

IceExplore TF Liner - Clinical Investigation Protocol

Efficacy of a perforated liner and socket system for individuals with trans-femoral amputation.

NCT05279885

Seal

CONFIDENTIAL DOCUMENT

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Table of Contents

1	How to Refer to This Document	7
2	Summary.....	7
3	Changes from Previous Revision	12
3.1	Changes for Revision 1.00.....	12
3.2	Changes for Revision 2.00.....	12
3.3	Changes for Revision 3.00.....	12
4	Abbreviations	13
5	Investigational Device.....	15
6	Justification for the Design of the Clinical Investigation	19
7	Objectives and Hypotheses.....	22
8	Design of the Clinical Investigation	23
8.1	General	23
8.2	Investigational Device(s) and Comparator(s).....	24
8.3	Subjects	25
8.4	Procedures.....	27
8.4.1	Recruitment	27
8.4.2	Test procedures.....	27
8.4.3	Measurements and data collection.....	31
8.5	Compensation.....	33
8.5.1	Subject.....	33
8.5.2	Investigational sites, SRT and Indiana University School of Medicine – ICRME.....	33
8.6	Responsibilities	33
8.7	Study monitoring and Oversight.....	34
9	Investigational Device Accountability	34
10	Statistical Considerations	34
10.1	Statistical design and procedures	34
10.2	Sample size calculation	35
10.3	Additional statistical matters.....	35
11	Amendments and Deviations from the Protocol (CIP).....	35
11.1	Amendments.....	35
11.2	Deviations	35
12	Statement of Compliance	36
13	Ethical Considerations	36
13.1	Anticipated clinical benefits.....	36
13.2	Device related risk	36
13.3	Risk of Study (To Patient).....	38
13.4	Risk Mitigation.....	38
13.5	Risk-to-Benefit Rationale	38
13.6	IRB/REB/REC Review and Communications.....	38
13.7	Vulnerable populations	38
13.8	Informed Consent	38
13.9	Participant confidentiality – Data management.....	39

14	Evaluation of Adverse Events and Device Deficiencies	39
14.1	Definitions of adverse events, effects and deficiencies	39
14.2	Reporting procedures	40
14.3	Suspension or premature termination of the clinical investigation.....	40
15	Publication Policy	40
16	References	41
17	Annex	Error! Bookmark not defined.
17.1	Humidity measurements - procedure	Error! Bookmark not defined.
17.2	MSR sensor and data logger instructions	Error! Bookmark not defined.
17.3	Questionnaires.....	Error! Bookmark not defined.
17.3.1	Subject Demographics	Error! Bookmark not defined.
17.3.2	CLASS	Error! Bookmark not defined.
17.3.1	Questionnaire	Error! Bookmark not defined.
17.4	Hazard Analysis	Error! Bookmark not defined.
17.4.1	AeroFit TF Liner.....	Error! Bookmark not defined.
17.4.2	Direct Socket TF / AeroFit TF Socket.....	Error! Bookmark not defined.

Tables

Table 1	Summary of procedures and visits	10
Table 2	Identification and Description of the Investigational Device.....	15
Table 3	Technical and functional features.....	18
Table 4	Area under curve (rH%) from liner on to exit hot room.....	21
Table 5	Area under curve (rH%) from enter hot room to exit hot room	21
Table 6	Endpoints, test methods and hypotheses.....	22
Table 7	Inclusion/Exclusion criteria	25
Table 8	Study events, timeline, visits length, no. of subjects, location, procedures	27
Table 9	Cut-off scores for increased risk of falls	32
Table 10	Events, Incidents and Injuries for Össur Seal-In[®] silicone liners from 2014-01 to 2021-05	37
Table 11	Events, Incidents and Injuries for Direct Socket from 2014-01 to 2021-05	37

1 How to Refer to This Document

[0] Document ID, Sub-Section Name, Creator

2 Summary

Device(s) being tested:	Investigational device: AeroFit Liner, not listed with FDA AeroFit Socket, not listed with FDA Comparator: Össur Seal-In Silicone Liner AeroFit Socket (vents sealed with silicone sheet), not listed with FDA Former names of the devices, during earlier development stages, were IceExplore TF Liner and IceExplore TF Socket.
Instruments and equipment:	• Pen/pencil • MSR147WD Data Logger with 5 humidity- and temperature sensors • MSR PC software (standard) • Smartphone/Tablet with Bluetooth (for remote control of the data logger) • Treadmill • Canes or sticks to mark squares on floor for Four Step Square Test • Stairs • Hypafix Tape for attaching sensors to skin and liner • Scissors • Pharm Chek Sweat Patches • Gloves • Plastic forceps • Alcohol swabs • Test tube • Standard laboratory analytical weighing balance • Heart rate monitor • Camera or smartphone with camera • Stopwatch • Heated room (28 degrees Celsius) • Case report forms (CRFs): ○ Enrollment Log ○ Medical history ○ Subject demographics and test information ○ Local Sweat Rates (LSR)Questionnaire ▪ CLASS ▪ In-house question on perceived sweat and other additional questions ▪ SCS ○ Sensor and data logger instructions

	○ Adverse event/ device deficiency form ○ Investigational device management form ○ Unscheduled visit form ○ Subject compensation ○ Protocol deviation/ violation																																																									
Subjects recruited: N=10	Inclusion criteria:	Exclusion criteria:																																																								
	50Kg< body weight < 136Kg	50Kg> body weight > 136Kg																																																								
	Cognitive ability to understand all instructions and questionnaires in the study;	Users with cognitive impairment																																																								
	Unilateral/ bilateral trans-femoral amputee	Participating in another research study																																																								
	Able to walk on a treadmill for 20 minutes	Previous diagnosis or history of cardiovascular disease																																																								
	Using Össur Seal-In Silicone Liner and Direct Socket																																																									
	Stump Length: Subjects must fall into the predefined criteria for minimum stump length dependent on liner size and residual limb shape <table><thead><tr><th colspan="2">Standard</th><th colspan="2">Conical</th></tr><tr><th>Liner size</th><th>Min. Stump Length</th><th>Liner Size</th><th>Min. Stump Length</th></tr></thead><tbody><tr><td>25</td><td>200</td><td>23,5</td><td>190</td></tr><tr><td>26,5</td><td>200</td><td>25</td><td>200</td></tr><tr><td>28</td><td>200</td><td>26,5</td><td>200</td></tr><tr><td>30</td><td>210</td><td>28</td><td>200</td></tr><tr><td>32</td><td>210</td><td>30</td><td>210</td></tr><tr><td>34</td><td>220</td><td>32</td><td>220</td></tr><tr><td>36</td><td>220</td><td>34</td><td>220</td></tr><tr><td>38</td><td>230</td><td>36</td><td>220</td></tr><tr><td>40</td><td>230</td><td>38</td><td>230</td></tr><tr><td>45</td><td>250</td><td>40</td><td>230</td></tr><tr><td>50</td><td>260</td><td></td><td></td></tr><tr><td>55</td><td>280</td><td></td><td></td></tr></tbody></table>	Standard		Conical		Liner size	Min. Stump Length	Liner Size	Min. Stump Length	25	200	23,5	190	26,5	200	25	200	28	200	26,5	200	30	210	28	200	32	210	30	210	34	220	32	220	36	220	34	220	38	230	36	220	40	230	38	230	45	250	40	230	50	260			55	280			
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	Direct Socket Length: Subjects must fall into the predefined criteria for minimum socket length dependent on liner size and residual limb shape. Measured from the distal end of the socket to the lowermost point on the medial side of the socket.																																																									

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	Willing and able to participate in the study and follow the protocol																																																						
	Confident prosthetic users for more than 3 months																																																						
	Older than 18 years																																																						
Objectives and Hypotheses	The primary objective of the investigation is to evaluate the efficacy of the perforated investigational device compared to conventional non-perforated suspension system regarding measured relative humidity on skin during increased perspiration. Secondary objectives are to evaluate if the measured moisture reduction during increased perspiration results in reduction in perceived moisture on skin Tertiary objectives are to evaluate equivalent perceived system stability, suspension and comfort between investigational device and comparator.																																																						
Procedures	0) Training and protocol test run Training and protocol test run will take place prior to start of formal investigation procedures and data collection. Sponsor research assistances will handle training and take part in protocol procedures test run. (1) Visit 1 – Informed Consent and Investigational Device fitting 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 <i>Informed consent</i>. Fitting of the investigational device: All subjects will be fitted within the standard methods of prosthetic fitting, alignment, introduction, training and walking on various terrain. Next, subject will be randomized into either group A or B. Group A will start with visit 2A, Group B will start with visit 2B.																																																						

	(2) Visits 2A and 2B – Humidity measurements in heated room (28 degrees Celsius), functional tests, and questionnaires. • Visit 2A: Investigational Device humidity measurements • Visit 2B: Comparator humidity measurements Visits 2A and 2B will take place on two separate days, during the same time of the day. Additionally, absorbent sweat patches will be placed on the participant's skin surface with the purpose of utilizing Gravimetric techniques for microbial analysis and in order to collect quantifiable measures on amount of sweat collected on subjects' skin after physical activity in heated room. (3) Visit 3 Fitting back to prescribed device. All subjects will be fitted within the standard methods of prosthetic fitting, alignment, introduction, training and walking on various terrain. See Table 1 and Figure 1 below.
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Table 1 Summary of procedures and visits

Study Events	Timeline	Visit length/ subject	NO. of Subjects	Location	Procedures
Screening	1-2 months prior pilot/test run	NA	10-12	SRT	Subject screening
Pilot/ test run	Pilot/ test run	1 day	1-2	SRT & ICRME	Protocol/ humidity measurement and equipment training Protocol and measurements test run with 1-2 subjects
Visit 1	Weeks 0-3	0,5 day/ subject	10	SRT	Enrollment log Informed Consent Form
					AeroFit Socket fabrication, investigational system fitting
					Randomization into groups
Visit 2A	Weeks 2-7	0,5 day/ subject	10	ICRME	Subject demographics
					Treadmill 20 minutes comfortable walking speed – humidity sensors on skin
					Functional tests: FSST and stairs
					Questionnaires: Perceived sweat, CLASS (stability, suspension, comfort), SCS

					Placement of sweat patches
Visit 2B	Weeks 2-7	0,5 day/ subject	10	ICRME	Subject demographics
					Treadmill 20 minutes comfortable walking speed – humidity sensors on skin
					Functional tests: FSST and stairs
					Questionnaires: Perceived sweat, CLASS (stability, suspension, comfort), SCS
					Placement of sweat patches
Visit 3	Weeks 3-10	1 hour/ subject	10	SRT	Fitting back to baseline system

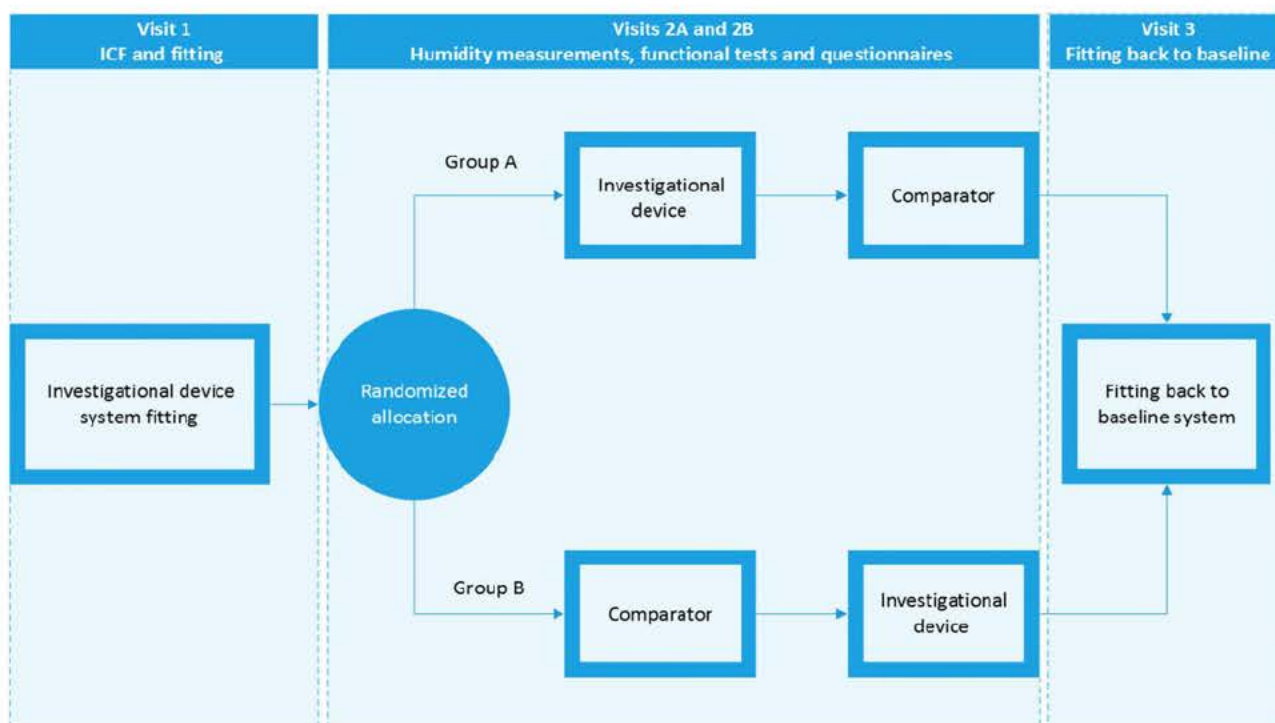


Figure 1 Clinical Investigation Procedure Flowchart

3 Changes from Previous Revision

3.1 Changes for Revision 1.00

Initial release.

3.2 Changes for Revision 2.00

Numbers in chapter 13.2 revised.

Minor edits to Table 1.

3.3 Changes for Revision 3.00

Previous diagnosis or history of cardiovascular disease added as subject exclusion criteria.

Sweat patches will be placed on the participant's skin surface with the purpose of utilizing Gravimetric techniques for microbial analysis and in order to collect quantifiable measures of fluid amounts will be added.

To mitigate a potential safety risk when exercising in hot environment the exclusion criteria has been adapted not to expose patient with cardiological condition to physically demanding activities.

Absorbent sweat patches added to **8.4.2 Test procedures** and **8.4.3 Measurement and data collection**. Heart rate monitor added to **8.4.3 Measurement and data collection**. **13.4 Risk Mitigation** updated.

Case report forms *Medical history* and *Local Sweat Rates* added to instruments and equipment. Instruments used for placement of sweat patches added.

4 Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AR	Adverse Reaction
CA	Competent Authority
CEP	Clinical Evaluation Plan
CER	Clinical Evaluation Report
CI	Co-Investigator
CLASS	Comprehensive Lower Limb Amputee Socket Survey
COI	Coordinating Investigator
CIB	Clinical Investigator's Brochure
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRF	Case Report Form
CRO	Clinical Research Organization
EC	Ethics Committee (see IEC, IRB, REB and REC)
EDS	Electronic Data capture Service
GCP	Good Clinical Practice
CIB	(Clinical) Investigator Brochure
ICF	Informed Consent Form
ICRME	Indiana Center for Regenerative Medicine and Engineering
IDMF	Investigational Device Management Form
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Independent/Institutional Review Board
LCI	Local Co-Investigator
LSR	Local sweat rates
LPI	Local Principal Investigator
LRA	Local Research Assistant
PI	Principle Investigator
REB	Research Ethics Board
REC	Research Ethics Committee
RL	Residual limb
ROI	Region of interest
SAE	Serious Adverse Event
SADE	Serious Adverse Device Event
SCS	Socket Comfort Score
SL	Sound limb
SOP	Standard Operating Procedure

SOTA	State-Of-The-Art
SRA	Sponsor Research Assistant
USADE	Unanticipated Serious Adverse Device Effect

5 Investigational Device

The investigational device is not listed with FDA and will be labeled according to regulations concerning 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:	AeroFit TF Liner The AeroFit TF Liner is a perforated silicone liner which allows for humid evaporation from the amputee's skin and through the liner. It is Class I, a low-risk product. Intended purpose The device is a prosthetic interface with suspension properties intended to be used as part of a system that replaces a missing lower limb Essential Design The device is cylindrically shaped with one closed end. The suspension is achieved with seal vacuum. Made of silicone and textile. The AeroFit TF Socket AeroFit TF Socket is similar to the already marketed Direct Socket TF. The AeroFit TF Socket is made in the same way as conventional Direct Socket, but in addition, perforations are drilled to the body of the socket and vents inserted into each perforation which allows for moisture evaporation from between liner and socket and out of socket. Overmolded textile on the outside of the vents covers the perforations to prevent dirt and dust to enter the socket. It is Class I, a low-risk product. Intended purpose The devices are intended to both fabricate and become a socket. The socket is intended as a part of a prosthetic system that replaces a missing lower limb Essential Design The device consists of tools and materials used to manufacture a definitive prosthetic socket The combined system, AeroFit TF Liner and AeroFit TF Socket will be referred to as the AeroFit TF System throughout this document. The AeroFit TF System is perforated which means that it allows for moisture evaporation from residual limb. Both devices, the liner, and the socket, are classified as FDA product classification title; <i>External limb prosthetic component</i> according to Title 21 CFR 890.3420, bearing the product code ISS: "prosthesis, thigh socket, external component". It is 510(k) and GPM exempt, except for general requirements.
Manufacturer of the investigational device:	Össur hf. Grjóthals 5 110 Reykjavík Iceland
Name or number of the model/type, including software version and accessories, if any, to permit full identification:	The devices are currently under development. Clinical Development stage: Pivotal Stage

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 devices serial numbers.
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) and/or limb deficiencies. Population: Amputees (bi- or unilateral) physically fit for using a prosthesis to replace the function of an amputated lower limb. It is intended for any user from the aforementioned group within the following criteria: Amputation level: Trans-femoral User activity levels/ impact level: Low-High User weight limit: up to 136Kg

Description of the investigational device:	See Table 3 below for descriptions of device features and their relation to the investigation. AeroFit TF Liner The AeroFit TF liner (Error! Reference source not found.) is similar in intended use, methods of operation and materials to other seal-in TF silicone liners manufactured by Össur. The main difference is that the internal structure of the predicate liner, i.e. silicone liner, is formed entirely of airtight silicone whereas the proximal 70% (approx.) of the AeroFit TF liner consists of a perforated structure, allowing water vapor to move both transversely away from the skin and longitudinally towards the proximal edge of the prosthetic socket. The AeroFit TF liner is for non-invasive, single patient use. Given proper hygienic care as stated in instructions for use, the product is reusable. The device is to be used in direct contact with the skin and during daily activities. The device does not incorporate, as an integral part, a substance or human blood derivative and is manufactured without utilizing tissues of animal origin. AeroFit TF Socket The AeroFit TF Socket () is a perforated version of the conventional Direct Socket. Perforations are drilled to the body of the socket, positioning and number of perforations are defined according to a certain criterion and depends on subject's limb length and circumference. Vents () snap fit into each perforation and allow for moisture evaporation. Overmolded textile on the outside of vents are to prevent dirt and dust to enter socket. The AeroFit TF Socket is non-invasive, single patient, reusable devices, compatible with Seal-In suspension and intended to be used by low to high active trans-femoral amputees. The user will utilize his/her device when he/she chooses to use it, which may be for many hours every day or just intermittently, as desired. The devices are to be used (worn) during daily-living activities. The device is not to be used in direct contact with the skin.  
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 an FDA listed device of a similar type. The device should be supplied and fitted by a certified CPO/CO/CP.
Specific medical or surgical procedures involved in the use of the investigational device:	N/A

Table 3 Technical and functional features

	#	Feature	Description	Covered by this investigation:
AeroFit TF Liner	1	Perforated silicone structure		√
	2	Seal membrane		√
	3	Silicone distal cup		√
	4	Distal cushioning zone		√
	5	Outer textile		√
AeroFit TF Socket	6	Soft Proximal Brim	See Figure 2	√
	7	Socket body	See Figure 2	√
	8	Injection molded vents	See Figure 3	√

6 Justification for the Design of the Clinical Investigation

The clinical investigation will be pre-market, confirmatory, pivotal clinical investigation. The clinical investigation will be designed to collect data on the effectiveness and clinical performance of the investigational devices. Burden to subjects is interventional.

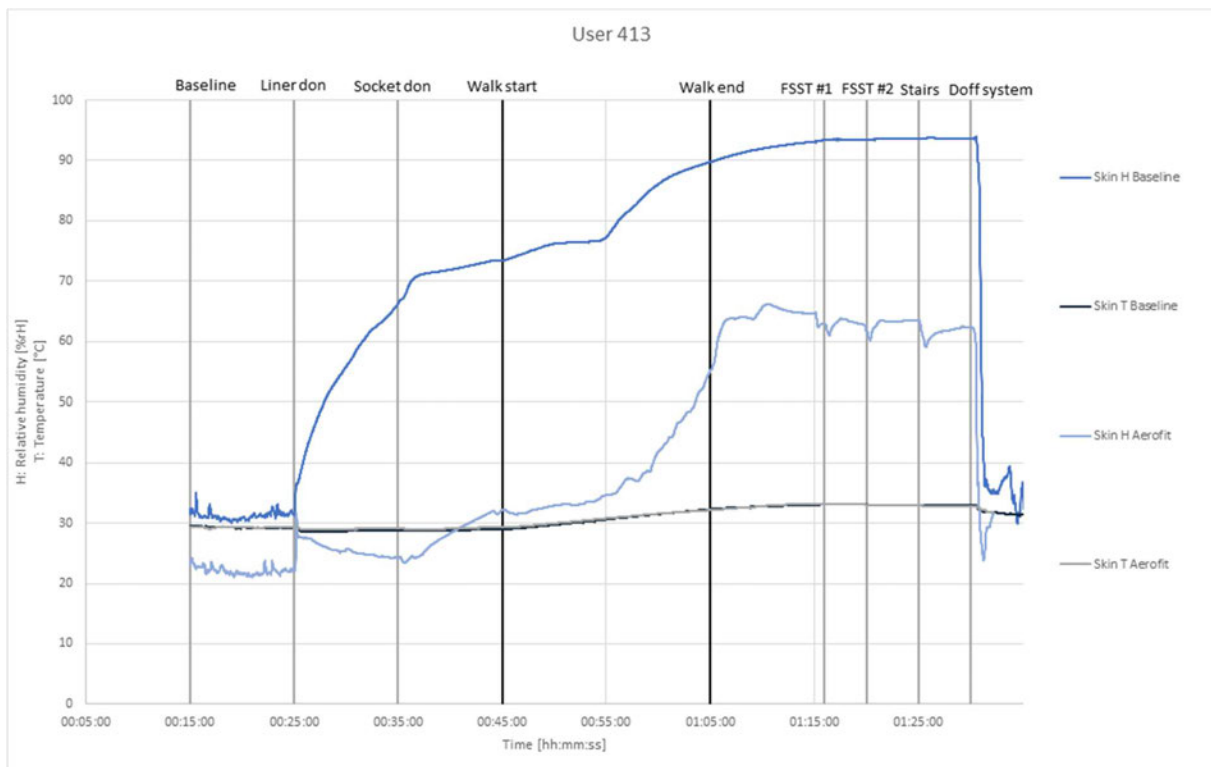


Figure 4 Relative humidity and temperature measurements during treadmill walking, FSST and stair walking. Dark blue line represents baseline (non-perforated system), and the light blue line represents AeroFit (perforated system). Black line shows temperature for baseline and grey line shows temperature for AeroFit. Grey and black vertical lines show the changes in user activity.

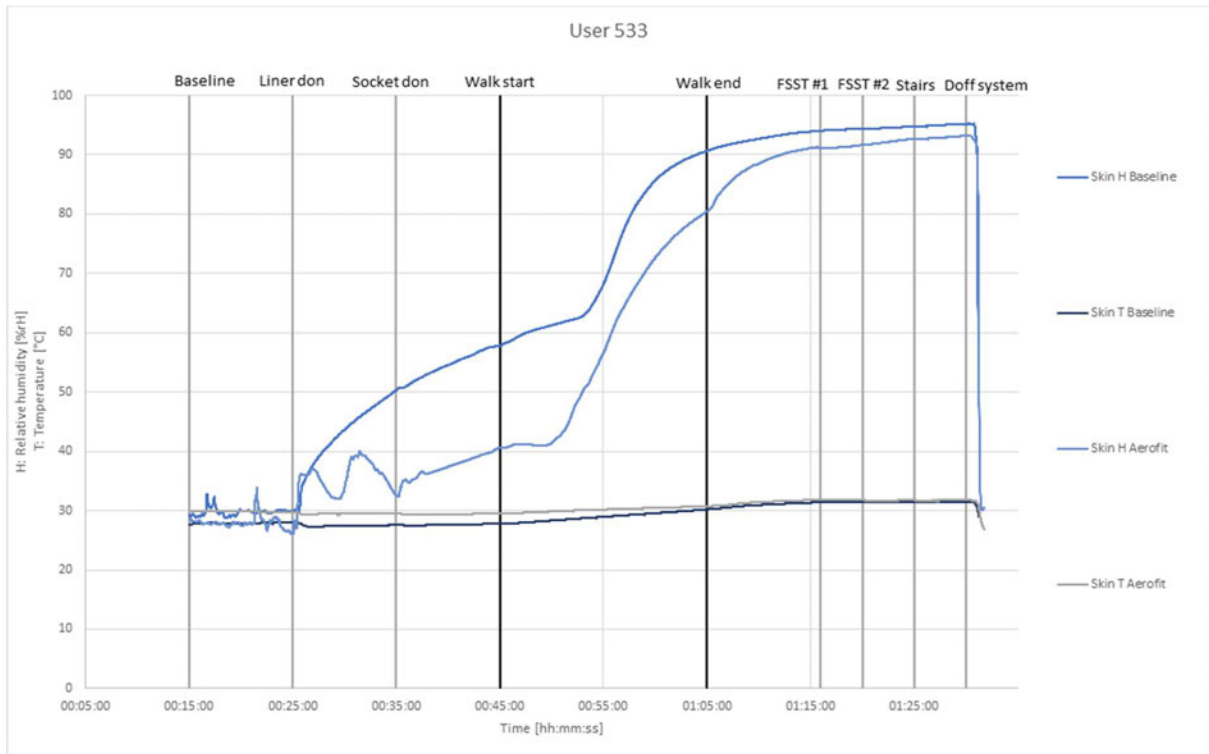


Figure 5 [REDACTED]. Relative humidity and temperature measurements during treadmill walking, FSST and stair walking. Dark blue line represents baseline (non-perforated system), and the light blue line represents AeroFit (perforated system). Black line shows temperature for baseline and grey line shows temperature for AeroFit. Grey and black vertical lines show the changes in user activity.

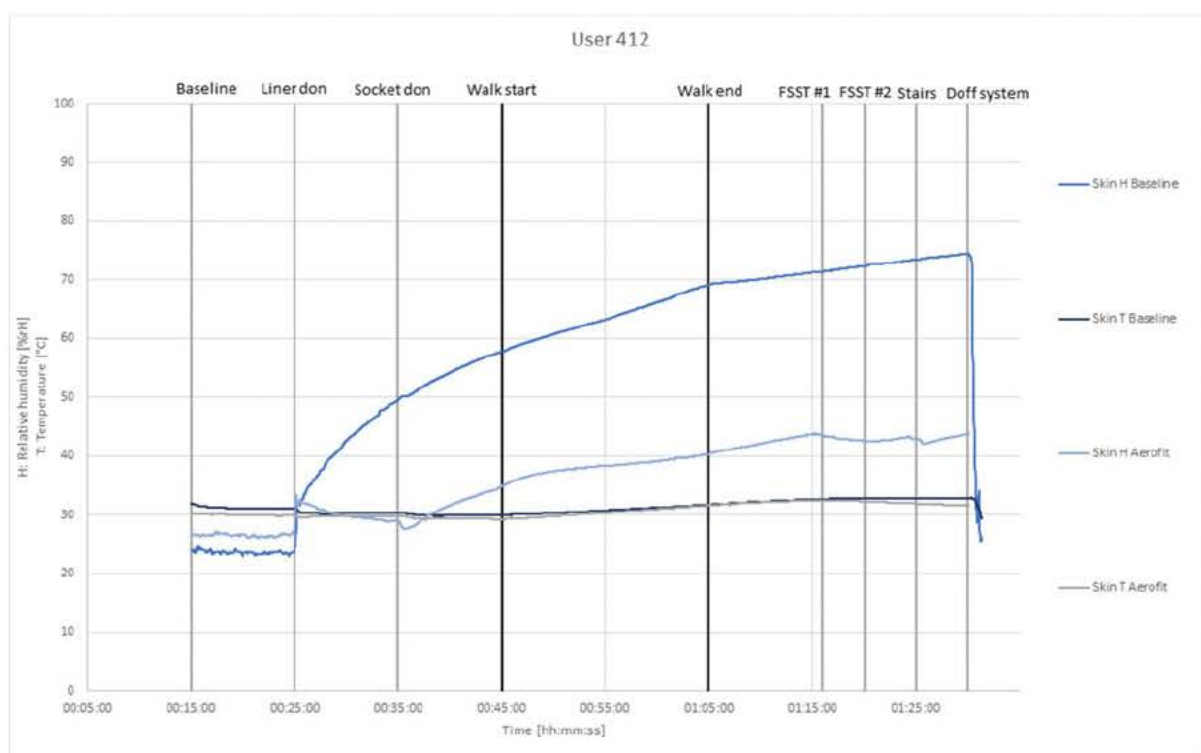


Figure 6 Relative humidity and temperature measurements during treadmill walking, FSST and stair walking. Dark blue line represents baseline (non-perforated system), and the light blue line represents AeroFit (perforated system). Black line shows temperature for baseline and grey line shows temperature for AeroFit. Grey and black vertical lines show the changes in user activity.

Area under the curve was calculated for both systems (see Table 4). Results show that humidity collected throughout the tests is in all cases less with perforated system (AeroFit) compared to non-perforated system (baseline).

Table 4 Area under curve (rH%) from liner on to exit hot room

	Baseline	AeroFit	Difference
■	3782.02	1927.81	1854.21
■	3343.22	2762.60	580.61
■	2924.78	1798.26	1126.53

Table 5 Area under curve (rH%) from enter hot room to exit hot room

	Baseline	AeroFit	Difference
■	2525.00	1391.95	1133.06
■	2374.43	2035.31	339.12
■	1969.68	1184.07	785.61

This pilot data from 3 subjects indicates that the perforated AeroFit system reduces the amount of humidity that is collected within the liner compared to non-perforated system. Further confirmatory investigation is needed with sufficient sample size to evaluate the efficacy of the investigational device compared to conventional non-perforated suspension system regarding measured relative humidity on skin during increased perspiration.

7 Objectives and Hypotheses

The primary objective of the investigation is to evaluate the efficacy of the perforated investigational device compared to conventional non-perforated suspension system regarding measured relative humidity on skin during increased perspiration.

Secondary objectives are to evaluate if the measured moisture reduction during increased perspiration results in reduction in perceived moisture on skin

Tertiary objectives are to evaluate equivalent perceived system stability, suspension and comfort between investigational device and comparator.

Absorbent sweat patches will be used to collect quantifiable measures on amount of sweat collected on skin after the physical activity. Outcome from sweat patches measurement will only be exploratory. The patches will be analyzed to generate a microbiology culture report for exploratory purposes without related hypothesis.

Outcomes from stair walking and FSST will also be exploratory

The following clinical claims are to be evaluated:

- Measured moisture on skin is reduced
- Perceived moisture on skin is reduced
- Perceived stability is no worse
- Perceived suspension is no worse
- Perceived comfort is no worse

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

The hypothesis and endpoints are specified in Table 6.

For all hypothesis:

μ_1 is average of measurements of comparator;

μ_2 is the average of measurements of investigational device;

and d is the margin of non – inferiority

Table 6 Endpoints, test methods and hypotheses

	Hypothesis	Test Method	Endpoint	Acceptance Criteria
A1	The AeroFit System reduces measured humidity on skin when compared to non-perforated silicone liner and socket (Direct Socket).	Treadmill walking, comfortable walking speed 20 minutes in heated room Humidity sensors	Area under the curve for relative humidity	$H_0: \mu_2 = \mu_1$ $H_1: \mu_2 \neq \mu_1$ P<.05
B1	The AeroFit System shall be perceived by users to reduce the humidity on the skin of the user when compared to using non- perforated silicone liner and socket (Direct Socket).	In-house developed question on perceived sweat inside prosthesis 1-10 (numerical rating scale)	Perceived sweat ratings	$H_0: \mu_2 = \mu_1$ $H_1: \mu_2 \neq \mu_1$ P<.05 And acceptance of A1

C1	The AeroFit System shall be perceived by users to offer no worse stability during increased perspiration compared to using non-perforated silicone liner and socket (Direct Socket).	CLASS stability section	CLASS stability	$H_0: \mu_2 - \mu_1 \leq -d$ $H_1: \mu_2 - \mu_1 > -d$ $d = 7.0\%$ $P < .0167$ And acceptance of B1
C2	The AeroFit System shall be perceived by users to offer no worse suspension during increased perspiration when compared to using non-perforated silicone liner and socket (Direct Socket).	CLASS suspension section	CLASS stability	$H_0: \mu_2 - \mu_1 \leq -d$ $H_1: \mu_2 - \mu_1 > -d$ $d = 7.0\%$ $P < .0167$ And acceptance of B1
C3	The AeroFit System shall be perceived by users to offer no worse comfort during increased perspiration compared to using non-perforated silicone liner and socket (Direct Socket).	CLASS comfort section	CLASS comfort	$H_0: \mu_2 - \mu_1 \leq -d$ $H_1: \mu_2 - \mu_1 > -d$ $d = 7.0\%$ $P < .0167$ And acceptance of B1

8 Design of the Clinical Investigation

8.1 General

The clinical investigation is a randomized cross-over 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.

Measurements on comparator and investigational device will be randomized.

As stated above the primary endpoint is measured relative humidity, secondary endpoint is perceived sweat and tertiary endpoints are perceived stability, suspension and comfort, in that respective order of significance. See previous chapter on objectives and hypothesis and Table 6 for rationale.

Drop-outs and withdrawals will be replaced.

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

See chapter **10.2 Sample size calculation** and Table 6 for analysis of variables.

Equipment required for each subject:

- Pen/pencil
- MSR147WD Data Logger with 5 humidity- and temperature sensors
- MSR PC software (standard)
- Smartphone/Tablet with Bluetooth (for remote control of the data logger)
- Treadmill
- Canes or sticks to mark squares on floor for Four Step Square Test
- Stairs

- Hypafix Tape for attaching sensors to skin and liner
- Scissors
- Pharm Chek Sweat Patches
- Gloves
- Plastic forceps
- Alcohol swabs
- Test tube
- Standard laboratory analytical weighing balance
- Heart rate monitor
- Camera or smartphone with camera
- Stopwatch
- Heated room (28 degrees Celsius)
- Case report forms (CRFs):
 - Enrollment Log
 - Medical history
 - Subject demographics and test information
 - Local Sweat Rates (LSR)
 - Questionnaire
 - CLASS
 - In-house question on perceived sweat
 - SCS
 - Sensor and data logger instructions
 - Adverse event/ device deficiency form
 - Investigational device management form
 - Unscheduled visit form
 - Subject compensation
 - Protocol deviation/ violation
- Investigational device: AeroFit System (liner and socket)
 - Sleeve for closing holes on AeroFit socket body for comparator testing
- Comparator: Seal-In Silicone Liner

The humidity and temperature sensors are sensitive, and care must be taken not to subject them to any impact. The sensors come ready to use and no calibration needed but all individual sensors need to be checked before every test start to make sure that they do not show abnormal values.

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

8.2 Investigational Device(s) and Comparator(s)

The subjects will use the investigational device (AeroFit System) for 3-10 weeks. Formal testing days for humidity measurements will be 2 days for each subject. Approximately 3-4 hours/day, one day for comparator testing and one day for investigational device testing.

Testing days will take place 2-9 weeks after the subject has been fitted to the investigational device. Minimum 2 weeks adaptation time will be required before testing takes place.

After testing days have been completed, subject will get a new appointment at the clinic, and will be fitted back to their prescribed device.

From being fitted to the investigational device and until subjects are back to prescribed device, subjects are expected to use the investigational device for their daily living activities as they would with any other prosthesis, for up to 18 hours a day depending on the amputee.

The comparator device will be Össur Seal-In Silicone Liner in combination with AeroFit Socket. The holes of the socket will be sealed with a silicone sheet during testing for the purpose of closing off holes and thereby prevent any moisture evaporation from the socket. The chance of moisture evaporation is extremely small when subject is

using enclosed silicone liner underneath an open socket, but to completely prevent the possibility, the holes will be sealed. The function of the AeroFit Socket, during comparator testing, will therefore be the same as a standard, enclosed, Direct Socket. The Össur Seal-In Silicone liner has the same intended use as the AeroFit Liner. Furthermore, it is indicated for the same condition and population group. It is a widely accepted device, providing clinical benefits to the user, and one of the most common type of such a device on the market.

The subject will be using the remaining part of their current prosthetic system (prosthetic knee and foot) with the investigational device, as it is used with the comparator device.

No other device, medication or intervention will be used.

10 subjects are to be enrolled and therefore 10 investigational systems (socket and liner) will be used for testing, as the devices are intended to be used by a single subject: one for each subject.

All subjects will be provided with two AeroFit TF liners to use during daily activities, before and after the humidity measurement days.

8.3 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;
- Fitted: Subject leaves the clinic on the investigational device;
- 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:
50Kg< body weight < 136Kg	50Kg> body weight > 136Kg
Cognitive ability to understand all instructions and questionnaires in the study;	Users with cognitive impairment
Unilateral/ bilateral trans-femoral amputee	Participating in another research study
Able to walk on a treadmill for 20 minutes	Previous diagnosis or history of cardiovascular disease
Using Össur Seal-In Silicone Liner and Direct Socket	
Stump Length: Subjects must fall into the predefined criteria for minimum stump length dependent on liner size and residual limb shape	

Inclusion: Only patients with the following characteristics are eligible for study entry:	Exclusion: Patients with the following characteristics are not eligible for study entry:																																																								
<table><tr><th colspan="2">Standard</th><th colspan="2">Conical</th></tr><tr><th>Liner size</th><th>Min. Stump Length</th><th>Liner Size</th><th>Min. Stump Length</th></tr><tr><td>25</td><td>200</td><td>23,5</td><td>190</td></tr><tr><td>26,5</td><td>200</td><td>25</td><td>200</td></tr><tr><td>28</td><td>200</td><td>26,5</td><td>200</td></tr><tr><td>30</td><td>210</td><td>28</td><td>200</td></tr><tr><td>32</td><td>210</td><td>30</td><td>210</td></tr><tr><td>34</td><td>220</td><td>32</td><td>220</td></tr><tr><td>36</td><td>220</td><td>34</td><td>220</td></tr><tr><td>38</td><td>230</td><td>36</td><td>220</td></tr><tr><td>40</td><td>230</td><td>38</td><td>230</td></tr><tr><td>45</td><td>250</td><td>40</td><td>230</td></tr><tr><td>50</td><td>260</td><td></td><td></td></tr><tr><td>55</td><td>280</td><td></td><td></td></tr></table>	Standard		Conical		Liner size	Min. Stump Length	Liner Size	Min. Stump Length	25	200	23,5	190	26,5	200	25	200	28	200	26,5	200	30	210	28	200	32	210	30	210	34	220	32	220	36	220	34	220	38	230	36	220	40	230	38	230	45	250	40	230	50	260			55	280			
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Direct Socket Length Subjects must fall into the predefined criteria for minimum socket length dependent on liner size and residual limb shape. Measured from the distal end of the socket to the lowermost point on the medial side of the socket. <table><tr><th colspan="2">Standard</th><th colspan="2">Conical</th></tr><tr><th>Liner size</th><th>Min. Socket Length</th><th>Liner Size</th><th>Min. Socket Length</th></tr><tr><td>25</td><td>220</td><td>23,5</td><td>220</td></tr><tr><td>26,5</td><td>230</td><td>25</td><td>220</td></tr><tr><td>28</td><td>230</td><td>26,5</td><td>220</td></tr><tr><td>30</td><td>240</td><td>28</td><td>230</td></tr><tr><td>32</td><td>240</td><td>30</td><td>230</td></tr><tr><td>34</td><td>240</td><td>32</td><td>240</td></tr><tr><td>36</td><td>250</td><td>34</td><td>250</td></tr><tr><td>38</td><td>250</td><td>36</td><td>250</td></tr><tr><td>40</td><td>260</td><td>38</td><td>250</td></tr><tr><td>45</td><td>270</td><td>40</td><td>260</td></tr><tr><td>50</td><td>290</td><td></td><td></td></tr><tr><td>55</td><td>300</td><td></td><td></td></tr></table>	Standard		Conical		Liner size	Min. Socket Length	Liner Size	Min. Socket Length	25	220	23,5	220	26,5	230	25	220	28	230	26,5	220	30	240	28	230	32	240	30	230	34	240	32	240	36	250	34	250	38	250	36	250	40	260	38	250	45	270	40	260	50	290			55	300			
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Residual limb profile: Standard or conical																																																									
Willing and able to participate in the study and follow the protocol																																																									
Confident prosthetic users for more than 3 months																																																									
Older than 18 years																																																									

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 PI/CI. 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 PI/CI 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 will 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 (SRT), the investigational site that they were contacted from.

The total time period required to implement the clinical investigation is expected to be 4 months. Each individual subject is expected to participate in the clinical investigation for 3-10 weeks. The estimated time needed to include this number (enrolment period) is 6-8 weeks.

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

8.4 Procedures

8.4.1 Recruitment

Potential subjects will be identified from the customer base of SRT, the National Prosthetic Center. Co-Investigator (CI) 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 CI will contact them via telephone. During the telephone call the CI will verify if they are interested in participating in a study. If interest is expressed at this point, CI will go through the enrollment log and if the eligibility criteria is met an appointment will be made for the first site 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.

The CI will communicate to the PI and study monitor the number of users he has identified that meet the inclusion criteria and are willing to participate.

8.4.2 Test procedures

There are six scheduled study events. See an overview on study events, timeline, location, procedures etc. in Table 8 below.

Table 8 Study events, timeline, visits length, no. of subjects, location, procedures

Study Events	Timeline	Visit length/ subject	NO. of Subjects		Procedures
Screening	1-2 months prior pilot/test run	NA	10-12		Subject screening
Pilot/ test run	Pilot/ test run	1 day	1-2		Protocol/ humidity measurement and equipment training Protocol and measurements test run with 1-2 subjects
Visit 1	Weeks 0-3	0,5 day/ subject	10		Enrollment log Informed Consent Form

					AeroFit Socket fabrication, investigational system fitting
					Randomization into groups
Visit 2A	Weeks 2-7	0,5 day/ subject	10		Subject demographics
					Treadmill 20 minutes comfortable walking speed – humidity sensors on skin
					Functional tests: FSST and stairs
					Questionnaires: Perceived sweat, CLASS (stability, suspension, comfort), SCS
					Placement of sweat patches
Visit 2B	Weeks 2-7	0,5 day/ subject	10		Subject demographics
					Treadmill 20 minutes comfortable walking speed – humidity sensors on skin
					Functional tests: FSST and stairs
					Questionnaires: Perceived sweat, CLASS (stability, suspension, comfort), SCS
					Placement of sweat patches
Visit 3	Weeks 3-10	1 hour/ subject	10		Fitting back to baseline system

1) Training and protocol test run

Training and protocol test run will take place prior to start of formal investigation procedures and data collection. Sponsor research assistances will handle training and take part in protocol procedures test run.

(4) Visit 1 – Informed Consent and Investigational Device fitting

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*.

Fitting of the investigational device: All subjects will be fitted within the standard methods of prosthetic fitting, alignment, introduction, training and walking on various terrain.

Next, subject will be randomized into either group A or B. Group A will start with visit 2A, Group B will start with visit 2B. Randomization allocation will be done using envelopes including either the letter A or B. 10 subjects are required to complete the protocol procedures and therefore 5 envelopes will be prepared per letter.

(5) Visits 2A and 2B – Humidity measurements in heated room (28 degrees Celsius), functional tests, and questionnaires.

- Visit 2A: Investigational Device humidity measurements
- Visit 2B: Comparator humidity measurements

Visits 2A and 2B will take place on two separate days, during the same time of the day.

Humidity measurement procedure is the same for investigational device and comparator. Only difference is that for comparator testing, additional silicone sheets will be used to close socket body holes prior to test procedures start [REDACTED]. Additionally, absorbent sweat patches will be placed on the participant's skin surface with the purpose of utilizing Gravimetric techniques for microbial analysis and in order to collect quantifiable measures on amount of sweat collected on subjects' skin after physical activity in heated room.

Humidity measurements - Protocol Part 2

Chronological procedure

TESTING START

STOPWATCH
TARGET TIME:

Resting

00:00:00 Start stopwatch.

User rests for 15 minutes with no liner or socket on. Data recording started. Sensors ID's noted and placed on the skin and sound side. Photos taken of the sensor placement. One sensor in environment.

Baseline - Steady state

00:15:00 Start timestamp: ____:____:____

User rests for 10 minutes with no liner or socket on.

Liner - Steady state

00:25:00 Don the liner. Timestamp: ____:____:____

User sits and rests for 10 minutes wearing the liner. Make sure not to touch the outside of the liner where the sensors on skin are placed.

00:35:00 **Socket - Steady state**

Don the socket. Timestamp: ____:____:____
User sits and rests on a chair for 10 min wearing the liner and socket. If possible, don't use any spray to don the socket.

00:44:00 When the stopwatch time hits 00:44:00, walk into the 28°C heated room to the treadmill to be ready to start walking when the stopwatch hits 00:45:00

Exercise

00:45:00 Start walking. Timestamp: ____:____:____
If first test: Set the treadmill to the previously chosen walking speed and walk for 20 minutes
Walking speed: ____
If second test: Set the treadmill to the same walking speed used in the first test and walk for 20 minutes

01:05:00 Stop timestamp: ____:____:____

Rest

User sits for 10 minutes with the socket and liner on in the heated room. Sensors still recording.

01:15:00 When the stopwatch time hits 01:15:00, exit the heated room and walk to the FSST to be ready to start the test when the stopwatch hits 01:16:00

Four Square Step Test

01:16:00 User performs FSST.

Timestamp: ____:____:____

User sits and rests until next trial.

Stairs

01:20:00 User goes up and down 3 steps in stairs, twice.

Timestamp at start: ____:____:____

User sits and rests after completing stair test

01:25:00 User removes socket and liner. Timestamp: ____:____:____

____:____:____

Data recording is stopped and sensors removed

User answers the questionnaire and CLASS.

TESTING COMPLETE

Comments:

Figure 7 Humidity measurements, functional tests and questionnaires protocol

(6) Visit 3

Fitting back to prescribed device. All subjects will be fitted within the standard methods of prosthetic fitting, alignment, introduction, training and walking on various terrain.

8.4.3 Measurements and data collection

8.4.3.1 Sensor placement

Sensors are fixed to the residuum and sound side using Hypafix tape.

On residual limb: Two sensors shall be positioned on skin laterally in perforated area, as distally as possible whilst ensuring they will only be covered by the perforated region of the investigational liner when the liner is donned (see Figure 8). The sensors shall be fixed in a position so that its opening window is orientated at 180° to the surface of the skin. The tape is also used to secure the cables to the residuum proximally.

Sound side: Two sensors also attached on sound side, lateral thigh. The sensor positions and serial numbers are recorded in the CRF's (more detailed description in Annex 17.2).

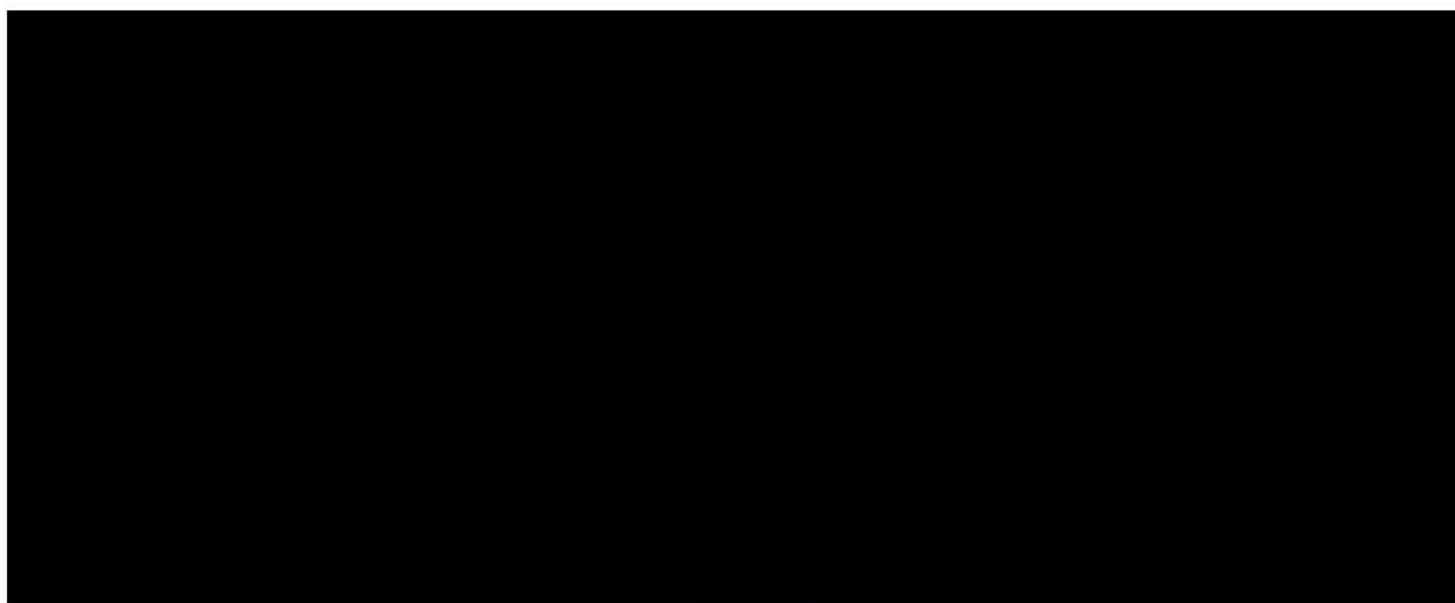


Figure 8 Sensor positioning on residual limb and sound side

Atmospheric Humidity:

One sensor is used to measure atmospheric humidity and shall be fixed to the outside of the subject's clothing, near to the pocket that the data logger (Figure 9) is stored in.

8.4.3.2 Data Logger

The MSR147WD Data Logger is used to record data collected from the sensors and is stored in the subject's pocket during the test.



Figure 9 MSR147WD Data Logger

8.4.3.3 Questionnaires

Subject demographics will be collected during the first visit. Subject demographics questionnaire consists of subject profile information such as age, gender, time from amputation, current prosthetic system etc.

Socket Comfort Score (SCS) will be collected during all visits and will serve as an indicator on subject socket comfort over the course of the study.

SCS was developed in an attempt to quantify the rather subjective experience of socket discomfort and pain. It is based on the numerical rating scale commonly used in pain clinics. However, because the scale assesses comfort rather than pain, the numerical values are reversed with higher SCS values assigned to a more comfortable socket fit.

The SCS is administered by asking the patient the following question: "If 0 represents the most uncomfortable socket fit you can imagine and 10 represents the most comfortable socket fit, how would you score the comfort of *the socket fit of your artificial limb at the moment?*" Despite its simplicity, the SCS has shown correlations between patient reports, clinical findings of the physician (redness, pressure marks, sores etc.), and the prosthetic fit as judged by the prosthetist. The measure has also demonstrated sensitivity to change as socket adjustments and socket replacements aimed at improving comfort resulted in higher SCS values. Ultimately, the SCS is intended to provide a level of standardization to a phenomenon that has historically been treated in purely descriptive forms.¹

Question on **perceived sweat** collected inside prosthesis will be an in-house developed self-report measure where subject rates the amount of sweat collected inside of their prosthesis during treadmill exercise. Subject will rate the amount of sweat both for comparator and investigational device. The question will be a Likert scale from 1-10 where 1 represents extreme amount of sweat, and 10 represents no sweat at all.

Comprehensive Lower-limb Amputee Socket Survey (CLASS)

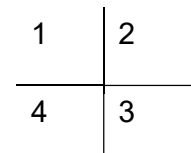
CLASS is a self-report measure of prosthetic socket satisfaction for lower limb amputees, designed to provide an effective means of communication for the patient to describe with clarity, the quality of their socket fit during common activities. CLASS evaluates static and dynamic features of socket stability, suspension, comfort and appearance and has been reported to be a reliable, quick and easy report measure.²

CLASS will be administered after treadmill walking exercise, both for comparator and investigational device.

8.4.3.4 Functional tests

8.4.3.4.1 Four Square Step Test (FSST)

The Four Square Step Test (FSST) was developed in 2002 to measure the rapid stepping that is often required when changing direction and avoiding obstacles while walking. Originally developed for older adults, the FSST has been widely used in neurological populations and in musculoskeletal conditions such as joint replacements, arthritis, osteoporosis, orthotic design for lower extremity trauma and amputees (Moore). The purpose of the test is to assess a persons' dynamic balance.^{3,4}



The patient is supposed to sequentially step over four canes set-up in cross configuration on the ground. The patient stands in square 1, facing square 2. The patient is required to step as fast as possible into each square in the following sequence: 2, 3, 4, 1, 4, 3, 2, and 1: this requires the patient to step forward, backward, and sideways and to the right and left. The time to complete this is recorded.

The FSST has excellent interrater and retest reliability in samples of healthy and impaired older adults, vestibular disorders and stroke. Its' validity is supported by good correlations with other balance and mobility tests.^{3,5}

Table 9 Cut-off scores for increased risk of falls

Diagnose	Cut-off score
Stroke ⁶	>15 seconds or failed attempt=increased risk of falls for acute stroke patients
Parkinson's Disease ⁷	> 9.68 seconds=higher risk of falls
Vestibular disorders ⁸	>12 seconds=increased risk of falls

Geriatrics ⁹	>15 seconds=greater risk of falls
Unilateral trans-tibial amputees ⁹	≥24 seconds=greater risk of multiple falls

8.4.3.4.2 Walking stairs

Subjects walk up and down 3 steps in stairs, twice.

8.4.3.4.3 Sweat patch placements

After the treadmill activity as defined in the protocol, the subjects will be asked to rest comfortably in a sitting position and doff the prosthetic device and rest for 2 minutes. While subject doffs and rests, take out the sweat patch from the outer packaging using the forceps provided with the sweat patches and place on the weighing balance. Take the weight measurement and note down in LSR measurement CRF. Wipe an area of interest on the residual limb and matching area on the sound limb. Now carefully wipe the ROI on both limbs with alcohol wipes. Wait for a minute for the alcohol to evaporate. Carefully remove the rest of the support material from the sweat patch and mark carefully as RL and save. Note down the time with a timer. Perform the same procedure to the sound limb. Label the support material from the sound limb as SL. Keep the pad in the area for 10 minutes and then remove carefully using the plastic forceps. Weigh the patch with the respective support materials and note down the number in LSR CRF. A difference in weight before and after 10 minutes will be calculated as the sweat amount in 10 minutes and rate may be calculated as sweat (g)/min. Finally, drop the sweat patches in individual tubes containing 5 mL of saline. Make sure the patch is immersed completely in saline. Wait 15 minutes and then remove the patches from saline and send the saline for culture in path lab.

8.4.3.4.4 Heart rate monitor

To ensure the safety of the participant, a heart rate monitor will be administered to all participants. Participant's will wear the heart monitor throughout the duration of the treadmill task.

8.5 Compensation

8.6 Responsibilities

Sponsor

- Identify sites
- Investigate possible vigilance cases/SAEs

Principal Investigator

- Screen subjects
- Explain investigation to participants
- Conduct investigational procedures at investigators' site
- Investigate possible vigilance cases/SAEs

Local Principal Investigator

- Screen subjects
- Explain investigation to participants
- Responsible for obtaining informed consent from test subjects
- Fit users with investigational device (and back to their current device)

Monitor

- Monitoring activities
- Analyze results
- Write report

Co-Investigator

- Collect Data
- Analyze results
- Write report
- Conduct investigational procedures at investigators' site

8.7 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/PI/CI of missing data or nonconformities to the study protocol.

The study monitor(s) and LPI/PI/CI will maintain communication on a minimum biweekly basis, via telephone and email. The LPI/PI/CI 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.

9 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
- Date of use
- Subject ID
- Date of device return
- Date of return of unused, expired or malfunctioning investigational devices, as applicable

10 Statistical Considerations

10.1 Statistical design and procedures

The area under the relative humidity curve from the time of donning the liner to the time of exiting the hot room will be the primary outcome to assess the efficacy of the intervention. The test liner will be compared to the control liner using a generalized linear model. Relative humidity at the time point immediately prior to liner donning will be included in the model as a covariate.

Perceived sweat will be compared with a one sample, two-tailed t-test. All CLASS subscales will be compared using a one tailed Wilcoxon-Signed-Ranks test.

Acceptance criteria for the data, as applicable, is defined in Table 6 **Endpoints, test methods and hypotheses**. Subgroup analysis will not be performed as no subgroups are defined.

10.2 Sample size calculation

It is expected that 10 subjects are required to complete the protocol with a power of 0.95 and significance at 0.05. Effect size was estimated based early feasibility investigation results.

For pass/fail criteria, see Table 6 **Endpoints, test methods and hypotheses**.

10.3 Additional statistical matters

There is no provision for interim analysis and 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. Dropouts 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.

11 Amendments and Deviations from the Protocol (CIP)

11.1 Amendments

Any amendments to this protocol must be first approved by the sponsor and PI, or LPI for single site studies, and then be evaluated by the IRB/REB/REC 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/REB/REC and, where appropriate, regulatory authorities can be sufficient.

11.2 Deviations

Investigators are not allowed to deviate from this protocol without a formal approval from the IRB/REB/REC, 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/REB/REC.

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/REB/REC. Such deviations shall be documented and reported to the sponsor and the IRB/REB/REC 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/REB/REC 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/REB/REC 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 wellbeing, and the scientific integrity of the clinical investigation the LPI shall be disqualified from further participation in the clinical investigation.

12 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 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/REB/REC, and regulatory authority as applicable, has been obtained.

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

13 Ethical Considerations

13.1 Anticipated clinical benefits

A patient using the investigational device may or may not benefit clinically from using the device vis-a-vis using another **Össur Seal-In® TF silicone liner** and **Direct Socket** commercially available.

Expected benefits while using the investigational device:

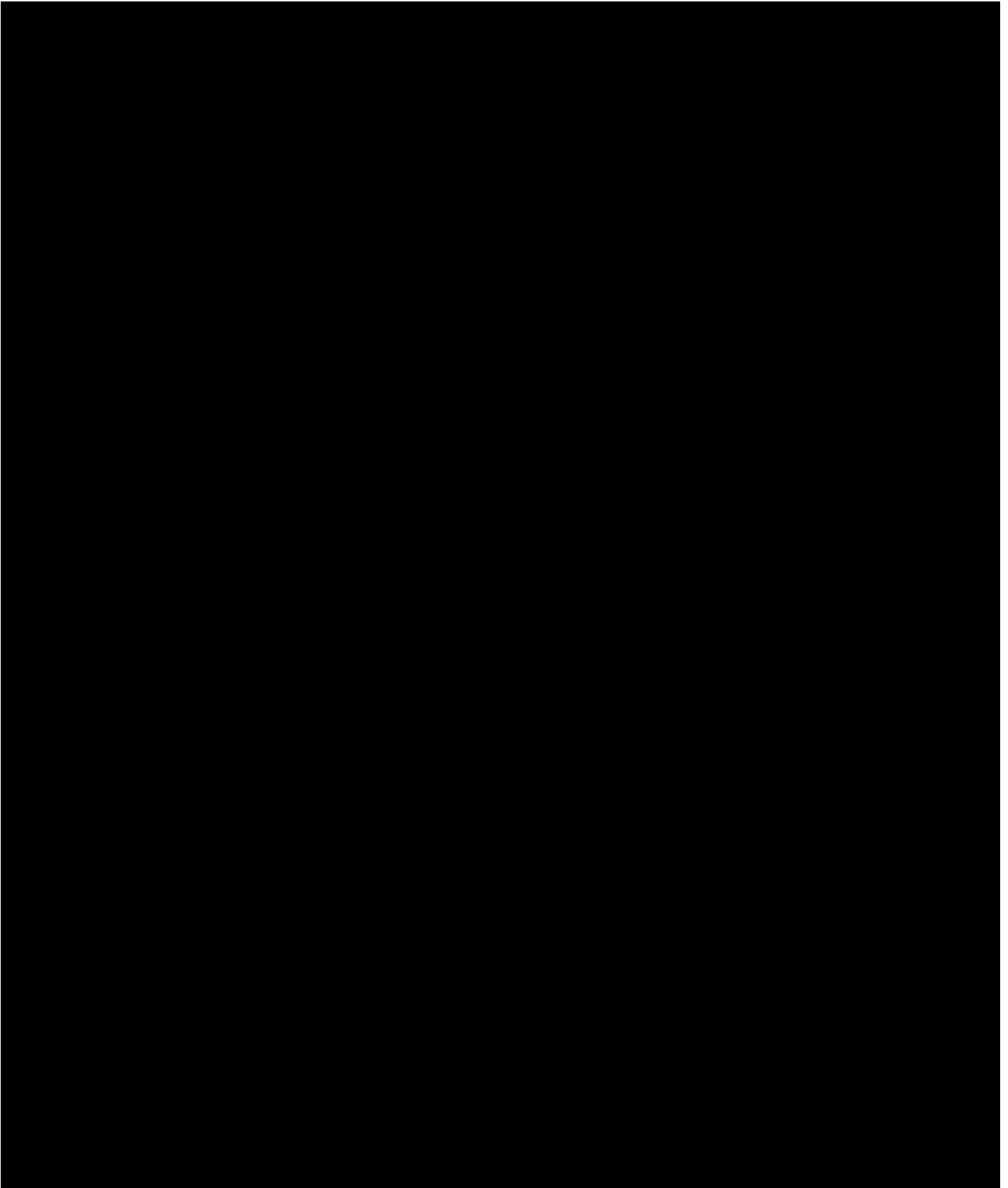
- Measured moisture on skin is reduced
- Perceived moisture on skin is reduced
- Perceived stability is no worse
- Perceived suspension is no worse
- Perceived comfort is no worse

Compared to not using an **Össur Seal-In® TF silicone liner** and **Direct Socket**, in combination with the remaining part of the prosthesis, 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 amputation.

Additionally, the benefit for the user during the testing is that he/she helps in developing a new and novel perforated Össur TF silicone liner and socket design.

13.2 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 QM1673 Risk Management process, based on ISO 14971 (Risk Management for Medical Devices). All changes performed to the functions of a device are submitted to multi-level verification and, as applicable, validation processes before being authorized for use in a



13.3 Risk of Study (To Patient)

At each visit the PI, a certified CPO, will be present to ensure the safety of the participants. The study adds no additional risk other than the risks identified above and in Hazard Analysis [REDACTED]

There is one harm (H0.56) that is additional to other normal silicone liners identified in the Hazard Analysis (see Annex 17.3.1), harm that relates to the skin contact surface of the investigational device (the liner) that has holes (for breathability). These holes might cause localized skin pressure and friction which results in skin irritation. This will be monitored during the study.

Additionally, holes will be drilled to the body of subjects' socket (proximal part). This is to add to the breathability of the complete liner/socket system. This will not affect the structural integrity of the socket.

Subjects will use the investigational device as their primary prosthetic liner in the same manner as they would normally do on their current liner. Thus, they are not required to do anything different from their routine clinical visit for acquiring a new liner and their daily living activities between study visits.

13.4 Risk Mitigation

For each device designed by Össur risk mitigation is part of the design process according to ISO 14971. Furthermore, each participant fitted with a liner 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 liner.

As part of the training process, the participant will be informed on the risks inherent in using a liner in an uncontrolled environment. Moreover, the participant will be provided with the product literature (Instructions for Use), as well as being informed and trained on how to use the product.

To mitigate a potential safety risk when exercising in hot environment the exclusion criteria has been adapted not to expose patient with cardiological condition to physically demanding activities and to monitor subjects heart rate during the physical activity in the heated room.

13.5 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.

13.6 IRB/REB/REC Review and Communications

The study protocol (CIP), informed consent form, and other study documentation forms require IRB/REB/REC review and approval. Communication to and from the IRB/REB/REC shall be directed from or to the primary Össur contact, the Study Monitor:

[REDACTED]

Continuous communication will be maintained between Össur and the IRB/REB/REC, as required. Moreover, communication will be maintained between the PI and the IRB/REB/REC, as required.

13.7 Vulnerable populations

No vulnerable populations will be enrolled.

13.8 Informed Consent

The Principal Investigator, 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.

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

13.9 Participant confidentiality – Data management

Subjects will be assigned a random 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. A list connecting the ID to the subject's name will be stored in a password secured file. This list will be destroyed at the end of the study. Only investigators involved in the investigation will have access to this information.

Frames in video recordings will only contain the lower extremities of subjects and any ambulatory assistance provided with their hands. Frames containing the face or other identifiable features of subjects will be deleted immediately, if accidentally captured.

A representative of the sponsor, sponsor research assistant, will only be present at the study location during test run and training, not during formal data collection. A declaration of confidentiality to be signed by the representative, ensures necessary data protection.

A Clinical Investigation Report (CIR) will be generated by 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.

14 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 subchapter 13.2 above.

14.1 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 14155:2011 for details.

14.2 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 e-mailed to the sponsor within 24 hrs. Within ten days the Sponsor will report to the IRB/REB/REC and relevant regulatory authority, FDA. Any serious device related adverse event will lead to the immediate termination of the investigation. In this case all participants will be contacted immediately and advised to go back to their current prosthesis and stop using the investigational device. An appointment will be made for them to return the investigational 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 will keep their previous prosthesis and will be free to use it if they experience any problems with the investigational device.

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

Contacts in case of unexpected adverse event:

()
()
()
()

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.

14.3 Suspension or premature termination of the clinical investigation

The sponsor/principal investigator, the IRBs/REBs/RECs, 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/REBs/RECs 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/REBs/RECs, 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 investigation, since group allocation is visible.

15 Publication Policy

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

16References

Internal Document References:

[1]	
[2]	

External Literature References:

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