Rheo Knee 4 - Clinical Investigation Protocol

An investigation on function and performance of a new microprocessor controlled prosthetic knee

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Rheo Knee

CONFIDENTIAL DOCUMENT

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[redacted].

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• Summary

Device(s) being tested:	**Device under evaluation**: Rheo Knee 4/Navii, a pre-market passive exo-prosthetic microprocessor controlled knee device. For simplification, the device under evaluation in this Clinical Investigation will be referred to as "investigational device" throughout this document. **Comparator**: Subjects prescribed passive microprocessor knee, marketed device.	
Instruments and equipment:	**Instruments**: -PEQ ambulation subscale (Questions 13A, 13B, 13C, 13D, 14E, 14F, 14G, 14H) -PEQ Utility questions (Questions 2G, 2F) -PEQ Satisfaction Questions (Questions 16A, 16B) -L-test -Mobility measures – PLUS M, 6MWT -AMPro at baseline and FU -Qualitative interview script **Equipment**: • Investigational device (see section 5 Investigational device) • Other components as applicable (prosthetic feet, adapters) • Tools for fitting • Detailed protocol • Case report forms (CRFs); in Smart-Trial – Tablet/computer OR Printed out Case report forms (CRFs including instruments listed above) • Stopwatch/phone for 6MWT • Markers and a measured corridor/course of known distance for 6MWT and L-test • Chair for L-test and AMPro • Measuring tape • 10cm obstacle for AMPro • Qualitative Interview script	
Subjects recruited:	Inclusion criteria:	Exclusion criteria:
Phase I: 17 Phase II: TBD	45Kg< body weight < 136Kg	-Users with stump pain*
	-Cognitive ability to understand all instructions and questionnaires in the study;	-Users with socket problems**
	-Unilateral TF/KD amputees that are regular prosthesis users for at least 3 months	-Pregnant Users
	-Current MPK users (passive MPKs only)	-Users using Power Knee, Kenevo or mechanical knees as their prescribed prosthesis

	-Age ≥ 18 years	-Alignment that cannot be matched with the Rheo Knee 4 setup, as described in Instructions for use.
	-Willing and able to participate in the study and follow the protocol	-Osseointegration
	-Moderate to high active users (PLUS M T-score>40[21])	
Procedures:	There are **three** scheduled study events. [redacted] At the initial visit, the first study event, for each subject a researcher qualified to obtain informed consent will seat the subject and proceed as described in chapter **13.8 Informed consent**. Prior to fitting the subject will be asked to provide feedback on the current prosthesis, by filling in a set of questionnaires (Including background information) **and perform functional tests**. The users will be fitted within the standard methods of prosthetic fitting, alignment, introduction, training and walking on various terrain. After initial fitting, subjects will receive standard training on the investigational device by a certified prosthetist (the LPI) with support from sponsor investigators. When training is complete, and subjects feel comfortable and safe they will leave the site on the investigational device to use as their primary prosthesis in their daily life for 3 weeks. During this 3 week period the LPI will be in weekly contact with subjects via telephone to check on any issues that may arise. The second visit will be at three weeks after visit 1. During this visit subjects will complete the same functional tests and questionnaires as at visit 1 (excluding background information) on the investigational device, with the addition of a usability questionnaire. They will then be fitted back to their prescribed device. The third visit will be three weeks later. During this visit subjects will complete the same functional tests and questionnaires as at visit 2 (excluding usability questionnaire) on their prescribed device, as well as completing a qualitative interview on their experiences with both microprocessor knee devices. [redacted]	

**Question on pain affecting their functional ability (yes/no)*

***Socket fit: Socket fit comfort score less than 5*

Table 1 Summary of procedures and visits

	Recruitment phase: 2-4 weeks prior to baseline	Subject visit 1: BL prescribed device	Subject visit 2: FU RK 4/Navii	Subject visit 3: FU Prescribed device
Potential subjects identified, fitting inclusion/exclusion criteria, by LPI from customer database	X			
LPI calls potential subjects and screens by telephone	X			
Subject signs ICF		X		
Subject fills in background information questionnaire (PIS)		X		
Subject fills in validated questionnaire (PEQ, PLUS-M, ABC)		X	X	X

Subject fitted with investigational device and receives training according to training protocol	X		
Subject fills in usability questionnaire for the investigational device		X	
Subject is fitted back to their prescribed prosthesis		X	
LPI prints out activity report from the investigational device/ prescribed device		X	X
Subject completes qualitative interview			X
End of study			X

Changes from Previous Revision

Changes for Revision 1.00

Initial release.

Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
ASADE	Anticipated Serious Adverse Device Effect
BL	Baseline
CI	Co-Investigator
COI	Coordinating Investigator
CIB	Clinical Investigator´s Brochure
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRF	Case Report Form
DD	Device Deficiency
EDS	Electronic Data capture System
FU	Follow-Up
GCP	Good Clinical Practice
ICF	Informed Consent Form
IDMF	Investigational Device Management Form
IFU	Instructions For Use
IRB	Independent/Institutional Review Board
LCI	Local Co-Investigator
LPI	Local Principal Investigator
LRA	Local Research Assistant
PI	Principle Investigator
PIS	Participant Information Sheet
SAE	Serious Adverse Event
SADE	Serious Adverse Device Event
SCI	Sponsor Co-investigator
SOTA	State-Of-The-Art
SRA	Sponsor Research Assistant
UE	Use Error
UADE	Unanticipated Adverse Device Effect

• Investigational Device

The investigational device is a pre-market device and will be labeled according to regulations concerning pre-marketed investigational devices.

See Table 2 for details on the investigational device.

Table 2 Identification and Description of the Investigational Device

Summary description of the investigational device and its intended purpose:	The investigational device, [redacted] is a passive microprocessor-controlled prosthetic knee. It is a Class I product and is a further development of a well-established technology. The device is classified as an "*External assembled lower limb prosthesis"* according to *Title 21 §890.3500*, bearing the product code *ISW (Assembly, Knee/Shank/Ankle/Foot, External)* It is 510(k) exempt, except for general requirements. It is composed of a microprocessor-controlled prosthetic knee, a power supply and a configuration software. [redacted] The investigational device supports prosthetic use from simple locomotion to ambulation with variable cadence and traverse of various terrains. Additionally, it offers features as step-over-step stairs and ramp walking, running, and cycling. Exo-prosthetic devices are by their nature non-invasive. The investigational device is a non-sterile, reusable (i.e. non-disposable), single user device, which is used as part of prosthetic system. The Investigational device is a programmable electrical medical system (PEMS). Its essential performance is defined as structural support, as loss of structural support does not allow the device to fulfill its intended use. Loss of the PEMS related operation on the other hand allows the user to continue walking even if the performance and feature set provided by the device are reduced. The Investigational device is an internally powered device when operated in its intended medical purpose. ***Device Intended purpose:*** The Investigational device is intended as part of a prosthetic system that replaces knee function of a missing lower limb.
Manufacturer of the investigational device:	Össur hf. Grjothals 5 110 Reykjavik Iceland
Name or number of the model/type, including	Model: NAVII [redacted]

software version and accessories, if any, to permit full identification:	
Traceability during and after the investigation:	Investigation Device Management Form (IDMF) will be used to track the use of each device within the clinical investigation using the device serial number.
Intended purpose of the investigational device in the proposed clinical investigation:	Intended purpose of the investigational device in the proposed clinical investigation is within the intended purpose as described above. See following chapters on the intended purpose of the investigational device in the proposed clinical investigation for details.
The populations and indications for which the investigational device is intended:	***Indications for use:*** Lower limb amputation(s). No contraindications for use are known for the investigational device. ***Intended patient population:*** *Medical conditions:* Unilateral transfemoral / knee disarticulation amputation; *Activity Level:* Moderate to high-active ambulators Community ambulators; Ambulation exceeding basic ambulation needs or skills. *Impact Level:* Low to high impact levels. *User Weight:* Higher than 45kg; Lower than 136kg (110kg for high impact use). [redacted]
Description of the investigational device:	See Table 3 below for descriptions of device features and their relation to the investigation.

	 **Figure 1 Rheo Knee 4/Navii final product** The investigational device is composed of a microprocessor-controlled prosthetic knee, a power supply and a configuration software. [redacted] The aspect of the prosthesis that is in direct physical contact with the amputee is usually a liner that serves as an interface between the amputee and the rest of the prosthesis. In other words, the device is usually not in direct physical contact with the amputee. As described above, the device is intended to be in contact with intact skin only. The device does not incorporate, as an integral part, a substance or human blood derivative and is manufactured without utilizing tissues of animal origin.
Summary of the necessary training and experience needed to use the investigational device:	Training requirements for subjects and procedures relating to fitting and use of a device will for all general purposes be equivalent to the training and procedures required for using a FDA approved/CE-marked device of a similar type. The device should be supplied and fitted by a certified CPO/CO/CP. For the purpose of this investigation training for subjects will be standardized to assure that all subjects will receive the same training.
Specific medical or surgical procedures involved in the use of the investigational device:	N/A

Table 3 [redacted]

[redacted]			

• Justification for the Design of the Clinical Investigation

The term microprocessor-controlled (MPC) refers to components that are intelligently regulated in real time by one or more onboard microprocessors that modify some characteristic of their behavior according to either environmental or user inputs.[1] MPC prosthetic knees, often referred to as MPKs, are battery-powered and use algorithms based on input received from load sensors, accelerometers, gyroscopes, and joint angles to initiate the transition from stance to swing phase [2-6]. MPC prosthesis have been shown to offer clinical advantages compared with mechanically controlled alternatives,[7] and appears to be the direction of development in contemporary prosthetic research and development.[8]

The main advantage is an increased ability to allow safe ambulation [2,4,5,9-11], reduced cognitive dedication to controlling the knee unit,[2,12] reduced force required to initiate knee flexion,[10] increased gait efficiency,[2,4] and increased overall user confidence with the prosthesis [2,5]. The MPC knee increases comfort and improves walking speed in active users. [4,6,13,14,] The main disadvantage has been the intolerance of dust or moisture, and its increased requirement for maintenance and repair.[15]

Microprocessor Controlled Knees (MPK) have become the standard of care for trans-femoral amputees of medium to high activity levels (K3-K4). While the functional principles of the different knee joints remain the same, differences in the mechanical design can be found.

The Rheo Knee 4/Navii is a microprocessor-controlled prosthetic knee and employs sensory information, to automatically adapt knee damping values to match the amputee's gait requirements, accounting for variations in forward walking speed, walking terrain, user gait styles and body size. The Rheo Knee 4/Navii technology generates resistances with a microprocessor-controlled, magnetorheological fluid, which enables continuous variation of knee joint resistances in both movement directions. The amount of current determines the viscosity of the fluid. Therefore, an adaptable friction moment is generated for both flexion and extension movements at the same time. In this study there are two types of comparator devices, hydraulic MPKs and previous version of the Rheo knee 4/Navii.

Hydraulic MPKs consist of an integrated microprocessor-controlled linear hydraulic system in combination with a control algorithm. They generate knee joint resistances hydraulically with microprocessor-controlled, motorized valves. This enables continuous variations in the hydraulic resistance to be set for both movement directions. The magnetorheological fluid creates shear forces in comparison to an increase of pressure in a hydraulic system. The increased system pressure can lead to higher temperatures and risk of leakage.

The previous version of the Rheo knee/Navii (RK III/RK XC) features the same intended use, same clinical purpose, same user population, same placement below the socket, uses a battery powered system and is controlled through a software application that can be user configured through a separate computer interface/mobile device. The Rheo Knee 4/Navii is an enhancement of the previous version, functional features and indication are equivalent to previous version and the same critical functions apply. Features that have been added include a mechanical stance locking feature that allows the user to manually lock the knee in 3 different positions in stance and the device will be waterproof. The Rheo Knee 4/Navii also includes functions that were only included in the Rheo Knee XC configuration of the previous version; automatic cycling and running detection and a stair ascent mode.

Results of a pilot stage exploratory clinical investigation including 25 subjects indicate that the investigational device had similar or better performance compared to previous versions of the Rheo knee regarding satisfaction on descending activities. This investigation is designed primarily to confirm these indications and that the performance of the investigational device regarding descending activities is comparable/no worse than hydraulic MPKs.

Considering previous experience with clinical investigations in prosthetics it was concluded to conduct a non-randomized prospective repeated measures (ABA) design, comparing subjects' current MPK at baseline and 3-week follow-up vs. the investigational device at 3-week follow-up. See Figure 2 Study design and instruments below;

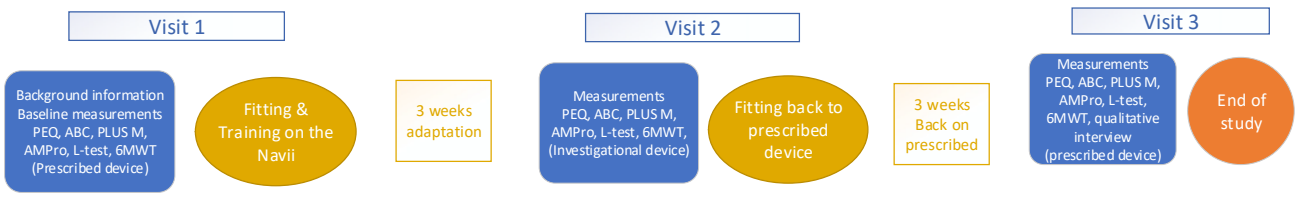

Figure 2 Study design and instruments

Repeated measures analysis has the advantage of increased power compared to group allocations and reduction in error variance associated with individual difference, as each subject acts as its own control. This is important for studying amputees as the group is a small proportion of the total population, and with specific inclusion/exclusion criteria the total eligible population becomes very small, making it difficult to find and recruit subjects to attain an

acceptable level of power. This limited population pool often results in a slightly heterogeneous sample, as the amputees available are few and far between, in every sense. Furthermore, no single amputation procedure and therefore amputated stump is exactly the same, making the experience of each amputee unique. The within-subject design significantly reduces the individual differences when comparing the two conditions.

Once on the market the investigational device will be intended for Unilateral hip-disarticulation or hemipelvectomy amputation and Bilateral amputations that combine unilateral amputation on one side with transfemoral level amputation or any amputation below that level on the contralateral side. But these will not be included in this investigation as the device has not been fully validated in those populations and, to reduce the variability of the sample.

The drawback of the design is the potential of “carryover effects”, i.e. experience from one condition can affect outcome or performance in the other condition, creating a confounding extraneous variable that varies with the independent variable. Such effects are: practice, positive carryover effect to the latter condition; and fatigue, negative carryover effect to the latter condition.

Along with evaluating the performance aspects listed in Table 4 in Ch. 7, the clinical investigation is designed to evaluate whether the investigational device is suitable for the purposes and the population for which it is intended (excluding unilateral hemi-pelvectomy and hip disarticulation and bilateral prosthesis users). It is designed in such a way as to ensure that the results obtained have clinical relevance and scientific validity and address the clinical investigation objectives.

The study design includes a qualitative interview at the end of the last follow up period. The interview is meant to gather additional information on the experiences of the subjects in general as well as on the investigational device and, the comparison with their prescribed device regarding specific aspects e.g. safety and security.

Several studies have provided evidence for the clinical performance of previous versions of the Rheo Knee, which is equivalent to the investigational device and has the same function and intended use, those are detailed in the Literature review device report **[1]**.

For full details of existing clinical data and pre-clinical data on the investigational device see Investigators Brochure **[2]**.

• Objectives and Hypotheses

The primary objective of this study is to evaluate the efficacy of the investigational device compared to other passive MPKs (Rheo Knee 4, C-leg 4, Genium, X3, Plié 3, Orion 3, Quattro, Allux) regarding satisfaction in descending activities for moderate to high active prosthesis users within the intended population for the investigational device.

Additionally, to evaluate the balance confidence, perception of safety and comfort in standing with the investigational device compared to other passive MPKs (Rheo Knee 4, C-leg 4, Genium, X3, Plié 3, Orion 3, Quattro, Allux).

For justification of study design please refer to **Chapter** □ above.

In phase I the performance in descending activities will be compared to any other passive MPK and in phase II there will be a subgroup analysis comparing to hydraulic MPKs and Rheo Knee 3, specifically.

The following clinical claims/MNBA items as defined in the Clinical evaluation plan **[3]** are to be evaluated:

[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

***Hydraulic MPK*

No risks or anticipated adverse device effects (ADE) are to be assessed.

The hypothesis and endpoints are specified in Table 5.

For all hypothesis:
$\mu_1 is\ average\ of\ measurements\ at\ baseline\ (comparator)$;
$\mu_2 is\ the\ average\ of\ measurements\ at\ 3\ week\ follow\ up\ (investigational\ device)$;
$\mu_3 is\ the\ average\ of\ measurements\ at\ 4\ week\ follow\ up\ (comparator)$;

Phase I – Pre-launch

[redacted]

Data collected at phase I may be used to inform sample size needed for phase II if needed, as researchers will be using the same procedures as in phase I.

Table 5 Phase I Endpoints, test methods and hypotheses

	Hypothesis	Test Methods	Endpoints	Acceptance Criteria
1A1	**Users rate their satisfaction in stair descent on the Rheo knee 4/Navii as no worse compared their prescribed MPK**	**Self report:** **Modified PEQ ampulation subscale (item 13D)** *Please rate how you felt about being able to walk down stairs when using your prosthesis/the test prosthesis?* *1=cannot, 10=No problem*	Rating (1-10)	No worse rating compared to prescribed MPK $(89\%\ HDI_{low} \geq 0$ $pd > 97{,}0\%$ $ROPE < 2{,}5\%)$
1A2	**Users rate their satisfaction in hill descent on the Rheo knee 4/Navii as no worse compared their prescribed MPK**	**Self-Report:** **Modified PEQ ambulation subscale (item 14F)** *Please rate your ability to walk down a steep hill when using your prosthesis/the test prosthesis?* *1=cannot, 10=No problem*	Rating (1-10)	No worse rating compared to prescribed MPK $89\%\ HDI_{low} \geq 0$ $pd > 97{,}0\%$ $ROPE < 2{,}5\%)$
1B	**Users balance confidence on the Rheo knee 4/Navii is no worse than on their prescribed MPK**	**Self-Report** (ABC Balance confidence scale) Support question:	ABC score (0-100%)	No worse ABC score than on prescribed MPK $89\%\ HDI_{low} \geq 0$ $pd > 97{,}0\%$ $ROPE < 2{,}5\%)$

		Modified PEQ Satisfaction Question (16A) *Please rate how safe you have felt with your prosthesis/the test prosthesis?* *(1=extremely unsafe, 10=extremely safe)*		
1C	**Users standing comfort on the Rheo knee 4/Navii is improved compared to on their prescribed MPK**	**Self-Report:** **PEQ item 1D** *Please rate your comfort while standing when* *using your prosthesis/the test prosthesis.* *(1=terrible, 10=excellent)*	Rating (1-10)	Rating of comfort improved compared to prescribed MPK $(89\%\ HDI_{low} \geq 0$ $pd > 97{,}0\%$ $ROPE < 2{,}5\%\ )$
Exploratory/Secondary				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Phase 2 (after launch)

Clarification: More subjects may be recruited after launch of the product in order to carry out a subgroup analysis, making a technology specific comparison (hydraulic & magnetorheologic MPKs compared to Rheo knee 4/Navii). Procedures will be the same as in phase I in order to be able to combine the data from all subjects in each subgroup. Therefore, subjects will be assigned to subgroups based on their prescribed MPK at the second phase of the analysis.

Data collected at phase I may be used to inform sample size needed for phase II, as researchers will be using the same procedures as in phase I.

Table 6 Phase II – Endpoints, test methods and hypotheses

#	Hypothesis	Test Methods	Endpoints	Acceptance Criteria
2A1	**Users satisfaction on functioning on the Rheo knee 4/Navii in <u>hill/ramp descent</u> is no worse compared to *hydraulic MPKs***	**Self Report:** **Modified PEQ ambulation subscale (item 14F)** *Please rate your ability to walk down a steep hill when using your prosthesis/the test prosthesis?* *1=cannot, 10=No problem*	Rating (1-10)	No worse rating compared to prescribed hydraulic MPK $(89\%\ HDI_{low} \geq 0$ $pd > 97{,}0\%$ $ROPE < 2{,}5\%)$
2A2	**Users satisfaction on functioning on the Rheo knee 4/Navii in <u>hill/ramp descent</u> is improved compared to *Rheo Knee 3***	**Self Report:** **Modified PEQ ambulation subscale (item 14F)** *Please rate your ability to walk down a steep hill when using your prosthesi/the test prosthesis?* *1=cannot, 10=No problem*	Rating (1-10)	Improved rating compared to prescribed magnetorheologic MPK $(89\%\ HDI_{low} \geq 0$ $pd > 97{,}0\%$ $ROPE < 2{,}5\%)$
2B1	**Users satisfaction on functioning on the Rheo knee 4/Navii in <u>stair descent</u> is no worse compared to *hydraulic MPKs***	**Self report:** **Modified PEQ ampulation subscale (item 13D)** *Please rate how you felt about being able to walk down stairs when using your prosthesis/the test prosthesis?* *1=cannot, 10=No problem*	Rating (1-10)	No worse rating compared to prescribed hydraulic MPK $89\%\ HDI_{low} \geq 0$ $pd > 97{,}0\%$ $ROPE < 2{,}5\%)$

2B2	**Users satisfaction on functioning on the Rheo knee 4/Navii in <u>stair descent</u> is improved compared to *Rheo Knee 3***	**Self report:** **Modified PEQ ampulation subscale (item 13D)** *Please rate how you felt about being able to walk down stairs when using your prosthesis/the test prosthesis?* *1=cannot, 10=No problem*	Rating (1-10)	Improved rating compared to prescribed magentorheologic MPK $(89\%\ HDI_{low} \geq 0$ $pd > 97{,}0\%$ $ROPE < 2{,}5\%\ )$

• Design of the Clinical Investigation

• General

The test will be a non-randomized single group open label prospective repeated measures (ABA) design.

Amputees are a small proportion of the general population. The population group specified in the inclusion/exclusion criteria is a further subsample of amputees. For practical reasons, i.e. to achieve statistical power, it is therefore more feasible to use within-subject comparison rather than creating study arms to compare. Furthermore, as mobile amputees generally have and use a prosthetic device for their daily activities, within-comparison is feasible comparing to the subject's previous device.

All investigational activities will be conducted at prosthetic out-patient clinics.

As stated above the primary endpoint is Satisfaction on descending stairs, see Table 5, and the secondary endpoints are satisfaction on descending ramps, balance confidence and standing comfort in that respective order of significance. In addition, there are two exploratory endpoints on mobility and balance during ambulation. See previous chapter on objectives and hypothesis and Table 5 for rationale.

Drop-outs and withdrawals may be replaced if deemed necessary to fulfil the methodological standards of the study.

Instruments for data collection will include the following:

<u>The Six Minute Walk test (6MWT</u>) is simply a record of the distance traveled by a given patient at his or her self-selected walking speed over a period of six minutes. All that is required is a stopwatch and a walking corridor or track of known distance[16,17].

<u>The Amputee mobility predictor (AMPro) is</u> a 20-item scale that was originally developed to provide a more objective approach to the assignment of Medicare K-levels. The scale includes tasks intended to assess sitting balance, transfers, standing balance, gait, and obstacle negotiation and takes around 15 minutes to administer[17].

<u>The Prosthesis Evaluation Questionnaire (PEQ)</u> measures prosthetic-related quality of life. It consists of 82 items grouped into nine subscales. In addition, there are individual questions not contained in the subscales regarding satisfaction, pain, transfers, prosthetic care, self-efficacy, and importance[18]. This study will include a set of subscales from the PEQ, including specific questions on descending activities.

<u>L-test of functional mobility</u> is a modified version of the Timed up and go test (TUG) developed for more active lower limb amputees. The patient begins the test seated in a chair, ideally positioned in an exam room and facing the entrance to the hallway. The patient rises from the chair, walks three meters into the hallway, turns 90 degrees and then walks an additional seven meters down the hallway. Upon completing seven meters, he turns 180

degrees, returns down the hallway, turns 90 degrees to face the exam room, and returns the three meters to his chair, where he retakes his seat[19]

The Plus-M is a self-report instrument for measuring mobility of adults (age 18+) with lower limb amputation who have experience of using a prosthesis. PLUS-M measures prosthetis users' mobility (i.e., their ability to move intentionally and independently from one place to another). The questions assess respondents' perceived ability to carry out specific activities that require use of both limbs. PLUS-M questions cover movements that range from basic ambulation such as walking a short distance indoors to more complex outdoor activities such as hiking for long distances[20,21].

Usability questionnaire: In-house generated questionnaire on specific features in the investigational device e.g. water proof, interaction with the app, running and cycling mode.

Video

Data logging by Össur Logic

Qualitative interview

See Error! Reference source not found. **Appendix I** for details of all instruments to be used and Error! Reference source not found. **Appendix II** for qualitative interview script.

See chapter **10.2 Sample size calculation** and **Table 5** for analysis of variables.

Equipment required for each subject:

- Investigational device (see section Investigational device)
- Other components as applicable (prosthetic feet, adapters)
- Tools for fitting
- Detailed protocol
- Case report forms (CRFs) in Smart-Trial – Tablet/computer **OR** Printed out Case report forms (CRFs including instruments listed above)
- Stopwatch/phone for 6MWT
- Markers and a measured corridor/course of known distance for 6MWT and L-test
- Chair for L-test and AMPro
- Measuring tape
- 10cm obstacle for AMPro
- Qualitative Interview script

The equipment used does not require specific monitoring, maintenance, or calibration procedures.

• Investigational Device(s) and Comparator(s)

The subjects will be asked to use the investigational device as their primary prosthesis for **3** weeks. Individual exposure will differ between subjects. Subjects are expected to use it for their daily living activities as they would with any other prosthesis.

Subjects will evaluate and provide feedback on their exposure of the comparator prior to them being fitted to the investigational device and again after 3 week follow up after completing follow up on the investigational device.

The comparator device **will be any other passive microprocessor controlled prosthetic knee** (excluding Kenevo as it does not have the same intended patient population as the investigational device). They have the same intended use as the investigational device. Furthermore, they are indicated for the same condition and population group. MPKs are widely accepted devices, providing clinical benefits to the user.

Where possible, the subject will be using the remaining part of their current prosthetic system with the investigational device, as it was used with the comparator device. In some cases where a subject is using components from other manufacturers (e.g. feet not validated for use with the investigational device) compatible components will be provided.

No other device, medication or intervention will be used.

For Phase I, 17 subjects are to be enrolled and therefore **20** investigational devices will be used, as the devices are intended to be used by a single patient; one for each subject. The number of 20 investigational devices includes replacement units in case of failure.

For Phase II, the number of investigational devices will depend on the sample size, which will determined using data from phase I.

• Subjects

All subjects will be dispositioned as follows:

- Screen Failure: Subject did not pass screening procedures, not called in for clinical visit;
- Candidate for enrollment: Passed screening procedures, accepts to come in for clinical visit;
- Enrolled: Subject signs informed consent and takes part in the first experimental session;
- Fitted: Subject leaves the clinic on the investigational device;
- Drop-out: Enrolled subject whose participation ended because they did not want to continue participation.
- Discontinued: Candidate for enrollment or Enrolled subject whose participation ended because they withdrew consent, were withdrawn by the Investigator, were lost to follow up, or died.

Table 7 Inclusion/Exclusion criteria

Inclusion: Only patients with the following characteristics are eligible for study entry:	**Exclusion**: Patients with the following characteristics are not eligible for study entry:
-45Kg< body weight < 136Kg	-Users with stump pain*
-Cognitive ability to understand all instructions and questionnaires in the study;	-Users with socket problems**
-Unilateral TF/KD amputees that are regular prosthesis users for at least 3 months	-Pregnant Users
-Current MPK users (passive MPKs only)	-Users using Power Knee, Kenevo or mechanical knees as their prescribed prosthesis
-Age ≥ 18 years	-Alignment that cannot be matched with the Rheo Knee 4 setup, as described in Instructions for use.
-Willing and able to participate in the study and follow the protocol	-Osseointegration
-Moderate to high active users (PLUS M T-score>40[21])	

**Question on pain affecting their functional ability (yes/no)*

***Socket fit: Socket fit comfort score over 5*

A subject can withdraw from participation at any time, at his/her discretion, and this will not have any consequences for the participant's treatment. In such cases a report stating reasons for discontinuation of the participant shall be prepared by the **LPI**. No further investigational procedures concerning the subject will be conducted, except for a statement explaining the reason for withdrawal, including but not limited to: interacting or interviewing the subject in order to obtain data on him/her; obtaining additional private information on the subject by either observing the subject or collecting or receiving such information from any source.

The **LPI** can withdraw the participant from the trial at any time. The reasons shall be documented. There are no pre-specified criteria for discontinuation of participants from the trial. The discontinuation of participants in the trial may result in replacement with new participants. If withdrawal is due to problems related to the investigational device the participant will be asked for permission to follow the status/condition outside the clinical investigation. The follow-up will be individualized.

Subjects will be enrolled at the clinic, the investigational site that they were contacted from.

The total time period required to implement the clinical investigation (**phase I**) is expected to be **8 weeks**. Each individual subject is expected to participate in the clinical investigation for **5 weeks**. The estimated time needed to include this number (enrolment period) is **2 weeks.**

The estimated time period needed to implement **phase II** will depend on the number of subjects needed for that phase, but it is anticipated it will take around **8-10 weeks.**

14 subjects are required to finish the protocol for statistical data analysis, as specified in chapter **10.2 Sample size calculation**.

- Procedures

i) Recruitment

Potential subjects will be identified from the customer base of the Local Principal Investigator (LPI). LPI evaluates, based on previous experience of interaction with and servicing of patients, if a potential participant **is cognitively capable.** If a potential participant fits the inclusion and exclusion criteria the LPI will contact them via telephone. During the telephone call the LPI will verify if they are interested in participating in a study. If interest is expressed at this point they will answer some screening questions and if the eligibility criteria are met an appointment will be made for the clinical visit and signing of the ICF. Questions relating to the duration of the study, number of clinical visits required and the investigational device will be answered.

Potential risk of participating in the investigation will be explained to the subject at this point to the candidate for enrolment.

The LPI will communicate to the study monitor and sponsor co-investigator the number of users he has identified that meet the inclusion criteria and are willing to participate.

ii) Test procedure

There are **three** scheduled study events. **Three sites** will be included in the study, **4-10 users** will be recruited at each site. At the initial visit, the first study event, for each subject a researcher qualified to obtain informed consent will seat the subject and proceed as described in chapter **13.8 Informed consent**.

Prior to fitting the subject will be asked to provide feedback on the current prosthesis, by filling in a set of questionnaires (Including background information) **and perform functional tests**. The users will be fitted within the standard methods of prosthetic fitting, alignment, introduction, training and walking on various terrain.

After initial fitting, subjects will receive standard training on the investigational device by a certified prosthetist (the LPI) with support from sponsor investigators. When training is complete, and subjects feel comfortable and safe they will leave the site on the investigational device to use as their primary prosthesis in their daily life for 3 weeks. During this 3 week period the LPI will be in weekly contact with subjects via telephone to check on any issues that may arise.

The second visit will be at three weeks after visit 1. During this visit subjects will complete the same functional tests and questionnaires as at visit 1 (excluding background information) on the investigational device, with the addition of a usability questionnaire. They will then be fitted back to their prescribed device.

The third visit will be three weeks later. During this visit subjects will complete the same functional tests and questionnaires as at visit 2 (excluding usability questionnaire) on their prescribed device, as well as completing a qualitative interview on their experiences with both microprocessor knee devices.

iii) Measurements and data collection

The same questionnaires, consisting of three valid instruments (PEQ questions, PLUS-M and ABC), will be used and filled in at three separate points in time. Background information will be collected at baseline only, usability questionnaire at visit 2 only and qualitative interview at visit 3 only. An activity report will be generated from the investigational device at visit 2 and an activity report from subjects prescribed device at visit 3, if applicable.

Table 8 Visit schedule and procedures

	Recruitment phase: 2-4 weeks prior to baseline	Subject visit 1: BL prescribed device	Subject visit 2: FU RK 4/Navii	Subject visit 3: FU Prescribed device
Potential subjects identified, fitting inclusion/exclusion criteria, by LPI from customer database	X			

LPI calls potential subjects and screens by telephone	X			
Subject signs ICF		X		
Subject fills in background information questionnaire (PIS)		X		
Subject fills in validated questionnaire (PEQ, PLUS-M, ABC)		X	X	X
Subject fitted with investigational device and receives training according to training protocol		X		
Subject fills in usability questionnaire for the investigational device			X	
Subject is fitted back to their prescribed prosthesis			X	
LPI prints out activity report from the investigational device/ prescribed device			X	X
Subject completes qualitative interview				X
End of study				X

For each subject there are **three** scheduled **visits** to the study site and **questionnaires and functional tests are** administrated **three** times during the course of the study.

- Compensation

iv) Subject

[redacted]

- Responsibilities

Sponsor Principal Investigator (PI)

- Identify sites
- Collect Data
- Investigate possible vigilance cases/SAEs
- Monitor trial
- Technical support

Monitor

- Train site staff on study procedures
- Monitor trial
- Analyze results
- Write report

Sponsor Co-Investigators (SCI)

- Train site staff on study procedures
- Collect Data
- Analyze results

- Write report
- Technical support
- Conduct Qualitative Interviews
- Support with study documentation

Sponsor Research assistants (SRA)

- Technical support

Local co-investigator

- Collect data

Local Principal Investigator (LPI)

- Screen subjects
- Explain trial to participants
- Responsible for obtaining informed consent from test subjects
- Conduct trial procedures at investigators' site
- Collect Data
- Fit users with trial device and provide training and back to their current prosthesis
- Manage study documentation

Study monitoring and Oversight

The study monitor(s) will monitor the study to ensure all procedures are followed correctly and according to the study protocol. The study monitor will gather and review all study data and inform the LPI of missing data or nonconformities to the study protocol.

The study monitor(s) and **LPI** will maintain communication on a minimum biweekly basis, via telephone and email. The **LPI** will provide the study monitor(s) with information of all scheduled study visits. The study monitor will visit each investigational site at least once while a study visit takes place.

Investigational Device Accountability

The investigational device will be provided as needed for the study population. Devices will not be packaged but will be labeled according to **FDA** regulatory requirements. Subjects will not be blinded.

The **LPI** will keep records documenting the receipt, use and return of the investigational device in the Investigational Device Management Form, including:

- Date of receipt
- ID of each investigational device
- Period of use
- Subject ID
- Date of device return
- Date of return of unused, expired or malfunctioning investigational devices, as applicable

Statistical Considerations

Statistical design and procedures

The design will be a non-randomized single group open label prospective repeated measures (ABA). Thereby, differences in efficacies of two classes of MPKs are investigated. For each hypothesis (1A1, 1A2, 1B, 1C), i, the population parameter for Rheo Knee 4/Navii, μ_{i1} is compared to the corresponding population parameter for other MPKs, μ_{i2}. For each research question i , the null and hypothesis is $H_{0i}: \mu_{i1} = \mu_{i2}$, and the alternative hypothesis is $H_{Ai}: \mu_{i1} \neq \mu_{i2}$. Hypotheses are investigated using a Bayesian regression framework. Evidence for H_{0i} or H_{1i} is collected using the posterior distribution of differences in efficacies for each hypothesis. Using the posterior distribution, statistical measures as the 89% high density interval (HDI), the percentage in the region of practical equivalence (% ROPE), and the probability of direction (PD) will be used to gather evidence for or against each hypothesis.

Acceptance criteria relate to the 89% HDI. An 89% HDI not covering 0 indicates a true difference between the two groups.

For trial phase II, a similar procedure will be performed and uses adjusted priors for model generation. These priors will be generated from the posterior distribution of the first trial, therefore making the prior more informative.

Using bayes theorem, the distribution of differences for each characteristic is represented by the posterior distribution and the high density interval will be used. A percentage of 89% for the HDI will be used because it was shown to be more stable than the 95% HDI. A specific significance level as in the frequentist approach is not used, although the % ROPE is related to a frequentists P value, and therefore a significance level.

For phase II, Bayesian power analysis will be performed to identify appropriate sample sizes. Sample sizes for each group that result in a power >80% are considered to be appropriate. Statistical power will be calculated using simulation studies. For any combination of sample sizes, the percentage of simulations where the minimum of the HDI will be >0 (therefore indicating a true effect (or difference) between the groups for a specific hypothesis) is equal to statistical power.

Repeated measures analysis has the advantage of increased power vis-à-vis group allocations and reduction in error variance associated with induvial difference, as each subject acts as its own control. This is important for studying amputees as the group is a small proportion of the total population, and with specific inclusion/exclusion criteria the total eligible population becomes very small, making it difficult to find and recruit subjects to attain an acceptable level of power. This limited population pool often results in slightly heterogeneous sample, as the amputees available are few and far between, in every sense. Furthermore, no single amputation procedure and therefore amputated stump is exactly the same, making the experience of each amputee a bit unique. The within-subject design significantly reduces the individual differences when comparing the two conditions.

The drawback of the design is the potential of “carryover effects”, i.e. experience from one condition can affect outcome or performance in the other condition, creating a confounding extraneous variable that varies with the independent variable. Such effects are: practice, positive carryover effect to the latter condition; and fatigue, negative carryover effect to the latter condition.

Sample size calculation

[redacted]

[redacted]

Total sample size = 14

Actual power = 0.9600638

It is therefore expected that **14** subjects are required to complete the protocol with a power of 0,**95** and significance at 0,**05**. Effect size was estimated based on previous in-house studies on the previous version of the product for the primary end-point.

Given a drop-out rate of **20**%, **17** subjects will be recruited.

For pass/fail criteria, see Table 4 **Endpoints, test methods and hypotheses**.

Phase II:

Sample size calculations for phase II will be done using data from phase I.

• Additional statistical matters

There is no criteria for early termination of the clinical investigation on statistical grounds.

Any deviations from the statistical plan provided in this protocol will have to be approved by the sponsor and the reasons for the deviation reported in the clinical investigational report. Drop-outs and withdrawn participants will be included in the data analysis for the procedures that they completed. They will be grouped together and compared to the group that finished the protocol. Any statistical differences of the two groups will be reported. If the participants have not provided any data, they will not be included in the data analysis. No particular information will be excluded from the statistical analysis and tests, as described above.

• Amendments and Deviations from the Protocol (CIP)

• Amendments

Any amendments to this protocol must be first approved by the sponsor and PI, and then be evaluated by the overseeing IRB and, where appropriate regulatory authorities, before being implemented.

For non-substantial changes (e.g. minor logistical or administrative changes, change of monitor(s), telephone numbers, renewal of insurance) not affecting the rights, safety and well-being of human subjects or not related to the clinical investigation objectives or endpoints, a simple notification to the IRB and, where appropriate, regulatory authorities can be sufficient.

• Deviations

Investigators are not allowed to deviate from this protocol without a formal approval from the IRB, if the deviation affects subject's rights, safety and wellbeing, or the scientific integrity of the clinical investigation. Any such deviation from the protocol is to be documented in detail and the report sent to the IRB.

Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the sponsor and the IRB. Such deviations shall be documented and reported to the sponsor and the IRB as soon as possible.

Investigators can request for an approval from the sponsor for a deviation if the deviation does not affect subject's rights, safety and wellbeing, or the scientific integrity of the clinical investigation.

In case of a deviation from this protocol taking place without prior approval from the sponsor, and IRB as applicable, it shall be reported to the sponsor within 24 hours of LPI knowledge of the deviation. The LPI responsible for the deviation is to send a report to the sponsor no later than five days after the deviation was reported. The report shall include:

- Reason for deviation

- When deviation took place
- Circumstances of the event
- Identification of all subjects affected by the deviation, if any
    - Details how each subject is affected, e.g. rights, safety or wellbeing
- Details how this deviation might affect the scientific integrity of the clinical investigation

The sponsor and the IRB will evaluate any deviations that take place without prior approval on a case-by-case basis. If the deviation affects subject's rights, safety and/or wellbeing, and the scientific integrity of the clinical investigation the LPI shall be disqualified from further participation in the clinical investigation.

• Statement of Compliance

The clinical investigation is sponsored by Össur Iceland ehf.

It shall be conducted:

- in accordance with the ethical principles that have their origin in the Declaration of Helsinki
- in compliance with the ISO 14155 [redacted] International Standard
- in compliance with any regional or national legislations, as applicable

The clinical investigation shall not commence until the required approval from the IRB, and regulatory authority as applicable, has been obtained.

Any additional requirements imposed by the IRB or regulatory authority shall be followed, as applicable.

[redacted]

• Ethical Considerations

• Anticipated clinical benefits

A patient using the investigational device may or may not benefit clinically from using the device vis-a-vis using another microprocessor controlled prosthetic knee (MPK) commercially available. Compared to not using a microprocessor controlled prosthetic knee the patient will benefit significantly in terms of mobility and ability to live independently. Further on the user will be trained on a new prosthetic component to experience the unprecedented functionality of the new component to mitigate the known deficiencies associated with his/her amputation. Within the test he/she will be trained on restoring physiological movement pattern closer to those of non-amputees.

Anticipated benefits include, among others: ramp navigation comparable to other passive MPKs; improved standing comfort and perception of safety comparable to other passive MPK. See chapter 6 for details.

Additionally, the benefit for the user during the testing is that he/she helps in developing a new microprocessor controlled prosthetic knee.

• Device related risk

Each device designed and manufactured by Össur is subjected to thorough risk assessment, analysis and control, with failure mode effect analysis and hazard analysis, according to PR-00032 Risk Management process, based on ISO 14971 [redacted] (Risk Management for Medical Devices). All changes performed to the software and/or functions of a device are submitted to multi-level verification and, as applicable, validation processes before being authorized for use in a clinical investigation.

The FMEA and hazard analysis are tools for identifying harms, the sequence of events, their probability, and the potential failures that can cause these harms. Anticipated adverse device effects and residual risks associated with the investigational device, are identified in the Hazard Analysis Documentation [redacted] and Chapter 7 in the Clinical Investigator´s Brochure [redacted].

The design criteria are an important input in the risk analysis but also the experience of existing products of similar function and/or type (Post market surveillance data). The Rheo Knee 3 (incl. XC configuration) is an equivalent device currently marketed by Össur; post-market surveillance reporting provides data on device related risks as experienced in the real-world application of the device:

Outcome from Post Market Surveillance (PMS) data has not given reason to update risk management documents. No new harm has been identified from the PMS data and results from analysis do not impact conclusion on final risk assessment.

The following reasonably foreseeable misuses have been identified based on current knowledge about transfemoral prosthetic devices and microprocessors-controlled prosthetic knees.

- Use of product by user exceeding the maximum user weight.
- Use of product by user not meeting the minimum user weight.
- Failure to properly maintain the product and/or maintain the product to the expected level of cleanliness.
- Product contamination by foreign substances or operation of the product in dirty or dusty environments.
- Failure to follow recommended or mandatory service schedule.

- Use of the product over the specified maximum life duration.
- User does not read user manual.
- User cannot read user manual.
- User's clinician is insufficiently trained.
- User receives insufficient training from clinician(s).
- Memory failure (user forgets clinicians' training/advice).
- Nascent Error (user performs well meant "optimization", short-cut or improvisation to unusual circumstances).
- User performs activity which subjects Rheo knee 4/Navii to undue mechanical stress (jumping off a wall for example).
- Dropping the Rheo knee 4/Navii (when removing their prosthesis amputees often lean their prosthesis up against a wall which frequently resulting in the limb falling to the ground).
- User does not charge the prosthetic knee.
- User does not have good control over the residual limb.

For a list of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation or treatment see Chapter 7, and applicable annexes, in the Clinical Investigator´s Brochure [redacted].

• Risk of Study (To Patient)

At each visit a **LPI**, **a certified CPO/CP or clinician**, will be present to ensure the safety of the participants. The study adds no additional risk other than the risks identified above. Subjects will use the trial device as their primary prosthesis in the same manner as they would normally do on their current prosthesis. Thus, they are not required to do anything different from their routine clinical visit for acquiring a new MPK (the Navii/Rheo Knee 4 investigational device) and their daily living activities between study visits.

• Risk Mitigation

For each device designed by Össur risk mitigation is part of the design process according to ISO 14971 [redacted]. Furthermore, each participant fitted with **the investigational device (Navii/[redacted])** for the first time, will be trained by a fully qualified professional until the user can demonstrate sufficient understanding of the product operation and demonstrate minimum ability level in its operation. This process is the same as the usual training process deployed for normal fitting of a **MPK device**.

As part of the training process, the participant will be informed on the risks inherent in using an investigational MPK device in an uncontrolled environment. Moreover, the participant will be provided with the product literature (e.g. Information for User), as well as being informed and trained on how to use the product.

• Risk-to-Benefit Rationale

The residual risks of the investigation and the investigational device are minimal and are significantly out weighted by the benefits of participating in the investigation.

• IRB/REB/REC Review and Communications

The study protocol (CIP), informed consent form, and other study documentation forms require IRB review and approval. Communication to and from the IRB shall be directed from or to the primary Össur contact, the **Sponsor co-investigator/Monitor**. Continuous communication will be maintained between Össur and the IRB, as required. Moreover, communication will be maintained between the **LPIs and PI** and the IRB, as required.

• Vulnerable populations

No vulnerable populations will be enrolled.

• Informed Consent

The Local Principal Investigator (LPI) at each site, or any researcher qualified, will obtain from the subject, written signed informed consent form to his/her inclusion in the study, after explaining the rationale for and the details of the study, the risks and benefits of alternative treatments, and the extent of the subject's involvement. The subject will receive a copy of the informed consent.

The subjects will be informed that their participation is voluntary and that they can withdraw from participation at any time, at his/her discretion and this will not have any consequences for the participant's treatment.

In case the information on the ICF changes, and subjects need to be provided with new information, the LPI will contact each subject by phone and explain the new information as required. If the study must be postponed until IRB approval of the amendment is obtained this will be explained to the patient.

Subjects that for any reason are unable to provide informed consent will not be enrolled in the study.

• Participant confidentiality – Data management

a) Subjects will be assigned a study identification (ID) number. This ID will be used in all relevant documentation. Confidentiality of all relevant subject feedback and information will be maintained through use of the identifying number only, in all documentation. The study sponsor, Össur, will remain the sole owner of the study data.

Data will be collected and stored either through the Electronic Data Capture (EDS) system Smart-Trial, or via paper based CRFs.

A list connecting the ID to the subject´s name will be stored either in the Electronic Data Capture (EDS) system Smart-Trial or in a locked file with the LPI at each site. Only appropriately qualified individuals designated by the Investigator will have access to this information. Access is controlled by password protected accounts. Accounts are enabled with designated permissions only.

b) Physical source data (e.g. signed Informed Consent forms and paper based forms as applicable) will reside in the Local Principal Investigator Site File. This will be physically locked and accessible to the Investigator only.

c) Case report forms in Smart-Trial are developed in accordance with this protocol and are quality checked against the protocol by the study team before use, the same is true in case of paper-based CRFs. In Smart-Trial, validated fields and reference rules are used to control quality of data on entry and where required the order of data collection. In case of paper based CRFs they are reviewed by the investigator and a study monitor to ensure completeness of data.

Data that are missing or collected out of timeframe will be flagged. Smart-Trial contains audit history and data query functionality, in case of paper based CRFs, data queries are raised by the investigator or study monitor. Data queries may be raised ad hoc or at scheduled monitoring visits. Data queries may be reconciled by designated individuals (by account permissions in Smart-Trial) only. Where physical records are used these will be stored as source data in the investigator site file and attached to Smart Trial forms as scans if applicable.

[redacted]

e) In case of electronic data collection; SMART-TRIAL (www.smart-trial.com) will be used as the primary Electronic Data Capture tool in this study. SMART-TRIAL is designed and developed in compliance with the PIC/S Guidance, PI-011-3 Good Practices for Computerized Systems in Regulated "GxP" Environments, with software validation based on IEC 62304. SMART-TRIAL is designed to enable the user to comply with Good Clinical Practice (ISO 14155:2020), ICH GCP and other industry requirements, such as FDA 21 CFR Part 11 and HIPAA. f) All data in SMART-TRIAL is collected, transferred, and stored encrypted in databases, which are hosted on Microsoft Azure ISO certified servers that are managed by SMART-TRIAL within the European Union (Dublin, Ireland). Backups are performed continuously throughout the day and stored within the same server. Given that Smart-Trial does send messaging to patients in research studies, as part of the informed consent process, (as reviewed by the IRB), patients will be asked to consent to communications through these channels. Smart-Trial is adherent to CAN-SPAM and international equivalents.

g) Photographs and frames in video recordings will only contain as far as possible the lower extremities of subjects *and any ambulatory assistance provided with their hands* only. Frames containing the face or other identifiable features of subjects will be blurred, cropped or deleted if accidentally captured. The data of subjects that are withdrawn from participation will be retained. Subjects may request that their research data is delinked from their personally identifiable data during the course of the study.

h) In case of EDS, database entry is locked after final patient data is entered. Database is closed and de-identified data exported by the sponsor Co-investigator/Monitor on completion of close-out monitoring activities including resolution of all data queries. Smart Trial audit history is extracted for records of monitoring activities. Exported de-identified data is stored on password protected PC intranet for analysis. In case of paper based data collection, de-identified data is scanned and shared with the sponsor Co-investigator/Monitor after data collection is complete.

Representatives of the sponsor, sponsor co-investigators and monitors, will be present at the study sites. A declaration of confidentiality to be signed by the representatives, ensures necessary data protection.

i) The data retention period for unlinked clinical data will be a minimum of 5 years in accordance with ISO 14155:2020. Clinical investigation documents, including but not limited to CIP, CIB, CRFs and clinical investigation report(s) should be incorporated into the device technical documentation under the quality management system of the manufacturer.

k) A Clinical Investigation Report (CIR) will be generated by Össur Medical Office. The report will be stored with the device technical file within Össur Quality Management System, along with the unlinked data and all accompanying investigational documents, according to the R&D and Quality documentation procedures. Subjects participating in the study can have access to the results, on demand, when the CIR is internally published.

Study results, data, and documentation will be stored for a minimum of 5 years.

• Evaluation of Adverse Events and Device Deficiencies

For a list of foreseeable adverse events and anticipated adverse device effects, together with their likely incidence, mitigation or treatment see chapter 13.2 above and 7 in the Clinical Investigator´s Brochure **[2].**

• Definitions of adverse events, effects and deficiencies

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

An adverse device effect (ADE) is any adverse event related to the use of an investigational medical device, including events resulting from insufficient or inadequate instructions for use, operation, malfunction, etc.

A serious/severe adverse event (SAE) is an AE that:

- Is life-threatening or fatal
- requires or prolongs hospitalization
- results in permanent impairment of a body function
- or results in permanent damage to a body structure.

A serious/severe adverse device effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a SAE.

An anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk management for the device.

An unanticipated adverse device effect (UADE) is a serious adverse effect on health or safety of participants caused by the device if not previously identified in nature, severity, or degree of incidence in the protocol (CIP) or the risk analysis for the device.

A device deficiency (DD) is the inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labelling.

A use error (UE) is an act or omission of an act that results in a different medical device response than intended by the manufacturer or expected by the user.

See ISO 14155 [redacted] for details.

• Reporting procedures

All device related adverse events will be investigated. Adverse events that are serious, unanticipated and (possibly) device related shall be reported to the sponsor by telephone as soon as possible. The complete adverse event investigation form shall be provided to the sponsor within 24 hrs via email. Within ten days the Sponsor will report to the IRB and FDA, as applicable. Any serious device related adverse event will lead to the immediate termination of the trial. In this case all participants will be contacted immediately and advised to stop using the investigational device. An appointment will be made for them to return the trial device.

Participants will be provided the contact information of the investigator and told to call them in the event of an adverse event. Furthermore, an investigator will contact them weekly to check up on any problems. The participants prescribed prosthesis will be kept at the study site while they use the investigational device. If they experience problems with the investigational device an appointment will be made with on site to investigate further.

The investigator shall supply a copy of the complete adverse event investigation form, together with a cover letter to the IRB when events are judged to be serious, unanticipated and (possibly) device related.

Contact in case of unexpected adverse event:

[redacted]

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

- if either suitable action had not been taken,
- if intervention had not been made, or
- if circumstances had been less fortunate,

shall be reported according to the same procedure as if an ADE had taken place, specified above.

Suspension or premature termination of the clinical investigation

The sponsor/principal investigator, the IRBs, and the regulatory authorities can decide about investigation continuation. The clinical investigation can be suspended or prematurely terminated if the serious adverse device effects are considered disproportionately large compared to the possible benefits of the intervention. If the investigation is terminated or suspended all participants will be informed and appropriate follow-up will be assured. If sponsor/principal investigator terminates or suspends the investigation the relevant IRBs and regulatory authorities will be provided with a detailed written explanation of the termination or suspension.

The sponsor/principal investigator can upon completion of the analysis of the reason(s) for a suspension decide to lift the suspension, when the necessary corrective actions have been implemented. The investigators, IRBs, and relevant regulatory authorities will be notified and provided with the relevant data supporting the decision.

Breaking of blinding will not be relevant in this trial, since group allocation is visible.

Publication Policy

These results are for internal consumption by Össur employees involved with the project, marketing and for regulatory documentation purposes.

Publication will be pursued if agreed by the Sponsor and Investigator.

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External Literature References: [X]

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