

Iceform - Clinical Investigation Protocol

Investigation into the functional performance of a new Thermoplastic Elastomer (TPE) transtibial liner

NCT02622919

TPE

CONFIDENTIAL DOCUMENT

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Investigator's Statement: I agree to conduct this clinical study in accordance with the design and specific provisions of this protocol; modifications to the study or protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to await IRB/EC approval for the protocol and informed consent before initiating the study, to obtain informed consent from subjects prior to their enrolment in the study, to collect and record data as required by this protocol and case report forms, to prepare adverse effect reports as required by this protocol, and to maintain study documentation for the period of time required.

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1 How to Refer to This Document

- [0] Investigation into the functional performance of a new Thermoplastic Elastomer (TPE) transtibial liner, Clinical Investigation Protocol, Internal Document CIP2015061050, Revision 1.0, Össur Iceland, August 2015.

2 Summary

Össur plans to launch a new prosthetic liner for transtibial amputees, made of Thermoplastic Elastomer (TPE). Össur is a leading company in the provision of liners made from silicone but has no prior experience working with TPE. To validate the design of the new ICEROSS TPE liner and substantiate claims set forth in the MNBA table a clinical test was therefore needed.

The R&D Engineering identified a suitable liner to use as a comparator device. All outcomes will be measured against the comparator liner, with the hypothesis that the new ICEROSS TPE liner is non-inferior.

The clinical investigation is designed as an uncontrolled open prospective, multicenter, 2 group, pre-test post-test study. Testing will be conducted in the USA at 3-6 clinics, depending on enrolment requirements. 20 subjects currently using the comparator liner will be recruited: 10 using cushion/sleeve and 10 using pin-lock.

The study consists of 4 study events, requiring subjects to visit the clinic at least 4 times; as this study requires the manufacturing of a new socket, more than one iterations might be required. These events will be as follows:

Table 1. Study timeline and events

Study Event	Study Visit	Timeline	Data Timeline	Activity
1	1	0	Baseline	Signing of ICF and study ID allocation. User profile and baseline measurements. Measurements/casting for socket manufacture
2	2	1-2 weeks		New socket and ICEROSS TPE fitted
	2a, 2b...	(1-2 weeks; stacks up)		Iterations as required
3	3	3-4 weeks	2 week follow up	Measurement set
4	4	6.5-7.5 months	6 month follow up	Measurement set

Total time needed to complete the test is expected to be 12 months.

3 Investigational Device

ICEROSS TPE liner is a TT prosthetic liners for suspension and cushioning purposes. The product is derived from ICEROSS Comfort liners that have been on the market since 1999.

The most significant difference is that the profile of the liner is made of Thermoplastic Elastomer (TPE) instead of Silicone Elastomer, as in other ICEROSS liners. The liner contains fabric cover on the outside similarly as current ICEROSS liners.

The liner will both be available with locking suspension and sleeve suspension (cushion liner) and the profiles and sizes will be the same as the available Comfort liners.

The ICEROSS TPE will be rolled on a lower limb residual (transtibial), so the product will be in direct contact with user's intact skin. The user will wear the liner throughout the day, or whenever ambulating.

It is intended to be fitted by a certified prosthetist. The product is intended for continuous use by transtibial amputees of low to moderate impact levels.

ICEROSS TPE is a predicate based product, meaning that this product provides clinical benefits that are matching a similar product that is already present in the market, it is based on known technology and has already been documented from a clinical benefits standpoint; that is on the knowledge of the clinical benefits of using a prosthetic liner.

Nevertheless, the main material in the product, that is the material that is in contact with the intact skin will not be the same as in previous Össur products and will therefore need to be thoroughly validated. The main material has been in some forms on the market in competitive prosthetic liners.

A prosthetic liner is a Class I medical device according to the FDA, and is 510(k) Exempt. It is classified as a Non-significant risk device.

[REDACTED]

4 Justification for the Design of the Clinical Investigation

One of the greatest challenges in prosthetic care is the interface that must occur between the skin of the residual limb and the artificial materials of the prosthesis. Our skin has numerous functions, including the insulation and temperature regulation of our bodies, providing sensation and the synthesis of Vitamin D. However, of its many functions, perhaps none is more important than maintaining a physical barrier to protect our bodies from the external environment.

The skin covering the residual limb of an amputee was not designed for loading and is prone to numerous abuses; shear forces, positive pressure of weight bearing, alternating positive and negative pressure (hickey effect), etc. While advances in materials have assisted in protecting this tissue, substantial challenges persist. Even small skin lesions can lead to larger problems, particularly among those patients with compromised vascularity in whom healing can be frustratingly slow. [1]

Given these challenges, it is not surprising to observe that skin problems are common among lower limb amputees, from fairly benign redness of the skin to more severe events that can force temporary disuse of the prosthesis or even revision amputation. [2]

Prosthetic users require a comfortable liner and good socket to avoid skin problems and to prevent discomfort while using the prosthesis for daily activities. Prosthetic liners have two main functions: to cushion the load between the socket and the residual limb and contribute to the suspension mechanism of the prosthesis. Additionally the tackiness of the material, combined with its elastic nature provide important features: they absorb much of the shear forces that come with normal standing, walking and turning and which would have otherwise be translated to the skin. [1]–[3]

Many choices of liner technology are available, mainly made from silicone or other elastomers: pin-locking liners, cushion liners, and seal-in liners. [3]

Prosthetic users have different experience of different types of liners. The process of choosing the most appropriate liner material for a patient remains very subjective. Just as individuals have different preferences regarding the stiffness of their mattress or their pillow, patients have different preferences regarding the material characteristics of their liners. [3]

The ICEROSS TPE liner is a non-invasive, non-sterile, reusable (i.e. non disposable) device, which is used as part of prosthetic system. An amputee typically wears a prosthesis and thereby utilizes the ICEROSS TPE liner, for up to 18 hours a day over duration of multiple months.

Based on evidence in the literature it is most appropriate to have an amputee compare the function and performance of liners between liners of the same types and that he/she is familiar with. This clinical investigation is therefore designed in such a way that amputees that are currently using a predicate liner will be asked to use the ICEROSS TPE. Performance and function of each liner will be evaluated subjectively by the amputees.

The predicate products which ICEROSS TPE is based on are defined as ICEROSS Comfort liner which is an Össur liner and main competitive liner OWW Alpha Classic. ICEROSS Comfort is a silicone liner while OWW Alpha Classic is a TPE liner. Amputees currently using OWW Alpha Classic users will therefore be recruited for this clinical investigation.

The clinical investigation is designed to evaluate whether the investigational device is suitable for the purposes and the population for which it is intended, low-moderate active. It is designed to demonstrate the product performance and safety based on product intended use and operating environment and on demonstrating that the clinical performance level is similar to predicate products, by using product line production parts.

It is designed in such a way as to ensure that the results obtained have clinical relevance and scientific validity and address the clinical investigation objectives.

5 Objectives and Hypotheses

5.1 Objectives

The purpose of the study is to validate functional and safety parameters of a new TPE liner via subjective feedback from users (n= 20). For that purpose the new TPE liner will be measured against subject's current liner, the comparison liner, (baseline) after 2 weeks of use, i.e. data collected at 2 weeks is used to evaluate the outcome of primary objectives.

Secondary objectives are: to evaluate whether an Iceross Comfort silicone liner can be retrofitted into a socket made for the ICEROSS TPE liner (to retrofit = minimally¹ adjust the socket an amputee is currently using so that the amputee may comfortably use a different kind of liner than he/she is currently using); evaluate the effects of long-term use, at 6 months.

6 Endpoints, Test methods and Hypotheses

The primary and secondary endpoints are specified in Table 1. The objective is to show that the new ICEROSS TPE liner is non-inferior to the OWW Alpha Classic liner.

For all hypothesis:

μ_1 is average of measurements at baseline (comparator);

μ_2 is the average of measurements at 2 week follow up (investigational device);

and $|M_{NI}|$ is the margin of non – inferiority

Table 2. Endpoints, test methods and hypotheses

	Hypothesis	Test Method	Endpoint	Acceptance Criteria
A	Users report on average no worse suspension in terms of security throughout the day than with predicate product	Self-report: <i>Suspension Questionnaire</i> (10 cm VAS)	<i>Difference in suspension score</i> (average of 7 items)	$H_0: \mu_1 \geq \mu_2 + M_{NI} $ $H_1: \mu_1 < \mu_2 + M_{NI} $ $ M_{NI} = 0,5 \text{ cm}$ $p < 0.05$
B	Majority of users report no worse skin reaction when compared to predicate product.	Self-report: <i>PEQ – Residual Limb Health</i> (10 cm VAS)	<i>Difference in PEQ – Residual Limb Health subscale score</i> (average of 6 items)	$H_0: \mu_1 \geq \mu_2 + M_{NI} $ $H_1: \mu_1 < \mu_2 + M_{NI} $ $ M_{NI} = 1,5 \text{ cm}$ $p < 0.05$
C	Socket fit comfort (ease of bending the knee, comfort while sitting and the overall comfort) should be on average no worse than previous socket fit.	Self-report: <i>VAS scales: Socket fit Comfort Score; Knee Bending Score; Single item; Comfort While Sitting Score;</i>	<i>Difference in comfort score for each item:</i> <i>All 3 items must pass the criteria</i>	$H_0: \mu_1 \geq \mu_2 + M_{NI} $ $H_1: \mu_1 < \mu_2 + M_{NI} $ $ M_{NI} = 0,5 \text{ cm}$ $p < 0.05$

¹ As limited as possible

D	All users should be able to use the trial liner as their primary prosthesis for the trial period	Observation	Number of subjects that drop out because of dissatisfaction with the liner (not socket related)	No drop-outs because of product dissatisfaction, at 6 months
E	Users rate the noise of the prosthesis as no worse with the test liner compared to their previous liner.	Self-report: M586 Liner User Questionnaire, Noise item: 5-point scale	Difference in satisfaction grade for noise generated	$H_0: \mu_1 \geq \mu_2 + M_{NI} $ $H_1: \mu_1 < \mu_2 + M_{NI} $ $ M_{NI} = 0,5$ $p < 0.05$
F	For locking liners only: All users report level of pistoning no worse than predicate product	Displacement test: Displacement of thigh and socket marker in stance (loaded) compared to unloaded 0Nm and with 30Nm pull condition on the prosthesis	Difference in thigh displacement	$H_0: \mu_1 \geq \mu_2 + M_{NI} $ $H_1: \mu_1 < \mu_2 + M_{NI} $ $ M_{NI} = 2.5 \text{ mm}$ $p < 0.05$
G	User can successfully retrofit from ICEROSS TPE to ICEROSS COMFORT liners	Self-report: VAS scale, Socket fit Comfort Score	Difference in socket fit comfort score	$H_0: \mu_1 \geq \mu_2 + M_{NI} $ $H_1: \mu_1 < \mu_2 + M_{NI} $ $ M_{NI} = 0,5 \text{ cm}$ $p < 0.05$

6.1 Device performance and Safety assessment

Table 3. Medical Necessity-Benefit Analysis

Specifics addressed	Device feature	To be measured	Testing method
Retrofittable to Iceross cushion & pin	Liner shape and thickness	Self-report	SFCS, VAS, Questionnaire
Durability	TPE with Matrix	Self-report, observation	Questionnaire, evaluation
Pistoning		Displacement of thigh and socket marker in stance (loaded) compared to unloaded 0Nm and with 30Nm pull condition on the prosthesis	Distance change in mm
Noise related to socket movement		Self-report	Questionnaire
Socket comfort		Self-report	SFCS, VAS

The liner show similar performance as the comparator device.

Device is safe to use as intended.

7 Design of the Clinical Investigation

7.1 General

i) Design

The study is of an uncontrolled open prospective multicentre 2 group pre-test post-test design. The study sample will consist of 20 subjects, but will be split into 10 subject groups for hypothesis relating to hypothesis A and F, specifically. The measures taken will be: subjective evaluation at Baseline, pertaining to users current liner; subjective fitting questionnaire relating to the socket used for the test (repeated as required); subjective questionnaires answered by the user at 2 weeks and at 6 months post successful fitting, pertaining to the ICEROSS TPE liner.

The study will be conducted in the US only.

Below knee amputees are a relatively small sub-sample of the US population. Amputees currently using OWW Alpha classic liners are an even further sub-sample of those. The inclusion and exclusion criteria ensure that the participants eligible for the clinical investigation are representative of the below knee amputated population, using a TPE liner.

As stated in table 1 above the primary endpoint is A, and the secondary endpoints are B, C, D, E, F, G in that respective order of significance.

Drop-outs and withdrawals will not be replaced.

ii) Equipment and instruments

Equipment required for each subject:

- Pen/pencil
- Printed out instruments
- Investigational device: ICEROSS TPE
 - Sleeve for cushion users, if required
- Retrofitting comparator: ICEROSS COMFORT
- Marker and measuring tape
- Camera

7.2 Investigational Device(s) and Comparator(s)

The investigational device is a liner of thermoplastic elastomer. It is being developed to broaden Össur's product line and offer solutions to a wider range of amputees that for some reason do not feel comfortable with a silicone liner.

The shape (profile) of the new ICEROSS TPE liner is based on the ICEROSS COMFORT while the TPE material is designed to behave in a similar way to an Alpha Classic liner. Alpha Classic has been selected as the industry standard to compare with, being identified by Össur engineers as the highest quality TPE liner currently on the market. By using the ICEROSS COMFORT profile it is expected that most users can retrofit between the silicone and TPE liners.

OWW Alpha Classic Uniform, 3 and 6 mm, and Tapered, 3 mm, will be used as the comparator medical device.

ICEROSS COMFORT will also be used for retrofitting evaluation.

As 20 subjects are expected to be enrolled in the study, 20 investigational devices will be used.

7.3 Subjects

The number of participants is limited by difficulties in identifying appropriate subjects for enrolment. The aim is to recruit 20 subjects in total; 10 using cushion suspension and 10 using pin-licking suspension. See chapter 8.1 Sample size calculation, for further details.

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 is fitted with a new socket and leaves the clinic wearing the ICEROSS TPE liner;
- 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;

i) Inclusion Criteria

Only patients with the following characteristics are eligible for study entry:

- Cognitive ability to understand all instructions and questionnaires in the study;
- Bi- or unilateral transtibial amputee, low to moderate impact
- Amputee currently using a cushion (n=10) or a locking (n=10) 3 or 6 mm OWW Alpha Classic Uniform, or 3 mm OWW Alpha Classic Tapered liner;
- Willing and able to participate in the study and follow the protocol;
- Confident prosthetic users for more than 3 months;
- Older than 18 years;

ii) Exclusion Criteria

Patients with the following characteristics are not eligible for study entry:

- Users with cognitive impairment;
- Transfemoral amputees;
- Amputees not using a prosthesis for daily activities;
- Amputees not using OWW Alpha Classic cushion (n=10) or a locking (n=10), 3 or 6 mm OWW Alpha Classic Uniform, or 3 mm OWW Alpha Classic Tapered liners, as part of their primary prosthesis;

iii) Subject withdrawal

A subject can withdraw from participation at any time, at his/her discretion, and this will not have any consequences for the participant's treatment.

In such cases a report stating reasons for discontinuation of the participant shall be prepared by the LPI.

In such a case 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.

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.

The relevant LPI can withdraw the participant from the trial at any time. The reasons shall be documented. There are no pre-specified criteria for discontinuation of participants from trial.

The discontinuation of participants in the trial will not result in replacement with new participants.

Withdrawn participants will be included in the data analysis, as applicable, for the procedures that they completed. If the participants have not provided any data, they will not be included in the data analysis.

Note that subjects can drop out after the 2 week visit without affecting evaluation of primary objectives.

iv) Point of enrolment

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

v) Time considerations

The total time period required to implement the clinical investigation is expected to be 12 months. Each individual subject is expected to participate in the clinical investigation for 6-7 months, depending on socket manufacture iterations. The estimated time needed to include this number (enrolment period) is 4 months.

7.4 Procedures

i) Recruitment phase

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

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

ii) Test procedure

3-10 users will be recruited at each site.

User Profile instrument will be filled in at the initial visit. It will be filled in by the CPI/LPI with input from the subject.

Baseline instrument will also be filled in at the initial visit. It consists of 5 parts: Usability, Suspension Questionnaire, PEQ – Residual Limb Health (PEQ-RLH), Comfort and other (noise and satisfaction). They only include VAS items and comment boxes. Additionally the pistoning test output is documented at the end.

The first part, socket fit comfort, of the Socket fitting instrument will be administrated each time as required, depending on iterations needed. CPO feedback, usability and comfort will only be administrated when the subject comes in for the first time for the fitting.

The 2 week follow up instrument will be administrated at the 2 week post successful fitting visit. It consists of 5 parts: Usability, Suspension Questionnaire, PEQ-RLH, and Comfort and Other; same as Baseline. Additionally the pistoning test output for both the trial liner (ICEROSS TPE) and is ICEROSS COMFORT is documented at the end.

The Retrofitting instrument is also administrated at study event 3 (expected visit 3).

The instrument used at the 6 month follow up consists of 4 parts: Suspension Questionnaire, PEQ-RLH, Comfort, and Other. The Other part has additional questions compared to the instruments used at earlier visits.

All items are in-house developed except for the socket fit comfort score[4] and PEQ-RLH[5].

iii) Visit Schedule and forms to fill out

There are at least four scheduled study events.

Each visit, except when fitting to trial product will take approximately 2 hours. The trial product fitting visits (event nr. 2, 2a, 2b, etc.) should last for no more than 30 minutes.

The first event is a visit within the normal treatment procedures of prosthetic care when the users are measured for a new socket. The ICF will be signed prior to any study activity. During the visit the subjects will also fill in the User Profile and Baseline instruments, with the help of their CPO as required.

This test, as is standard for liner testing, requires that the users will be fitted with a new socket. Attaining a proper fit of a new socket requires at least one iteration, often more, and few days to complete, and hence some users might require more study visits than others.

The second study event will be 1-2 weeks post first visit, when the new socket is ready. Subjects will come in and fit the new socket while wearing the investigational device. To verify that the socket is acceptable subjects will be

asked to fill in the Socket fitting instrument. If the outcome is positive the subject will be scheduled for the 2 week follow up and subject goes home with the new prosthetic liner. If not, a new socket must be made or adjustments to the one manufactured and another visit set up for this event.

The third study event is the 2 week follow up. During the visit the subject will fill in the 2 week follow up instrument and the Retrofitting instrument, after retrofitting. Subject keeps using the investigational device.

The final study event, and expected fourth visit, is at 6 months post successful fitting. The subject fills in the 6 month follow up instrument, receives compensation as applicable and ends study participation.

The subjects will return the trial device at the 6 month visit.

Table 4. Test procedure and schedule

Activity	Pre-study task	Study Visit 1	Study Visit 2	Study Visit 2a),b)...	Study Visit 3	Study Visit 4
Screen patient	X					
Sign informed consent		X				
Assign study ID		X				
Complete User Profile instrument		X				
Liner Measurement Set (Baseline instrument)		X				
Pistoning measurement		X				
Measurements for socket manufacture		X				
Fit to investigational device and new socket			X			
Verification of study socket (Socket fitting instrument)			X			
Fit to trial product - visits as iterations require				(X)		
Verification of study socket (Socket fitting instrument)				(X)		
Liner Measurement Set (2 week follow up instrument)					X	
Pistoning measurement					X	
Retrofitting ICEROSS COMFORT					X	
Retrofitting instrument					X	
Liner Measurement Set (6 months follow up instrument)						X
Fit to previous prosthesis						X

Return of investigational device	X
Payment for subject participation	X
End of study participation	X

For each subject there are at least 4 scheduled visits to the study site and questionnaires administrated each time during the course of the study.

7.5 Compensation

i) Subject

[REDACTED]

ii) Clinic

[REDACTED]

Table 5. Compensation for clinic, on per subject basis

Study Event	Study Visit	Timeline	Data Timeline	Activity	Expected work/time compensation
I	I	I			
I	I				
I	I				
I	I				

* [REDACTED]

² [REDACTED]

7.6 Responsibilities

Sponsor Principal Investigator

- Identify clinics
- Collect Data
- Investigate possible vigilance cases/SAEs

Co-Investigator

- Collect Data
- Analyze results
- Write report

Monitor

- Monitor trial
- Analyze results
- Write report

Local Principal Investigator (LPI)

- Screen subjects
- Explain trial to participants
- Responsible for obtaining informed consent from test subjects
- Conduct all trial procedures at investigators' site
- Fit users with trial prosthesis and back to their current prosthesis

7.7 Study monitoring and Oversight

██████████ will monitor the study to ensure all procedures are followed correctly and according to the study protocol. He will gather and review all study data and inform the Local Principal Investigator of missing data or nonconformities to the study protocol.

The study monitor and LPI will maintain communication on a minimum biweekly basis, via telephone and email. The LPI will provide the study monitor with information of all scheduled study visits. The study monitor, or a Sponsor Co-Investigator on his behalf, will visit each investigational site at least once while a study visit takes place.

8 Investigational Device Management

The trial device will be provided as needed for the study population. Devices will not be packaged but will be marked according to FDA requirements. Subjects will not be blinded.

The #1CI will keep records documenting the receipt, use and return of the investigational device, 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

9 Statistical Considerations and Data Analysis

9.1 Sample size calculation

The number of participants is limited by difficulties in identifying appropriate subjects for enrolment. With respect of the acceptance criteria, twenty users will be asked to participate in the study, 10 from each group.

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

9.2 Data analysis and acceptance criteria

The Suspension Questionnaire will be used as the primary endpoint.

The dataset will be assessed with Descriptive Statistics and within-subjects t-tests only, comparing the means and variance for the two data points: prior-evaluation (current TPE liner) and post-evaluation (ICEROSS TPE liner). Acceptance criteria is defined in Table 1 **Endpoints, test methods and hypotheses** under Section 5.2

No particular information will be excluded from the test. Subgroup analysis will be performed for hypothesis A, E and G.

For pass/fail criteria, see Table 1. If the null hypothesis is not rejected, that the performance/safety of the ICEROSS TPE is not inferior to the users' current prosthetic liner, that means the device is ready to progress with no further functional design changes. Conversely if the null hypothesis is rejected, suggestion inferiority of the trial device, that will trigger rework and subsequent retesting of the device. All device failures will be investigated and acted upon.

9.3 Drop-outs, withdrawals and deviations

Drop-outs and withdrawals will be grouped together and their baseline data compared to the baseline data of the subjects that finished the investigational procedures. Any statistical differences of the two groups will be reported.

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.

10 Amendments and Deviations from the Protocol (CIP)

10.1 Amendments

Any amendments to this protocol must be first approved by the sponsor and PI 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.

10.2 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 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/EC 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.

11 Statement of Compliance

The clinical investigation 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.

12 Ethical Considerations

12.1 Risk of Device

For each new product a thorough risk analysis is carried out according to hazard analysis. The hazard analysis study helps quantifying the criticality and probability of the failures. The design criteria is an important input in the risk analysis study but also the experience of existing products of similar function. ICEROSS TPE development processes are performed following the guidelines of Risk Management for Medical Devices (ISO14971). The liner is submitted to multi-level verification and validation processes before being authorized for field testing and subsequent release.

i) Anticipated adverse device effects

There are no serious non unanticipated adverse device effects. See chapter 12.3.

ii) Residual risks

The ICEROSS TPE is intended to provide the same function as any other cushion or pin-lock liner. However, as with any new development, possible negative effects cannot be eliminated, e.g. the liner performing in a non-predictable way. The odds are considered low and have been further minimized by careful review of the design with an associated risk assessment. See chapter 12.3.

12.2 Risk of Study (To Patient)

At each visit the Local Principal investigator, a certified prosthetist and orthotist, 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 a part of their primary prosthesis in the same manner as they would normally do on their current liner. Thus, aside from filling in a set of questionnaires and take part in a single measurement during study visits they are not required to do anything different from their routine clinical visit for acquiring new prosthesis and their daily living activities between study visits.

12.3 Risk mitigation

Each participant fitted with an ICEROSS TPE liner (cushion or pin-locking) 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 prosthetic liner.

As part of the training process, the participant will be informed on the risks inherent in using a prosthetic liner made from TPE. 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.

12.4 Benefit for participant

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. Compared to not using a prosthesis the patient will benefit significantly in terms of mobility and ability to live independently. The benefit for the user during the testing is that he/she helps in developing a new liner.

12.5 Risk-to-benefit rationale

The development of a prosthetic liner is controlled by a multi-level verification and validation processes before being authorized for field testing and subsequent release. The Validation & Verification process execution, coupled to the risk management and control strategy deployed for the new TPE liner ensure that the residual risk associated with use of the device in typical daily living conditions does not exceed risks level associated with the operation of any prosthetic liner under similar condition.

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

12.6 IRB/EC 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/Study Monitor: Benedikt Þorri Sigurjónsson. Continuous communication will be maintained between Össur and the IRB. Moreover, communication will be maintained between the local Principal investigator and the IRB.

12.7 Informed Consent

The Local Principal Investigator will obtain from the user, 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.

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.

12.8 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 until the end of the study at which point it will be destroyed. Only investigators involved in the trial will have access to this information.

Unlinked data will be stored indefinitely on a secure SharePoint server location together with other Research and Development files. The screening form will be in paper format and will be stored by the principle investigator in a locked container.

[REDACTED]

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13 Evaluation of Adverse Events and Device Deficiencies

13.1 Definitions of adverse events and device deficiencies

An adverse event (AE) is any undesirable clinical occurrence in a subject, whether or not considered related to the trial intervention.

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 one 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 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 analysis 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.

13.2 Reporting procedure of adverse events and device deficiencies

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

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.

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14 Suspension or Premature Termination of the Clinical Investigation

The sponsor/principal investigator, the IRB, and the regulatory authorities can decide about trial 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 trial is terminated or suspended all trial participants will be informed and appropriate follow-up will be assured. If sponsor/principal investigator terminates or suspends the trial the relevant IRB 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/ECs, and relevant regulatory authorities will be notified and provided with the relevant data supporting the decision.

15 Publication Policy



16References

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