reveal complaints or adverse events, these will be reported on the Adverse Event form.

Training Requirements

The Investigator and investigational site personnel will be given training on the study requirements and an overview of the study devices prior to data collection for study patients. Training on the study requirements will include Investigator responsibilities and requirements, review of the study data collection protocol, review of the Electronic Data Capture (EDC) system with the paper and eCRF's, and study administration. The Investigator will also be responsible for completing Human Subject Protection Training that meets their IRB requirements at the initial review submission, if not already completed. In addition, the Investigator will be responsible for ensuring their certification, if required by the IRB, is current throughout the lifetime of the study, and will submit to the Sponsor a copy of the current certification each time it is renewed.

All training will be documented using training records including the elements of training completed, the trainers that delivered the training and the signatures of the participants. Site initiation visits or conference calls may be made by a Sponsor-appointed Monitor to review the Study Protocol and documentation requirements with the Investigator and clinic support staff involved in the study. The Sponsor will then determine if additional center-specific training is needed and will ensure that all researchers involved in the project have adequate training. Study activities may only be performed once the Sponsor confirms activation of the investigational site.

In addition to training, at a minimum, the following documentation must be in place at the investigational site before patient enrollment begins:

- Current Investigator's and Sub-Investigator's CVs
- Signed study agreement
- Completed training in human research subject protection or an overview of Good Clinical Practice if required by the IRB.
- IRB approval letter for the Study Protocol and amendment(s)
- Patient Informed Consent approved by both the IRB and Otto Bock Healthcare Products GmbH

Adverse Events

Adverse Event Definition

An adverse event is any untoward medical occurrence in a patient. An underlying disease or symptoms associated with the underlying disease that were present prior to the fitting of study devices are not reportable. However, any increase in severity of the underlying disease or symptoms since a study fitting is to be reported as an adverse event. If an adverse event leads to multiple outcomes that sequentially worsen during the course of the study, the worst event is reported. For example, skin irritation leading to a wound infection would be reported as infection.

Adverse Event Reporting

Once a subject is enrolled, all adverse events must be reported until the subject is withdrawn or is terminated from the study.

Adverse Event Adjudication

Events will be adjudicated per the definitions below.

Serious Adverse Event

A Serious Adverse Event (SAE) is an Adverse Event that:

1. led to a death;
2. led to a serious deterioration in the health of the patient that
    - results in a life-threatening illness or injury;
    - results in a permanent impairment of a body structure or a body function;
    - requires hospitalization or prolongation of existing hospitalization;
    - results in medical or surgical intervention to prevent permanent impairment to body structure or a body function; or
3. led to fetal distress, fetal death or a congenital abnormality or birth defect.

Relatedness

Each adverse event will be assessed regarding relatedness to the study device or the fitting procedure. In addition, the level of relatedness will be classified according to definitions as presented in Table 3.

Table 3 Rating the Relatedness of Adverse Events

Relatedness:	Description:
Highly Probable	The adverse event follows a reasonable temporal sequence from receipt (or attempted receipt) of the device treatment or procedure.
Probable	The adverse event follows a reasonable temporal sequence from receipt of the device treatment or procedure and the possibilities of factors other than the device treatment or procedure, such as underlying disease, concomitant drugs, or concurrent treatment can be excluded.
Possible	The adverse event follows a reasonable temporal sequence from receipt of the device treatment or procedure and the possibility of device treatment or procedure involvement cannot be excluded. However, other factors such as underlying disease, concomitant medications, or concurrent treatment are presumable.
Unlikely	The adverse event has an improbably temporal sequence from receipt of the device treatment or procedure, or it can be reasonably explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.
Not Related	The adverse event has no temporal sequence from receipt of the device treatment or procedure, or it can be explained by other factors, including underlying disease, concomitant medication, or concurrent treatment.

Severity Rating

The severity of adverse events will be classified according to definitions as presented in Table 4.

Table 4 Rating of the Severity of Adverse Events

Severity:	Description:
Mild	Usually transient, requiring no special treatment, does not interfere with the patient's daily activities.
Moderate	Low-level inconvenience or concern to the patient, may interfere with daily activities, usually resolved by simple therapeutic non-interventional methods.
Severe	Interruption in patient's daily activity requiring systemic drug therapy or other treatment.

Statistical Considerations and Data Analysis

Sample Size

The sample size for the study will be a minimum of 24 existing ESR users. A sample size of 22 subjects is required to provide 80% power to detect a difference of 5 points on the PLUS-M scale using Wilcoxon's matched pairs signed ranks test and alpha of 0.05. A standard deviation of 7.7 was used to calculate the sample size. The TAPES-AR endpoint requires 21 subjects to achieve the same level of

power using a difference of 0.2 and standard deviation of 0.3. The maximum number of subjects allowed in the feasibility study was increased to 30 to allow for early study exit and/or missing data.

Interim analysis and adaptive study design

This investigation will make use of an adaptive study design. An interim analysis will be performed after all eligible patients (n=24) have completed the second study period (Period II). After the interim analysis, it will be decided whether (1) the assumptions regarding expected observed differences and standard deviations for the primary objectives are confirmed, (2) adjustments must be made in the sample size to ensure 80% power to achieve the study objectives or (3) the study must be terminated for futility. The interim analysis will be performed by an independent statistician. Review of the results and a decision on the different options will determined by the Sponsor.

It is the intention of the Sponsor that this study would be a part of an adaptive, seamless study design in which, in the case that the feasibility study successfully achieves the primary objectives, a pivotal trial may follow with an increase in enrollment to allow for adequate statistical power to address both primary and secondary objectives. The final analysis of the pivotal trial would use data from subjects enrolled before and after the adaptation. Sample size calculations for the pivotal trial would be based on observed differences and standard deviations in outcomes measures from the feasibility study.

Hypothesis

It is expected that subjects will demonstrate better outcomes on primary and secondary endpoint measures with the Revo-M compared to their everyday feet.

Outcome measures obtained after using the Revo-M foot for 8 weeks will be compared to baseline measures obtained using everyday feet with a 2-sided Wilcoxon matched pairs signed ranks test. The Hochberg method will be used to adjust alpha for the multiple primary effectiveness endpoints, thereby limiting the family-wise alpha to 0.05. In this method, p-values are ranked from highest to lowest for each primary endpoint tested. If the highest p-value is ≤ 0.05, all null hypotheses will be rejected and no further adjustment will be made. If, however, the highest p-value is > 0.05, alpha will be adjusted to 0.025 (alpha/2). The remaining p-value must be ≤ 0.025 in order to be statistically significant. Adjustment of alpha will continue in this manner for all primary effectiveness endpoints. Two-tailed p-values $\leq$ the Hochberg adjusted alpha will indicate statistical significance. Primary efficacy endpoints (2 endpoints) will be considered one family and secondary efficacy endpoints (3 endpoints) will be considered a second separate family. The Hochberg method will not be applied to exploratory endpoints.

If the observed p-value is $\leq$ the Hochberg adjusted critical value, the difference will be regarded as statistically significant. Because this is a randomized crossover study, the Revo-M may be either the first or second new foot used after baseline measures with the everyday feet. It is important to assess whether differences between Revo-M and everyday feet scores are influenced by the order in which the new feet are assigned. To evaluate this a difference score will be computed by subtracting everyday feet scores from Revo-M scores. Difference scores for subjects receiving the Revo-M foot first will be compared to those of subjects who received the Revo-M foot second (after a comparative foot) using Wilcoxon's rank sum test. A resulting p-value ≤ 0.05 will indicate that differences in the specified outcome measure may depend on the order in which the Revo-M was

assigned and not simply due to the Revo-M itself. Interpretation of differences between Revo-M and everyday feet scores will be modified accordingly.

Primary Efficacy Endpoints

Primary Efficacy Endpoint #1: Perception of mobility as measured by the PLUS-M. It is hypothesized that PLUS-M scores will be higher for subjects when they are using the Revo-M compared to their everyday feet. In statistical terms the null and alternative hypotheses are as follows:

H_O: $\mu_{Revo\text{-}M} \leq \mu_{Everyday}$

H_A: $\mu_{Revo\text{-}M} > \mu_{Everyday}$

Where H_O is the null hypothesis, $\mu_{Revo\text{-}M}$ is the mean PLUS-M score using the Revo-M, $\mu_{Everyday}$ is the mean PLUS-M score using the everyday feet and H_A is the alternative hypothesis indicating that perception of mobility as measured by the PLUS-M is greater for Revo-M than for everyday feet.

The hypothesis will be tested using a 2-sided Wilcoxon matched pairs signed ranks test. If the observed p-value is ≤ the Hochberg adjusted critical value and the mean of PLUS-M scores using the Revo-M foot is greater than PLUS-M scores using the everyday feet, the null hypothesis will be rejected in favor of the alternative hypothesis and the superiority of the Revo-M will be supported.

Primary Efficacy Endpoint #2: Level of activity restrictions as measured by the Trinity Amputation and Prosthesis Experience Scales Activity Restrictions subscale (TAPES-AR). It is hypothesized that TAPES-AR scores will be lower for subjects when they are using the Revo-M compared to their everyday feet. In statistical terms the null and alternative hypotheses are as follows:

H_O: $\mu_{Revo\text{-}M} \geq \mu_{Everyday}$

H_A: $\mu_{Revo\text{-}M} < \mu_{Everyday}$

Where H_O is the null hypothesis, $\mu_{Revo\text{-}M}$ is the mean TAPES-AR score using the Revo-M, $\mu_{Everyday}$ is the mean TAPES-AR score using the everyday feet and H_A is the alternative hypothesis indicating that level of activity restrictions as measured by the TAPES-AR is less for Revo-M than for everyday feet.

The hypothesis will be tested using a 2-sided Wilcoxon matched pairs signed ranks test. If the observed p-value is ≤ the Hochberg adjusted critical value and the mean of TAPES-AR scores using the Revo-M foot is less than TAPES-AR scores using the everyday feet, the null hypothesis will be rejected in favor of the alternative hypothesis and the superiority of the Revo-M will be supported.

Secondary Efficacy Endpoints

Secondary Efficacy Endpoint #1: Level of walking endurance as measured by the distance walked in the six-minute walk test (6MWT) and the perceived exertion (RPE) measured by Borg CR100. No hypothesis will be tested. Instead, the percentage of subjects (along with the exact 95% binomial confidence interval) with either a clinically meaningful improvement in the distance walked in the six minute walk test or a clinically meaningful decrease in the rating of perceived exertion (RPE) while wearing the Revo-M foot compared to the everyday foot will be computed. A clinically-significant improvement in the 6MWT is defined as a change in distance of greater than 45 meters [Resnik 2011]. A clinically-significant improvement in the RPE is defined as a change greater than 10 points [Ries 2005].

Secondary Efficacy Endpoint #2: Perception of balance confidence as measured by the extended Activities-specific Balance Confidence (ABC) Scale. It is hypothesized that ABC scores will be higher for subjects when they are using the Revo-M compared to their everyday feet. In statistical terms the null and alternative hypotheses are as follows:

H_O: $\mu_{Revo\text{-}M} \leq \mu_{Everyday}$

H_A: $\mu_{Revo\text{-}M} > \mu_{Everyday}$

Where H_O is the null hypothesis, $\mu_{Revo\text{-}M}$ is the mean ABC score using the Revo-M, $\mu_{Everyday}$ is the mean ABC score using the everyday feet and H_A is the alternative hypothesis indicating that balance confidence as measured by the ABC scale is greater for Revo-M than for everyday feet.

The hypothesis will be tested using a 2-sided Wilcoxon matched pairs signed ranks test. If the observed p-value is ≤ the Hochberg adjusted critical value and the mean of PLUS-M scores using the Revo-M foot is greater than PLUS-M scores using the everyday feet, the null hypothesis will be rejected in favor of the alternative hypothesis and the superiority of the Revo-M will be supported.

Secondary Efficacy Endpoint #3: Level of functional satisfaction as measured by the TAPES Functional Satisfaction (TAPES-FUN) subscale. It is hypothesized that TAPES-FUN scores will be higher for subjects when they are using the Revo-M compared to their everyday feet. In statistical terms the null and alternative hypotheses are as follows:

H_O: $\mu_{Revo\text{-}M} \leq \mu_{Everyday}$

H_A: $\mu_{Revo\text{-}M} > \mu_{Everyday}$

Where H_O is the null hypothesis, $\mu_{Revo\text{-}M}$ is the mean TAPES-FUN score using the Revo-M, $\mu_{Everyday}$ is the mean TAPES-FUN score using the everyday feet and H_A is the alternative hypothesis indicating that level of functional satisfaction as measured by the TAPES-FUN subscale is greater for Revo-M than for everyday feet.

The hypothesis will be tested using a 2-sided Wilcoxon matched pairs signed ranks test. If the observed p-value is ≤ the Hochberg adjusted critical value and the mean of TAPES-FUN scores using the Revo-M foot is greater than TAPES-FUN scores using the everyday feet, the null hypothesis will be rejected in favor of the alternative hypothesis and the superiority of the Revo-M will be supported.

Exploratory Efficacy Endpoints

Although hypotheses have not been specified, statistical testing will be done using Wilcoxon's matched pairs signed ranks test comparing Revo-M to both comparative devices, the Taleo and the ProFlex, and comparing the Revo-M to the everyday foot (baseline at the end of Period I and crossover at the end of Period IV). However, as these objectives are exploratory in nature, any statistically significant differences will be considered to be hypothesis generating and not definitive. These results may be used to guide future studies with prosthetic feet.

Time Period

Data collection for all subjects will be collected from the time of enrollment until the end of Period IV. Patients may be given the opportunity to continue in Phase V for continued follow-up with the Revo-M for an additional 6 months.

Data Analysis

Data analysis will be primarily descriptive in nature. Categorical variables (such as gender) and ordinal variables (such as severity of adverse events) will be summarized by absolute and relative (percentages) frequencies. Continuous variables (such as age) will be summarized by the mean, median, standard deviation, minimum and maximum values observed. In addition, change in continuous measures of effectiveness (such as PLUS-M scores) will be evaluated by subtracting baseline from follow-up scores. The mean, median, standard deviation, minimum and maximum values observed will be used to summarize change scores. In addition, the significance of differences between baseline and follow-up scores may be tested using Wilcoxon's matched pairs signed ranks test. Two-tailed p-values ≤ 0.05 will indicate statistical significance. Each variable will be analyzed separately. For each variable analyzed, only subjects with valid values will be included in the analysis. A subject need not have valid values on all variables to be included in the analysis of any given variable.

Risk-Benefit Analysis

The potential risks and benefits of the Revo-M as well as the comparative devices, Taleo and ProFlex XC, are identified in the Instructions for Use.

Risks and Minimization of Risks

The Revo-M devices to be assessed in this study will have undergone thorough verification testing. The risk analysis for the Revo-M prosthetic foot resulted in a list of known or expected risks as shown in the table below. All were deemed "As Low As Reasonably Possible."

Risk	Potential harm		
	Injury	Function lost	Health hazard
Damage/ Break of load bearing parts	X		
Break of functionally relevant parts	X		
Failure of the guide elements for the tension element	X	X	
The connection to the prosthesis is lost	X		
Foot twists	X		
Damage to the product during manufacture or use	X		
Incorrect alignment	X		
Not compliance with the assembly guidelines	X		
Mechanical damage	X		
Mechanical damage of load bearing parts	X	X	

Risk	Potential harm		
	Injury	Function lost	Health hazard
Use not according to the MOBIS classification	X		
Use without foot cover	X		
Overload of the prosthesis caused by unsuitable combination of prosthetic components	X		
Weight limit is not specified or not readable	X		
Safety instructions are not sufficiently described			X
Use on more than one user	X	X	
Product is used too long	X		
Exceeding the time-stability of supporting structures	X		

The following risk-minimizing measures will be taken:

- The subjects will be individually fit by an experienced CPO and instructed to report to the CPO all the problems with the prosthesis. The CPO will be trained by Ottobock in the handling of the new prosthetic foot.
- The first steps with the new prosthesis will be deliberately accompanied by exercises which accelerate adaptive behavior and train proper behavior in critical situations.
- The subjects will be instructed that in case of any technical issues concerning the prosthesis, they should stop using it until the issue is resolved and to contact the investigational site to schedule further steps.
- The participants will be informed that they should refrain from performing any activity if they do not feel confident or safe.
- All activities during in-clinic tests will be performed under the close supervision of qualified personnel.
- The Revo-M investigational device used in the study has passed a fatigue test for 750,000 gait cycles corresponding to approximately 9 months of use.

The risks to subjects inherent in study procedures are limited to those associated with the six-minute walk test. Complications associated with this test include excessive fatigue, angina, or light-headedness. Subjects' blood pressure and resting heart rate will be measured prior to the test in accordance with recommendations from the American Thoracic Society (ATS Statement, 2002). Subjects will be encouraged to stop during the test if needed to catch their breath, and the test may be stopped by the investigator if subjects exhibit symptoms listed above.

Benefits

Subjects may or may not experience benefits such as improved walking performance during the course of the study while wearing the study devices. In any case, all subjects will need to return the study devices at the end of the study and return to using their existing ESR feet. However, the study

results may help the Sponsor identify ways to improve future versions of the Revo-M. In addition, by characterizing the comparative safety and effectiveness of the Revo-M (relative to both existing ESR feet and the two comparative study feet), society, the O&P industry, and the Investigators may also benefit from the knowledge gained.

Study Management

Sponsor Responsibilities

Sponsor responsibilities include:

1. Ensuring the study is designed and managed in compliance with all appropriate regulatory standards and is conducted according to the Study Protocol.
2. Selecting Investigators qualified by training and experience to participate in the study.
3. Providing adequate training to Investigators, site research staff, and all Sponsor representatives.
4. Monitoring study data at investigational sites, including that proper informed consent is obtained prior to data collection and that patient confidentiality remains acceptable for the duration of the study.
5. Ensuring that prior to commencement of the study in each participating center, Sponsor has on file:
    a. Written IRB approval
    b. Signed Investigator's Agreement
    c. Investigator's current curriculum vitae

Investigator Responsibilities

The Investigators will strictly follow requirements as stated in the Declaration of Helsinki and applicable local laws and regulations governing the conduct of clinical studies and subject data protection. They will be responsible for conducting the study as described in the Study Protocol and for the clinical well-being of the patients involved.

Records and Reports

The Investigator must retain all records and reports pertaining to this study. Electronic CRFs will be completed via Electronic Data Capture system by the Investigator. Completed originals of the source documents will be kept by the Investigator, if applicable. In addition, the following documents will be retained by the Investigator in each study site:

1. IRB correspondence, including approval letter, approved consent forms and annual or final reports if applicable
2. Sponsor correspondence
3. Source documents, signed data collection forms, medical records, office charts

4. Qualifications and evidence of training
5. Signed informed consent forms
6. Original Study Protocol and all revisions
7. Signed Study Agreement
8. Records concerning adverse events

All study documents will be retained by the Sponsor and Investigators for at least 2 years following the end of the study or earlier if approved by the Sponsor. No study documents will be destroyed or moved to a new location without prior written approval from the Sponsor. If the Investigator relocates, retires, or withdraws from the study for any reason, all records required to be maintained for the study should be transferred to an agreed-upon designee, such as another Investigator, or the institution where the study was conducted.

Investigator Reports

Table 5: Investigator Reports

Report	Submit To	Description
Unanticipated Adverse Device Effects	IRB, Sponsor	Notification within five working days after the investigator first learns of the event.
Withdrawal of IRB Approval	Sponsor	Notification within five working days

Sponsor Records

Sponsor will maintain the following records at a minimum:

- All significant correspondence which pertains to the investigation
- Signed Investigator agreements and curriculum vitae
- System/fitting related Adverse Device Effects and complaints
- All case report forms, including samples of patient informed consents, submitted by the Investigator and the Study Protocol
- Clinic staff training and study visit reports
- Sponsor will own and store the clinical data gathered in this study

Sponsor Reports

Table 6: Sponsor Reports

Report	Submit To	Description
Unanticipated Adverse Device Effects (US)	Investigators, IRB	Notification within five working days after the sponsor first learns of the event.
Withdrawal of IRB Approval	Investigators, IRB	Notification within five working days
Annual Report	Investigators	Report detailing the annual progress of the study.
Final Report	Investigators, IRB	Sponsor will notify the Investigator(s) within 30 working days of the completion or termination of the study. The Investigators will in turn inform their IRB. A final report will be submitted to the Investigator(s) after completion or termination of this study. The Investigator should confirm the receipt of the final report composed by Sponsor. The Investigator will also forward a copy of the report to their IRB.

Monitoring procedures

The study site is required to conduct the study in accordance with the Study Protocol, all applicable laws and Federal regulations and any conditions or restrictions imposed by the reviewing IRB. The Sponsor will incorporate monitoring of the study with attention to verification of clinical requirements, adherence to Study Protocol, and compliance with applicable government and institutional regulations. If necessary, the Investigator will provide the monitor access to all necessary records to ensure the integrity of the data.

The Investigator(s) and institution(s) will permit monitoring, audits, IRB review, and regulatory inspections and provide direct access to source documents. Study sites may be monitored on a periodic basis throughout the course of the study.

Study monitors

Sponsor designated Clinical Research Specialists or appropriately trained staff will complete any monitoring for this study.

Site Visits

Site initiation visits may be made by the Monitor to review the Study Protocol and documentation requirements with the Investigator and clinic support staff involved with the study. The Sponsor will ensure that all researchers involved in the project have adequate training.

Ongoing monitoring visits of the study centers may be conducted to compare the data recorded in the eCRFs with the information contained in the original source documents (source data verification). Monitoring, when conducted, will include at a minimum the following items:

- Patient identification number
- Patient signed informed consent obtained

- Medical record of Adverse Events

Management of the study sites will be predominantly achieved by communications via letter, fax, electronic mail and/or telephone.

Site closure activities will be conducted after all patients have been enrolled and data collection has been completed if deemed necessary. Site closure may be conducted by site visits or by telephone as determined by the Sponsor.

Monitoring Reports

Reports of any monitoring visits will be prepared and maintained by the Sponsor which include:

- The date of the visit
- The name of the individual who conducted the visit
- The name and address of the Investigator visited
- Statement of the findings, conclusions and actions taken to correct any deficiencies noted during the visit

Study Discontinuation or Termination

Investigational Site Termination

The Sponsor reserves the right to terminate a research site for any of the following reasons:

1. Failure to secure Informed Consent from a patient enrolled into the study
2. Repeated Study Protocol violations
3. Repeated failure to complete Electronic Case Record Forms on a timely basis
4. Failure to report Adverse Events on a timely basis
5. The Investigator requests discontinuation

Premature Discontinuation of the study

If the study is prematurely terminated or suspended, the Sponsor or designate will promptly inform the Investigators/institutions of the termination or suspension and the reason(s) for the termination or suspension. The IRB will be informed promptly, if applicable, and provided with a detailed written explanation for the termination or suspension by the Sponsor or by the Investigator/institution, as specified by the applicable regulatory requirement(s).

Ethical Statement

Institutional Review Board (IRB)

Prior to initiation of the study, the Study Protocol, patient informed consent, and any other relevant study documentation will be submitted to a central IRB. For each participating center, IRB approval must be obtained, either through the central or local IRB, and forwarded to the Sponsor before data collection at the site can be initiated. Furthermore, any necessary extension or renewal of the IRB approval must be obtained and forwarded to the Sponsor. In particular, change(s) to any aspect of

the study, such as modification(s) of the Study Protocol, the written informed consent form, or any written information provided to patients must be approved, in writing, by the IRB.

The Investigator at the study site will report promptly to the IRB any new information that may adversely affect the conduct of the study. Similarly, the Investigator will submit written summaries of the study status to the IRB annually, or more frequently, if requested by the IRB. Upon completion of the study, the Investigator will provide the IRB with a brief report of the outcome of the study, if required.

Ethical conduct of the study

The study is to be conducted according to the approved Study Protocol. The Guidelines of the World Medical Association Declaration of Helsinki and the HIPAA Privacy Rule will be strictly followed as well as any other applicable rules and regulations.

Disclosure of data and publication policy

Disclosure of data

By signing the final Study Protocol, every participating Investigator agrees to keep all information and results concerning the study confidential for as long as the data remain unpublished. The confidentiality obligation applies to all personnel involved at the investigational site. Publication of study results requires mutual agreement between the Investigator(s) and the Sponsor.

Sponsor may disclose data derived from the study to other Investigators and domestic or foreign regulatory authorities.

Publication policy

Any proposed publications that are to make public any findings, data, or results of the study shall be submitted to the Sponsor for review and comment at least sixty (60) days prior to submission of manuscript for an abstract. In addition, the Researchers shall delay any proposed publication/presentation an additional sixty (60) days in the event Sponsor so requests in order to enable Sponsor to secure patent or other proprietary protection for any invention(s) disclosed in such publication/presentation. Sponsor reserves the exclusive right to publish the complete multicenter, accumulated results of the study and to decide, based on study conduct, compliance, and willingness of the Investigators to accept the responsibilities of authorship, which Investigators will be authors and the order of authorship e.g., first author, second author, and third author, etc., for the study group. In all publications, credit shall be given to Sponsor for its sponsorship of the study.

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Contracts, finances

In addition to the Study Protocol, study-related duties, functions and financial aspects will be specified in a separate contract between the Sponsor and the Investigator as well as any other parties involved with the study.

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