

Iceform - Clinical Investigation Protocol

Investigation on Failure Time Analysis of a new TPE Material in the Iceform liner

Locking

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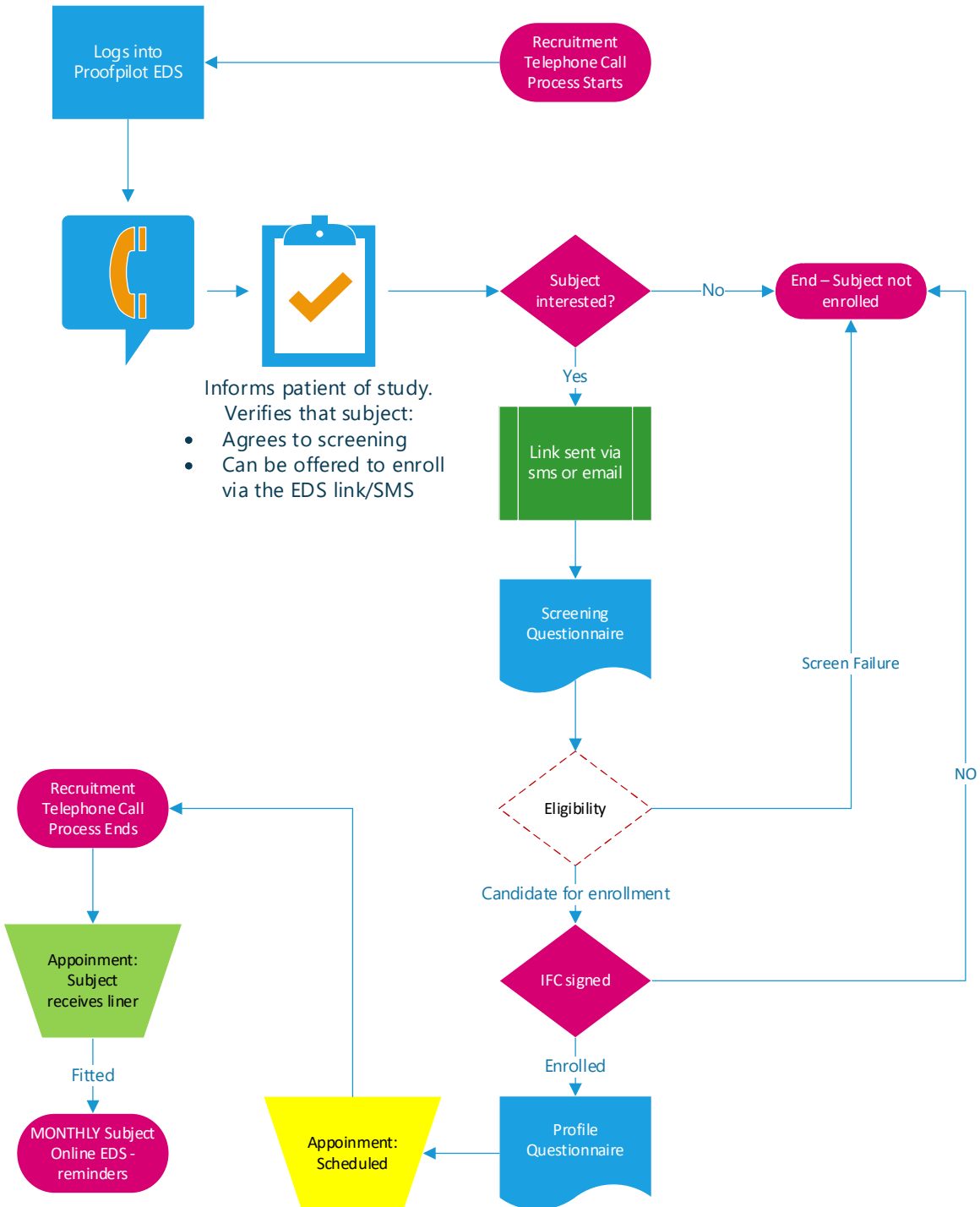
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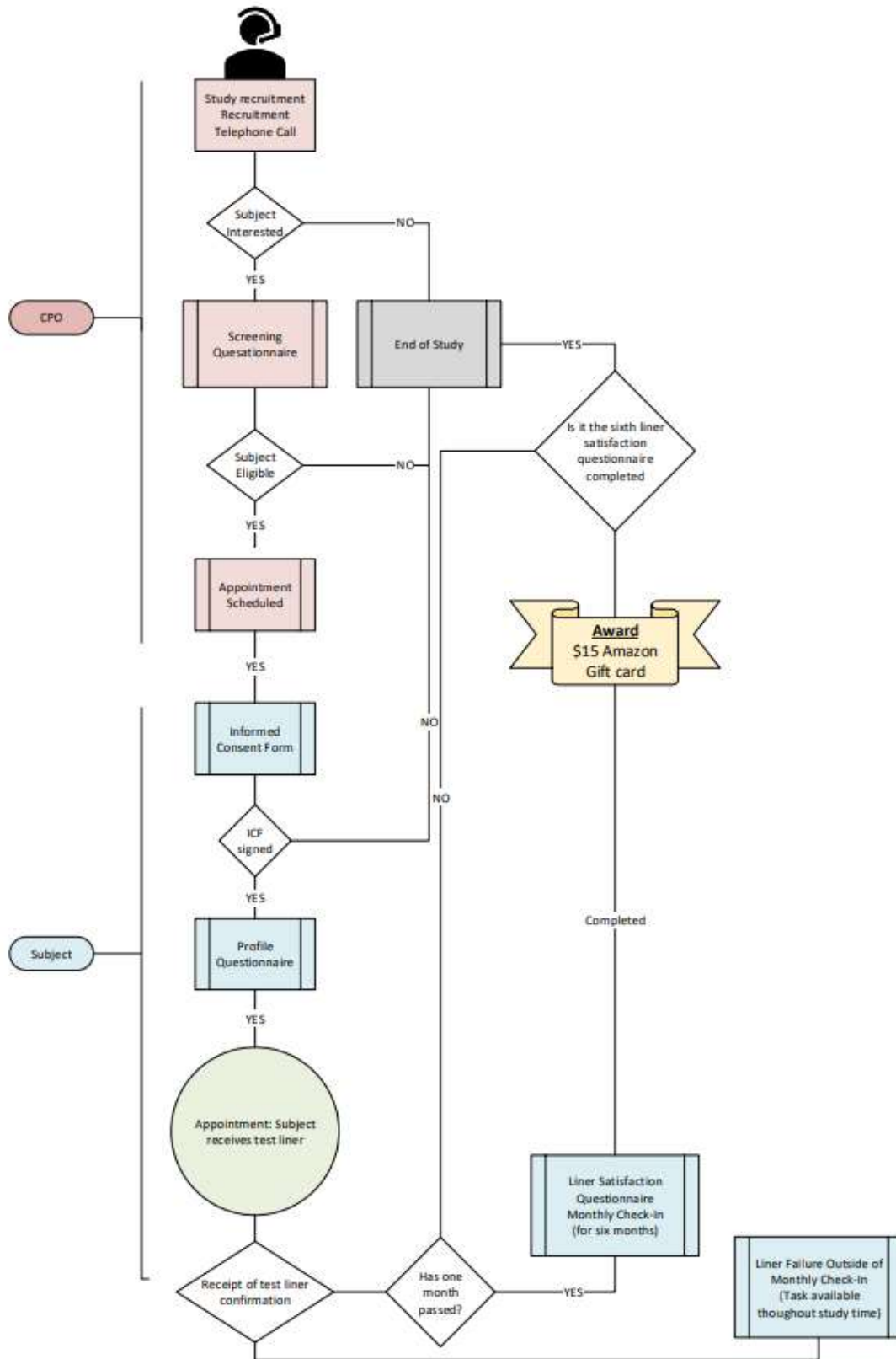
2 Summary

Device(s) being tested:	Proprietary name of device: ICEFORM: Iceform Cushion, Iceform Locking, Iceform Sleeve Version: TPE material 565	
Instruments and equipment:	Instruments consist of self-report questionnaires via an online EDS system on the subjects use and condition of the investigational device.	
Subjects recruited:	Inclusion criteria:	Exclusion criteria:
70 subjects are to be recruited	Transtibial amputee	Participating in another research study
	Uses an Iceform or Willow Wood Alpha Classic (Uniform profile) liner	Participants of another research study during previous 2 months.
	Willing and able to participate in the study and follow the protocol	
	Confident prosthetic users for more than 3 months	
	Older than 18 years	
Procedures:	See Flowcharts 1 and 2 below.	

Flowchart 1 Recruitment and Consent Procedures



Flowchart 2 Subject Study Procedure



3 Changes from Previous Revision

3.1 Changes for Revision 1.00

Initial release.

4 Abbreviations

ADE	Adverse Device Effect
AE	Adverse Event
AR	Adverse Reaction
BL	Baseline
CA	Competent Authority
CEP	Clinical Evaluation Plan
CER	Clinical Evaluation Report
CI	Co-Investigator
COI	Coordinating Investigator
CIB	Clinical Investigator's Brochure
CIP	Clinical Investigation Plan
CIR	Clinical Investigation Report
CRF	Case Report Form
EC	Ethics Committee (see IEC, IRB, REB and REC)
EDS	Electronic Data capture Service
FU	Follow-Up
GCP	Good Clinical Practice
CIB	(Clinical) Investigator Brochure
ICF	Informed Consent Form
IDMF	Investigational Device Management Form
IEC	Independent Ethics Committee
IFU	Instructions for Use
IRB	Independent/Institutional Review Board
LCI	Local Co-Investigator
LPI	Local Principal Investigator
LRA	Local Research Assistant
PI	Principal Investigator
PIS	Participant Information Sheet
REB	Research Ethics Board
REC	Research Ethics Committee
SAE	Serious Adverse Event
SADE	Serious Adverse Device Event
SOP	Standard Operating Procedure
SOTA	State-Of-The-Art
USADE	Unanticipated Serious Adverse Device Effect

5 Investigational Device

The investigational device is a modification on a previously marketed device and will be labeled according to regulations concerning investigational devices.

See Table 1 for details on the investigational device.

Table 1 Identification and Description of the Investigational Device

Summary description of the investigational device and its intended purpose:	The device is a prosthetic liner. It is Class I, a low-risk product, and is a further development of a well-established technology. ICEFORM liners are new trans-tibial prosthetic liners for suspension (with/without a suspension sleeve) and cushioning purposes for prosthetic legs. The product is derived from competitor liner Willow Wood Alpha Classic (Uniform profile). Thermoplastic properties make the liner thermo-formable, that is, it can be permanently re-shaped to an individual's residual limb shape. Profiles, sizes and suspension options are as follows: Suspension options: Locking and Cushion Profile: Uniform Fabric: Current Iceform fabric Anterior thicknesses: 3,6,9 mm Sizes: Small, Medium, Medium+, Large, Large+, Extra large The ICEFORM sleeve is a prosthetic suspension sleeve, based on current Össur ICEROSS Sleeve. The suspension sleeve is intended to be used with a cushion liner in order to obtain a passive vacuum prosthetic suspension. The fabric contains a matrix limiting stretching of the TPE material in the transverse plane while not limiting stretching in the sagittal plane. Both the sleeve and liners are made from thermoplastic elastomer (TPE), covered with Iceform textile fabric. The textile is composed of 66% polyester, 17% Nylon and 17% Spandex (elastane). Final color of the textile is dark blue: Pantone 7546C. The liner is non-invasive, single patient use. Given proper hygienic care as stated in Instructions for use, the product is reusable. The liner is intended to be rolled on a lower limb residual (trans-tibial), the product will therefore be in direct contact with user's intact skin. The user will wear the liner throughout the day, or whenever ambulating. The device is not sterilized, and is supplied in a sealed plastic bag and enclosed in a carton box for protection The device is classified as external limb prosthetic component according to Title 21 §890.3420, bearing the product code ISS: "prosthesis, thigh socket, external component". It is 510(k) and GPM exempt, except for general requirements. 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.
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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:	Proprietary name of device: ICEFORM: Iceform Cushion, Iceform Locking, Iceform Sleeve Version: TPE material 565 Product Number: <u>Liners</u> • T-TTPPSS: ○ TT: Type ▪ 01: locking (pin-lock) ▪ CL: cushion ○ PP: Profile ▪ 03/06/09 mm ○ SS: Sizes ▪ 15/18/20/25/28/33 <u>Sleeve</u> • S-2011SS ○ SS: Size ▪ 35/41/49/55/62
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 lot number and item 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:	The device is part of a prosthesis system targeted for trans-tibial amputees (bi- or unilateral) physically fit for using a prosthesis to replace the function of an amputated lower limb. It is intended for continuous use by trans-tibial amputees of low to moderate impact levels. Indication: Trans-tibial amputation.
Description of the investigational device:	See above and Table 2 below for descriptions of device features and their relation to the investigation. The TPE material, inner surface of the device is in direct contact with the skin. 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 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	N/A

use of the investigational device:	
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Table 2 Technical and functional features

#	Feature	Description (if not obvious)	Covered by this investigation:
1	New TPE material (#565)	Thermoplastic elastomer gel that makes up most of the liner/sleeve	Yes
2	Textile fabric cover	Textile holding the TPE material; the outer surface of the liner	Yes (indirectly)
3	Hard TPE cap (locking liner only)	Cap for attaching pin	No

6 Justification for the Design of the Clinical Investigation

Primary function of a liner is to provide a suspension mechanism between the amputees' residual limb and the prosthesis, and to provide a cushioning interface between the skin and the prosthesis.

Thermoplastic elastomer (TPE) combines the advantages thermoforming like a thermoplastic with the cushion and resiliency of urethane. TPE exhibits elements of an elastomer with thermoplastic binding in a SBS block structure. SBS or styrene-butadiene-styrene creates a structure with butadiene "blocks" in a microscopic cross-linked nanostructure linked by polystyrene clusters linked in a covalent thermoplastic structure. The polystyrene acts as microscopic crosslinks that can be loosened and broken with heat, but reform during cooling. This allows the material to be stretched twice its original length repeatedly and return to the original shape. TPE can be formed in a semi liquid state with high-pressure injection molds and the cross-linking will reform.

Being a thermoplastic, TPE can be reformed to a shape using moderate temperature but has the tendency of thinning more than urethane with repeated loading. TPE can be made extremely soft and can be made softer with the addition of skin friendly softening oils such as mineral oil soften the material further. TPE can be extremely soft from the mid 20's to low 30's on the shore 00 scale. Softness is typically correlated to durability, but not necessarily to thermoform ability. Materials that are softer typically have less shear resistance and poor notch sensitivity meaning they tear more easily. TPE has a very low durometer and was not a viable product until it could be reinforced with fabric

During development of the liner a literature review was conducted to evaluate the safe use of TPE liners. Furthermore, a clinical investigation was conducted at multiple sites in USA and Canada. During the investigation some failures were identified, and the design was adjusted. These new iterations were also tested within the investigation. However, due to the changes in the study and the liner design very few individual liners were used for a long duration (i.e. more than 3 months). The liners were considered safe to use and to perform as well, and in some aspects better than the Willow Wood Alpha Classic (Uniform profile) competitor liner.

After a few months on the market Össur started receiving a lot of complaints that the TPE material in the liner was failing:

"TPE liners cracking in distal/proximal direction after relatively short use. Multiple customer returned samples show abnormal wear where there are cracks in the TPE, in some cases single crack but others were had the posterior side completely cracked.

Test results provide evidence that the chemical resistance of the current TPE material is very limited against organic oils. Many common cosmetics used on skin include these oils and therefor likely to come to contact to the TPE.

Furthermore oils are produced naturally by the skin. Tests with artificial body fat crack the TPE liner when applied under tension while competitor TPE shows no failure. This indicates that the current TPE is not resistant to body fat and liner likely to fail/crack early if user has fatter skin or does not wash liner often."

Effectively, the TPE material blend was not resistant to the body fat of most people.

This failure slightly increases the risk of blisters but was otherwise not considered to increase risk of suspension if the liner was used as intended – i.e. the liner became obviously unusable. A prosthetic liner is not designed to last long, however these types of failures should not have come up except in extreme cases after a long duration of use.

A new TPE material blend has been developed and tested in mechanical simulated use under different conditions. The liner containing this material blend, but otherwise of the same design, is ready to be tested in real world situation.

To evaluate the durability of a new material blend in the liner an investigation of liner durability (survival) analysis is appropriate, where a large sample of the indicated population uses the liner for at least 6 months, with regular prompts on the durability of the liner.

7 Objectives and Hypotheses

The primary objective of this study is to evaluate the durability of the investigational device over its intended use lifetime (i.e. warranty period), specifically relating to any defect in the TPE material. Additionally, to gather information on the rate of side-effects, i.e. skin rashes, sores, etc.

Secondary objectives relate to gather information on how amputees use the liner, specifically:

- Intensity of use (days/week and hours/day)
- Alternation; i.e. switching every other day between liners
- Use of personal hygiene or cosmetic products

The following performance and safety aspects are to be verified (relating to features in table 2 above):

- The ICEFORM line of devices are durable over their intended use lifetime.

The rate and nature of side-effects will be evaluated.

The hypothesis and endpoints are specified in Table 3.

For all hypothesis:

cf_r is the cumulative failure rate at the time of evaluation;

Table 3 Endpoints, test methods and hypotheses

	Hypothesis	Test Method	Endpoint	Acceptance Criteria
A	Users report less than 2.5% cumulative failure rate of the TPE material (relating to the material defect) at 3 months	Self-report: <i>EDS in-house generated questions on liner failure</i>	Cumulative failure rate	$H_0: cf_r \geq X_{cf}$ $H_1: cf_r < X_{cf}$ $p < 0.05$
B	Users report less than 2.5% cumulative failure rate of the TPE material (relating to the material defect) at 6 months	Self-report: <i>EDS in-house generated questions on liner failure</i>	Cumulative failure rate	$H_0: cf_r \geq X_{cf}$ $H_1: cf_r < X_{cf}$ $p < 0.05$ And acceptance of hypothesis A

8 Design of the Clinical Investigation

8.1 General

The investigation will be of a single group, prospective, non-blinded design. Bias is not expected to significantly affect the outcome of the investigation as the endpoint is an objective outcome. Underreporting is likely the most significant source of bias. Measures, i.e. using a state-of-the art EDS tool have been taken to minimize that bias.

Initial fitting of the investigational device will be conducted at prosthetic out-patient clinics. All further activities will be conducted via an EDS online service.

As stated above the primary endpoint is cumulative failure rate, see Table 3. See previous chapter on objectives and hypothesis and Table 3 for rationale. Drop-outs and withdrawals will not be replaced.

No measuring equipment or published instruments will be used. The EDS system will prompt subjects to fill in basic information on their usage of the device and if they notice any failures.

See chapter **10.2 Sample size calculation** and Table 3 for analysis of variables.

Equipment required for each subject:

- Device with an internet connection
- Investigational device: Iceform liner (two liners for each subject)
 - Sleeve for cushion users, if required.

Study subjects will each receive two liners because many amputees are used to alternate between liners on a day-to-day basis. Only providing one liner would require a behavior change for some subjects that might affect the accuracy of some of their questionnaire responses. All subjects will have to answer if they are alternating between the two liners provided.

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

8.2 Investigational Device(s) and Comparator(s)

The subjects will be asked to use the investigational device as their primary prosthesis for 6 months. Individual exposure will differ between subjects. Subjects are expected to use it for their daily living activities as they would with any other prosthesis, for up to 18 hours a day depending on the amputee

In this investigation there is no comparator device.

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.

No other device, medication or intervention will be used.

70 subjects are to be enrolled and therefore 140 investigational devices will be used, as the devices are intended to be used by a single subject; two for each subject.

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 electronic 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 4 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:
Trans-tibial amputee	Participating in another research study
Uses an Iceform or Willow Wood Alpha Classic (Uniform profile) liner	Participants of another research study during previous 2 months.
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 not 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 is expected to be 8 months. Each individual subject is expected to participate in the clinical investigation for 6 months. The estimated time needed to include this number (enrollment period) is 2 months.

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

8.4 Procedures

i) Recruitment

Potential subjects will be identified from the customer base of a relevant clinic. If a potential participant may fit the inclusion and exclusion criteria, he/she will be contacted by a Co-Investigator (CI) via telephone. During the telephone call the CI will verify if they are interested in participating in a study and will initiate the enrollment procedure. If interest is expressed at this point they will answer some screening questions and if the eligibility criteria is met the subject is offered to enroll by getting a study invite through ProofPilot, the EDS, and an appointment to come in for initial fitting will be set up. Questions relating to the duration of the study, number of clinical visits required, and the investigational device will be answered at this time.

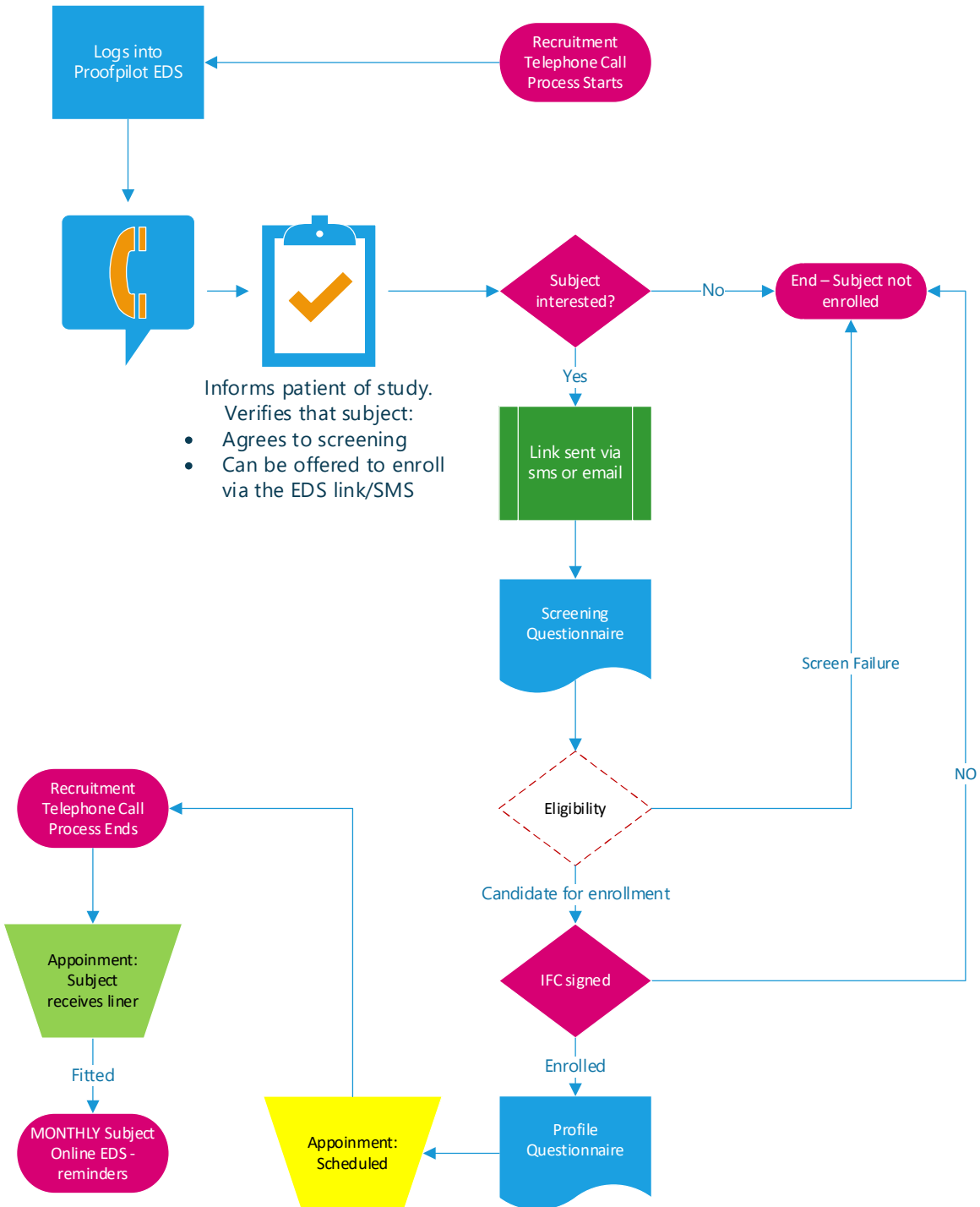
Following this the subject will log into ProofPilot online and go through the e-ICF, if signed, the subject will answer a profile questionnaire.

The next step will then be the appointment when the subject comes into their clinic and gets the investigational device. In some cases, the subject will get the liner shipped to their home address. This will only be done upon subjects request due to long distance from clinic. And only for very confident prosthetic users which are used to handle a new liner by themselves.

Potential risk of participating in the investigation will be explained to the subject at this point. The CIs will communicate to the study monitors the number of users that have been identified that meet the inclusion/exclusion criteria and are willing to participate.

See flow-chart below for the recruitment and enrollment procedure. Additionally, refer to chapter 13.8 Informed consent.

Flowchart 3 Recruitment and Consent Procedures



ii) Test procedure

There are seven scheduled study events: 1 visit to the clinic and 6 online questionnaires to be filled in. 5-30 subjects will be recruited at each site.

During the clinical visit the subjects will only be fitted to the Iceform investigational liner. Profile and relevant contact information will already have been collected via the EDS.

Subjects will then receive a prompt monthly, either via email, SMS or smartphone notification, to fill in the EDS questionnaire, and perform any tasks as applicable. If a subject reports a failure he/she will be instructed to stop using the liner, the remaining gift cards will be delivered and their participation ends. Otherwise, participation will end at 6 months.

The subject gets to keep the investigational device at the end of the study, therefore there is no need for an additional visit.

Subjects that report a failure of the TPE material may be contacted by the Coordinating Investigator or CI if the root cause of the failure cannot be confidently determined from the data collected with the EDS system.

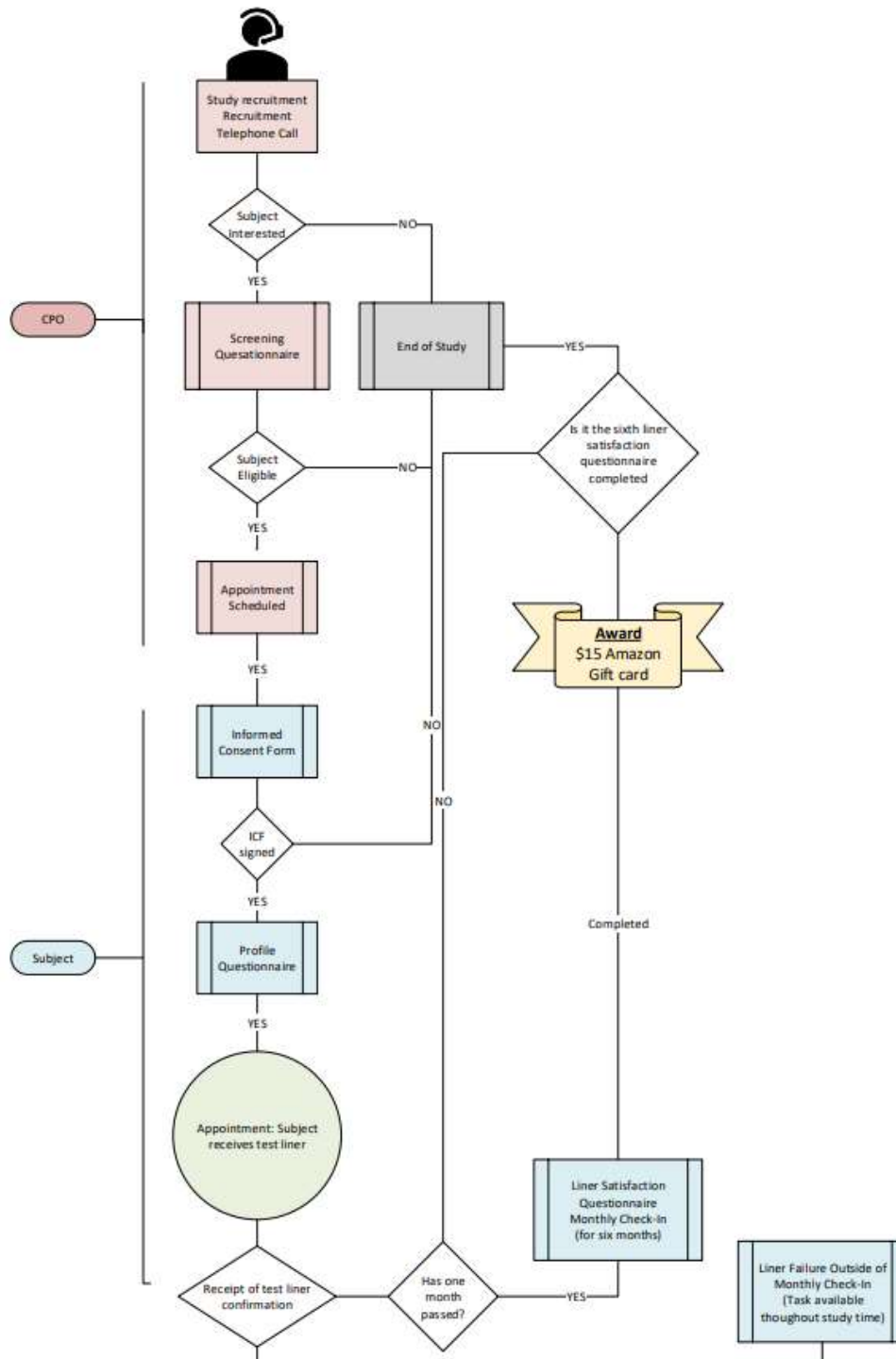
See flowchart below for details.

iii) Measurements and data collection

The same questionnaires, consisting of questions regarding the use of the investigational device and its condition will be used and filled in at six separate points in time. See flowchart below and questionnaires in appendix for further details.

For each subject there is one scheduled visit to the study site (in most cases) and questionnaires/tasks administrated seven (one at baseline and six follow-up prompts) times during the course of the study.

Flowchart 4 Subject Study Procedure



8.5 Compensation

Subjects will be compensated for their participation with an Amazon.com e-gift card delivered via the EDS, see plan in Table 5 Compensation for Clinic and Subject below.

For all Clinical Testing activity, compensation for the clinic will be as follows:

- 400US\$ for each estimated half day (1-4 hours) and
- 800US\$ for each estimated full day (4-8 hours)

Table 5 Compensation for Clinic and Subject

Event #	Event description	Activity	Subject compensation	Clinic compensation
-1	Screening	Phone call screening; EDS link sent	0	400-1200 USD
0	Study visit	Site visit and fitting of liner; Subject profile completed in EDS	0	400-2000 USD
1	1-month follow-up	EDS link with questionnaire sent	15 USD	0
2	2-month follow-up	EDS link with questionnaire sent	15 USD	0
3	3-month follow-up	EDS link with questionnaire sent	15 USD	0
4	4-month follow-up	EDS link with questionnaire sent	15 USD	0
5	5-month follow-up	EDS link with questionnaire sent	15 USD	0
6	6-month follow-up	EDS link with questionnaire sent	15 USD	0
Total			90 USD	800-3200 USD

Expected compensation is 800-3,200 USD per clinic, depending on the number of subjects recruited.

Any deviation from this expected compensation plan must be duly justified.

8.6 Responsibilities

Sponsor Coordinating Investigator

- Identify sites
- Investigate possible vigilance cases/SAEs

Monitor

- Monitor trial
- Analyze results
- Write report

Co-Investigators (CI)

- Collect Data
- Screen subjects
- Explain trial to participants
- Responsible for obtaining informed consent from test subjects if not obtained via EDS system
- Conduct all trial procedures at investigators' site

- Fit users with the investigational device

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 CI of missing data or nonconformities to the study protocol.

The study monitor(s) and PI/CI will maintain communication on a minimum bimonthly basis, via telephone and/or email. The PI/CI will provide the study monitor(s) with information of all scheduled study visits. No monitoring study site visits are required for this study.

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 CI will keep records documenting the use of the investigational device in the Investigational Device Management Form, including:

- Lot no. and item no. of each investigational device
- Date of delivery
- Subject ID
- Date of return of unused, expired or malfunctioning investigational devices, as applicable

10 Statistical Considerations

10.1 Statistical design and procedures

The dataset will be assessed with inferential statistics based on the acceptance criteria for the data, as applicable, as described in Table 3 Endpoints, test methods and hypotheses.

Standard methods of survival analysis will be used to evaluate the end points in addition to modeling and/or stratifying with baseline characteristics or time-variant covariables, as applicable.

10.2 Sample size calculation

Failure rate related to defects in the TPE material were estimated from the Össur complaints database, for the period from when the devices entered the market until May 2019. The relevant data were used as an input for an online sample size calculator¹; sample size for a single arm study, 1 sided test using survival probability with alpha = 0.05 and power = 0.8, and parameters:

Accrual time = 2

Follow-up time = 6

Null survival prob = 0.975

Alt survival prob = 0.9075

At time = 6

Gives a sample size of 66, with approximate lower and upper critical values at 0.93 and 1 respectively.

Minimum 5 and maximum 20 subjects will be recruited at each site.

Given a drop-out rate of 5%, 70 subjects will be recruited.

For pass/fail criteria, see Table 3 **Endpoints, test methods and hypotheses**.

10.3 Additional statistical matters

The failure rate will be monitored during the trial. An interim analysis of n = 33 at 2 and 3 months. If the TPE material failure rate is above 5%, with respect to the hypothesis described in chapter 7, at either follow-up the trial shall be terminated as the liner will have failed its requirements.

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 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.

¹ <http://stattools.crab.org/Calculators/oneArmSurvivalColored.html>

11.2 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 PI knowledge of the deviation. The PI/CI 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 wellbeing, and the scientific integrity of the clinical investigation the PI 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, and regulatory authority as applicable, has been obtained.

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

Subjects are provided with health insurance with expenses covered of up to 100.000 USD relating to any adverse health outcomes in relation to the clinical investigation [insurance policy].

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 prosthetic liner commercially available.

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

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 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 Chapter 7 in the Clinical Investigator's Brochure.

The design criteria are an important input in the risk analysis but also the experience of existing products of similar function and/or type. The device and similar devices are currently marketed by Össur; post-market surveillance data provides data on device related risks as experienced in the real-world application of the device, see Clinical Investigator's Brochure [1] for details.

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 [1].

13.3 Risk of Study (To Patient)

At the visit, a PI/CI, a certified CPO/CO/CP, 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 prosthetic liner and their daily living activities for their duration of the study.

13.4 Risk Mitigation

For each device designed by Össur risk mitigation is part of the design process according to ISO 14971 [2]. Furthermore, each participant fitted with the Iceform prosthetic liner 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 prosthetic 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 (e.g. Information for User), as well as being informed and trained on how to use the product.

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 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 Study Monitor. Continuous communication will be maintained between Össur and the IRB, as required. Moreover, communication will be maintained between the PI and the IRB, as required.

13.7 Vulnerable populations

No vulnerable populations will be enrolled.

13.8 Informed Consent

The subject will receive the consent information within the EDS and be able to accept it prior to their first visit. Screening will be done via telephone call conducted by the PI/CI, and if screening is past during the telephone call the subject is offered to sign the ICF. The potential subject can raise any questions regarding the consent or any other study issue directly to the PI/CI. If the consent has not been completed prior to the first visit the Principal Investigator, or any researcher qualified, will obtain from the user, electronic informed consent for 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 be given the opportunity to ask questions.

In case the information on the ICF changes, and subjects need to be provided with new information, the PI/CI will contact each subject by phone and explain the new information as required.

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.

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 via the online EDS ProofPilot.

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 the EDS system ProofPilot. This list will be destroyed at the end of the study. Only investigators involved in the trial will have access to this information.

All online data will be collected via the online EDS ProofPilot. ProofPilot maintains a continuous review for adherence to HIPAA and CFR Part 11. All data will be stored in an encrypted format in servers located in the USA or Canada. ProofPilot's platform is hosted at Amazon Web Services (AWS) data centers, which are highly scalable, secure, and reliable. AWS complies with leading security policies and frameworks, including SSAE 16, SOC framework, ISO 27001 and PCI DSS. Given that ProofPilot does send messaging to participants in research studies, as part of the informed consent process, (as reviewed by the IRB), participants will be asked to consent to communications through these channels. ProofPilot is adherent to CAN-SPAM and international equivalents.

The screening form will be filled in via the online EDS ProofPilot.

Non-identifiable data will be downloaded at the end of the trial and stored on a password secured computer and intranet.

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 chapter 7 in the Clinical Investigator's Brochure [1].

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 faxed to the sponsor within 24 hrs. Within ten days the Sponsor will report to the IRB and FDA. 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 go back to their current prosthesis and 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 will keep their previous liner and will be free to use it if they experience any problems with the trial device.

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:

Justin's Pratt mobile: +1 (720) 442-3759; email: jpratt@ossur.com

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.

15 Publication Policy

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

Results will not be submitted for publication.

16 References

Internal Document References:

[1]	CIB2019061418, Clinical Investigator's Brochure, Benedikt Þorri Sigurjónsson
[2]	RMR2016031758, Risk Management Report, Linda Rós Birgisdóttir

17 Appendix

17.1 Questionnaires

17.1.1 Screening Form

1. Are you trans-tibial (below knee) amputee? Y/N
2. Are you currently using an Iceform OR Willow Wood Alpha Classic Uniform liner? Y/N
3. Can you read and write English? Y/N
4. Are you participating in another research study? Y/N
5. Have you been in another research study during previous 2 months? Y/N
6. Are you 18 years old, or older? Y/N

17.1.2 Profile Questionnaire

1. Please select the most appropriate option that describes your activity level:
 - a) I only move around in the home, short distances and on level ground only.
 - b) b) in addition to a) I can overcome small obstacles, i.e. curbs and single staircases.
 - c) c) in addition to b) I can walk at varied speeds for extended time, overcome obstacles and overall I have small limitations in mobility.
 - d) d) in addition to c) I am mobile without any limitations.
2. What is your current liner brand?
 - a) Össur Iceform
 - b) WillowWood Alpha Classic Uniform liner
3. Do you usually alternate between two or more liners? Y/N
4. What is your current liner size? Please see photos explaining where to find the size of your liner (see red square).



- a) Small
- b) Medium
- c) Medium+
- d) Large
- e) Large+
- f) X-Large

5. I use a:
 - a) Locking liner
 - b) Cushion liner with a sleeve
6. What is the name of your clinic?

17.1.3 Liner Satisfaction (monthly for 6 months)

1. How many days a week do you use the Iceform trial product(s)?
 - a) 1 day
 - b) 2 days
 - c) 3 days
 - d) 4 days
 - e) 5 days
 - f) 6 days
 - g) 7 days
2. How many hours a day do you use the Iceform trial product(s)?
 - a) 1-2 hours
 - b) 2-4 hours
 - c) 4-6 hours
 - d) 8 hours+
3. Are you alternating between two liners? Y/N
(If YES to previous question)
 - Why are you alternating between two liners?
 - a) My liner doesn't suit all my daily activities.
 - b) My liner is uncomfortable.
 - c) MY liner is failing.
 - d) The liner needs to be rested intermittently.
 - e) Purely out of habit.
4. Compared to the socket fit with your previous liner, please rate the fit of your socket when using the Iceform trial liner.

Tighter/Same/Looser
5. Do you apply any lotions or creams on your residual limb before you put on the Iceform trial product(s)? Y/N
(If YES to previous question)
 - Please specify the brand and model of the lotion/cream you use. E.g. NIVEA - smooth sensation body lotion.
6. Have you experienced any rashes on your residual limb over the past four weeks? Y/N
(If YES to previous question)
 - Over the past four weeks, rate any rash(es) that you got on your residual limb:
7. Have you experienced any blisters or sores on your residual limb over the past four weeks? Y/N

→Over the past four weeks, rate any blisters or sores that you got on your residual limb.
8. With only your Iceform liner on (without socket), how would you rate the ease of bending your knee compared to your previous liner?
Worse/Same/Better
9. Have the Iceform trial product(s) conformed/adapted to the shape of your residual limb in the last 4 weeks?
Y/N
10. Compared to your previous liner, how would you rate the smell of your Iceform trial product(s) after use?
Worse/Same/Better
11. Are you able to observe any cracking in the white liner/sleeve material (the TPE gel)? Y/N
12. Is it otherwise functioning as expected?
(If NO to previous question)

→Please explain why:

13. If you had the choice, which liner type would you prefer to continue using at this stage?

Iceform

My previous liner

14. Please explain why:

15. Any other comments?