# Clinical Study Protocol:

## «Descriptive Study of Receptive Fields in lower limb Amputees and the Effect of a related Stimulation System on selected Gait Parameters»

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| Study Type: | Clinical trial with Medical Device (MD) |
| Study Categorisation: | Clinical investigations or other studies of medical devices, risk category A |
| Study Registration: | The study is intended to be registered on the SNCTP (automatically through this application) and before initiation of the project also in a WHO primary register (ClinicalTrials.gov) |
| | Identification Numbers: |
| Study Identifier: | Not applicable |
| Sponsor, Sponsor-Investigator or Principal Investigator: | Dr. med. Groegli Marion |
| | Rehaklinik Bellikon (SUVA) |
| | Sportmedizin und Rehabilitation |
| | Rehaklinik Bellikon |
| | Mutschellenstrasse 2 |
| | 5454 Bellikon |
| Investigational Product: | Phantom Stimulator (Cort X Sensorics, Spaichingen, Germany) |
| Protocol Version and Date: | Protocol Version 01, 08.09.2017 |

# Signature Page(s)

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|---|---|
| Study number | RKB-SMR-01 |
| Study Title | «Descriptive Study of Receptive Fields in lower limb Amputees and the Effect of a related Stimulation System on selected Gait Parameters» |

The Sponsor-Investigator and trial statistician have approved the protocol version 01 (dated 08.09.2017), and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm if applicable and the local legally applicable requirements.

Sponsor-Investigator:

Dr. med. Groegli Marion

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| Place/Date | Signature |

Local Principal Investigator at study site*:

I have read and understood this trial protocol and agree to conduct the trial as set out in this study protocol, the current version of the World Medical Association Declaration of Helsinki, ICH-GCP guidelines or ISO 14155 norm and the local legally applicable requirements.

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| Site | Rehaklinik Bellikon<br>Mutschellenstrasse 2<br>5454 Bellikon |
| Principal investigator | Dr. med. Groegli Marion |

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| Place/Date | Signature |

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# STUDY SYNOPSIS

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|---|---|
| **Sponsor / Sponsor-Investigator** | Dr. med. Groegli Marion<br>Rehaklinik Bellikon<br>Sportmedizin und Rehabilitation<br>Rehaklinik Bellikon<br>Mutschellenstrasse 2<br>5454 Bellikon |
| **Study Title:** | «Descriptive Study of Receptive Fields in lower limb Amputees and the Effect of a related Stimulation System on selected Gait Parameters» |
| **Short Title / Study ID:** | Receptive Fields and their stimulation, RKB-SMR-01 |
| **Protocol Version and Date:** | Protocol Version 02, 10.10.2017 |
| **Trial registration:** | The study is intended to be registered on the SNCTP (automatically through this application) and before initiation of the project also in a WHO primary register (ClinicalTrials.gov) |
| **Study category and Rationale** | Clinical investigations or other studies of medical devices, risk category A.<br>This study is a clinical evaluation as it involves the direct testing of patients. The risk category A is justified as the medical device bears a conformity marking, and is used in accordance with the instructions. |
| **Clinical Phase:** | Descriptive study of the receptive fields and phase of final evaluation of efficacy on patients of the stimulation system. |
| **Background and Rationale:** | It has been observed that patients subjected to amputations develop so called receptive fields, which time of occurrence and localization over time are yet not examined systematically.<br>A receptive field is defined as skin area anywhere on the same side of the body as the amputation, which when stimulated by others, causes phantom sensations in the amputated extremity.<br><br>Furthermore, a device has been developed and certified, which can stimulate these receptive fields, and though evoke those sensations, through conventional TENS-Electrodes. |
| **Objective(s):** | This clinical trial aims to investigate the reliability in detecting these receptive fields as well as their incidence and changes over time.<br><br>Further it aims to evaluate the acute effect of the stimulating system (“Phantom Stimulator” (Cort X Sensorics, Spaichingen, Germany)) on selected gait parameters measured tough a gait analysis system (“OprtoGait” (Microgate, Bolzano, Italy)) as well as on phantom sensations measured through a questionnaire. |

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| **Outcome(s):** | The primary outcomes are the changes in size and position over time and their timed occurrence after the amputation of these receptive fields as well as the inter-/intratester reliability in their detection.<br><br>The secondary outcomes are the change in selected gait parameters and phantom sensations through the application of the stimulating system ("Phantom Stimulator" (Cort X Sensorics, Spaichingen, Germany)). |
| **Study design:** | The primary outcome is of mere descriptive nature. Therefore, no control group is created and the participants are not blinded or randomized.<br><br>For the secondary outcomes, every tested subject serves as its own control (cross over). The gait analysis as well as the questionnaire are performed three times. The two measurements after the first familiarization measurements are performed in a randomized order. |
| **Inclusion / Exclusion criteria:** | <u>Inclusion criteria for descriptive study:</u><br>-Lower limb amputation (independently of side or height of amputation)<br><br><u>Inclusion criteria for Phantom stimulator:</u><br>-Receptive fields present at testing day 31 (last regular assessment of the receptive fields)<br>-Lower limb amputation below the knee (if both sides the system is applied to the dominant side)<br><br><u>Exclusion criteria:</u><br>-Implanted devices (defibrillator or pacemaker)<br>-Pregnancy |

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| **Measurements and procedures:** | Before enrollment into the study, the possibility of participation is assessed through an internal screening of the database of the Rehaklinik Bellikon as well as through a telephonic/personal Interview with the interested people. A Pregnancy test is also conducted.<br><br>**<u>Receptive Fields:</u>**<br><br>After the inclusion into the study the procedures are planned as follows:<br><br>-Day 1: detection of the receptive fields by one single tester at a self-selected time of day.<br>-Day 2: detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1.<br>-Day 7: detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1.<br>-Day 14: detection of the receptive fields at the same time of day as on day 1 by another tester as on day 1.<br>-Day 21: detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1.<br>-Day 28: detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 14.<br>-Day 31: detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1.<br><br>The expression “same time of day” stands for:<br>-at maximum 1-hour difference in timing between the measurements.<br>-similar sleeping and dietary pattern 12 hours prior the measurement (assessed through a questionnaire).<br><br>The detection of the receptive fields is planned as follows:<br>1. performed by two specifically trained testers<br>2. performed through tactile stimulation of the skin surface with a brush (mild toothbrush or similar)<br>3. the receptive fields are determined through the dialogue with the participant. Here he can signal the presence of a receptive field with the word “Yes”. Important in this setup is that the participant does not look at the inspected site or the tester<br>4. the receptive fields are drawn on to the skin with a commercial eyeliner pencil<br>5. the drawn receptive fields are photographed from different locations under standardized conditions (distance and angle) |

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| | 6. this photo is imported in the program Photoshop (Adobe Photoshop Version 2017.1.1) where the respective area and position can be determined.<br><br>This testing Phase consists of 7 meetings of approximatively one hour. Therefore, the expenditure of time is of approximatively 7 hours over one month.<br><br>**<u>Phantom Stimulator:</u>**<br><br>Participants qualifying for the Phantom Stimulator are tested within 1 week after day 31. These tests are performed on one single half-day. Therefore, the expenditure of time for this phase is of approximatively 4 hours. The “Phantom Stimulator is worn for approximatively 3 hours during that phase.<br><br>This day is planned as follows:<br>-first (for familiarization): Walking for 1000 Steps with a step counter, questionnaire and 10 runs of gait analysis<br>-second: The Phantom Stimulator (Cort X Sensorics, Spaichingen, Germany) will be installed<br>-third: Participants will perform A or B in a randomized and balanced order:<br>A. walking with the functioning (ON) Phantom Stimulator (1000 steps), questionnaire and 10 runs of gait analysis<br>B. walking with the unfunctional (OFF) Phantom Stimulator (1000 steps), questionnaire and 10 runs of gait analysis<br><br>For gait analysis, subjects will be walking in maximally possible self-selected speed for 10 runs (both directions are analyzed).<br>The recorded parameters during the gait analysis are:<br>• Step width<br>• Step length<br>• Ground contact time<br>• Cadence<br>• Walking speed<br><br>The 1000 steps during the familiarization and testing phases are recorded/controlled through a pedometer (Omron Walking Style One 2.0, Mannheim, Germany).<br><br>The questionnaire evaluating the short-term effects of the Phantom Stimulator on phantom sensations addresses the existence of these sensations and their nature with a VAS from 0-10 and is performed directly after the 1000 steps (right before the gait analysis). |

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| | Summarizing we calculate a time expenditure of approximatively 10 to 11 hours for the whole study. This is distributed over the timespan of approximatively 6 weeks. |
| **Study Product / Intervention:** | "Phantom Stimulator" (Cort X Sensorics, Spaichingen, Germany)<br><br>This system consists of a pressure sensing insole connected to regular TENS-Electrode patches which are applied to the receptive fields of the patients (evoking the sensation of heel and forefoot). These electrodes produce a voltage of 5-10 Volt at a frequency of 70 Hertz. The individually adjusted stimulation intensity on the systems regulatory box through a socked screw is set at the beginning of the testing phase (as described below), and not changed anymore.<br><br>The current is applied to mimic the roll-off-sensation while walking. This is done by locating two sets of electrodes on the receptive fields representing the heel and the ball of the foot respectively. Now the current is applied in an alternating manner coordinated with the walking of the participant (receptive fields representing the contact points are stimulated). The coordination is made able through the pressure sensing insole.<br><br>If the system (sensory insole) is not loaded (no Walking is performed), the system sets itself into standby where the current flow is turned off.<br><br>The current is adjusted to mimic the wanted sensations without causing any direct sensing of the current on the stimulated skin patch. |
| **Control Intervention (if applicable):** | Not applicable. |

<table>
<tr><td>Number of Participants with Rationale:</td><td>As this study is a first in this field (Pilot), regarding literature is not present and different assumptions (professional guesses) must be made.<br><br>We define a change in Size of the receptive field if over the 31 days the size change is of more than 10%.<br>We anticipate a change in size and position of 30% of the measured receptive fields between day 1 and 31 to be clinically significant for the purposes of our and further studies. In this case significant means that the attached electrodes at day 1 would not be touching the receptive field anymore at day 31.<br>From previous studies concerning the two-point discrimination (Catley M. J. (2014)) we know that the standard deviation (Streuung) between similar population subgroups (chronic pain patients) is of 0.27%.<br><br>Therefore, the effect size is d = 1.11 with $\mu_i$ = 0.3 and SD = 0.27.<br>We set the significance level at 5% and the power at 0.8.<br>Using the paired t-test these values originate the following N´s:
<table>
<tr><th>$\mu_i$</th><th>d</th><th>N</th></tr>
<tr><td>0.25</td><td>0.93</td><td>40</td></tr>
<tr><td>0.3</td><td>1.11</td><td>28</td></tr>
<tr><td>0.35</td><td>1.23</td><td>24</td></tr>
</table>
<br>As we assume a dropout rate of 10% we aim at 31 Participants for the duration of this study.</td></tr>
<tr><td>Study Duration:</td><td>For each subject, the study lasts about 5 to 6 weeks.</td></tr>
<tr><td>Study Schedule:</td><td>First subject: 24.10.2017<br>Last subject: 08.05.2018</td></tr>
<tr><td>Investigator(s):</td><td>Pleus Michael,<br>Dr. med. Groegli Marion,<br>Sportmedizin und Rehabilitation<br>Mutschellenstrasse 2<br>5454 Bellikon</td></tr>
<tr><td>Study Centre(s):</td><td>Rehaklinik Bellikon<br>Mutschellenstrasse 2<br>5454 Bellikon</td></tr>
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**Statistical Considerations:**

**Statistical Analysis:**

The statistical analysis is performed with the program “R” and ”Excel”.

For the primary outcome, the pictures are evaluated for size and position with the computer program “Photoshop”.
We define a change in size if a difference of more than 10% is detected in comparing a receptive field of two measurements.
We define a change in position if the summed area of the two overlapping receptive fields exceeds the area of the bigger of the two single receptive fields by more than 20%. So, if the two receptive fields overlap completely (even if different in size) we do not count it as a change in position (only change in size).

For the secondary outcomes; a mean for every one of the parameters of 10 runs of gait analysis is created. These data is compared between the two randomized protocols (A and B).

All the results are treated as significant if the significance level of 0.05 is achieved.

**Power Analysis/Sample size:**

As this study is a first in this field (Pilot), regarding literature is not present and different assumptions (professional guesses) must be made.

We define a change in size of the receptive field if over the 31 days the size change is of more than 10%.
We anticipate a change in size or position of 30% of the measured receptive fields between day 1 and 31 to be clinically significant for the purposes of our and further studies. In this case significant means that the attached electrodes at day 1 would not be touching the receptive field anymore at day 31.
From previous studies concerning the two-point discrimination (Catley M. J. (2014)) we know that the standard deviation (Streuung) between similar population subgroups (chronic pain patients) is of 0.27%.

Therefore, the effect size is d = 1.11 with $\mu_i$ = 0.3 and SD = 0.27.
We set the significance level at 5% and the power at 0.8.
Using the paired t-test these values originate the following N´s:

| $\mu_i$ | d | N |
|---|---|---|
| 0.25 | 0.93 | 40 |
| 0.3 | 1.11 | 28 |
| 0.35 | 1.23 | 24 |

As we assume a dropout rate of 10% we aim at 31 Participants for the duration of this study.

| | |
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| **GCP Statement:** | This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements. |

# ABBREVIATIONS

| | |
|---|---|
| AE | Adverse Event |
| CA | Competent Authority (e.g. Swissmedic) |
| CEC | Competent Ethics Committee |
| CRF | Case Report Form |
| ClinO | Ordinance on Clinical Trials in Human Research *(in German: KlinV, in French: OClin)* |
| eCRF | Electronic Case Report Form |
| CTCAE | Common terminology criteria for adverse events |
| DSUR | Development safety update report |
| GCP | Good Clinical Practice |
| IB | Investigator's Brochure |
| Ho | Null hypothesis |
| H1 | Alternative hypothesis |
| HFG | Humanforschungsgesetz (Law on human research) |
| HMG | Heilmittelgesetz |
| HRA | Federal Act on Research involving Human Beings |
| IMP | Investigational Medicinal Product |
| IIT | Investigator-initiated Trial |
| ISO | International Organisation for Standardisation |
| ITT | Intention to treat |
| KlinV | Verordnung über klinische Versuche in der Humanforschung *(in English: ClinO, in French OClin)* |
| LPTh | Loi sur les produits thérapeutiques |
| LRH | Loi fédérale relative à la recherche sur l'être humain |
| MD | Medical Device |
| OClin | Ordonnance sur les essais cliniques dans le cadre de la recherche sur l'être humain *(in German : KlinV, in English : ClinO)* |
| PI | Principal Investigator |
| SDV | Source Data Verification |
| SOP | Standard Operating Procedure |
| SPC | Summary of product characteristics |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |

# STUDY SCHEDULE

**Pre-Study**

1) Screening for suitable candidates at Rehaklinik Bellikon

2) Enrollment and signing of informed consent if suitable candidate

**Phase 1** (Assessment of primary outcome, 7h)

| | Day 1 | Day 2 | Day 7 | Day 14 | Day 21 | Day 28 | Day 31 |
|---|---|---|---|---|---|---|---|
| Testing recepive fields (ca. 1h) | 1x | 1x | 1x | 1x | 1x | 1x | 1x |
| Tester | A | A | A | B | A | B | A |
| Time of day | X | X | X | X | X | X | X |

**Phase 2** (Assessment of secondary outcomes, 4h)

1. Familiarization followed by installation of Phantom Stimulator

Randomisation

A. testing with the functioning (ON) Phantom Stimulator → B.

B. testing with the unfunctional (OFF) Phantom Stimulator → A.

# 1. STUDY ADMINISTRATIVE STRUCTURE

No committees have been formed. All critical decisions were taken in plenum by the involved personnel.

## 1.1 Sponsor, Sponsor-Investigator

Dr. med. Groegli Marion
Sportmedizin und Rehabilitation
Rehaklinik Bellikon
Mutschellenstrasse 2
5454 Bellikon

## 1.2 Principal Investigator(s)

Dr. med. Marion Groegli, Pleus Michael, Senn Isabelle
Sportmedizin und Rehabilitation
Rehaklinik Bellikon
Mutschellenstrasse 2
5454 Bellikon
Tel.: +41 (0)56 485 56 90
Mail: studie@rehabellikon.ch

## 1.3 Statistician ("Biostatistician")

All the statistical considerations are performed by Pleus Michael. This is always done in accordance with Dr. Groegli Marion as well as qualified statisticians of the ETH Zürich.

## 1.4 Laboratory

No laboratory is involved in the study.

## 1.5 Monitoring institution

Rehaklinik Bellikon
Mutschellenstrasse 2
CH - 5454 Bellikon

## 1.6 Data Safety Monitoring Committee

In this study of risk category A no specific DSMC is needed. All the interventions performed and the Product tested are associated with extremely low risk factors and therefore possible safety issues can and will be reported and handled in plenum by the principal investigators and responsible personnel.

## 1.7 Any other relevant Committee, Person, Organisation, Institution

Not applicable.

# 2. ETHICAL AND REGULATORY ASPECTS

## 2.1 Study registration

The study is intended to be registered on the SNCTP (automatically through this application) and before initiation of the project also in a WHO primary register (ClinicalTrials.gov).

## 2.2 Categorisation of study

Clinical investigations or other studies of medical devices, risk category A.

## 2.3 Competent Ethics Committee (CEC)

The responsible investigator at Rehaklinik Bellikon ensures that approval from the Ethikkommission Nordwest- und Zentralschweiz (EKNZ) is sought for the clinical study.

The responsible investigator as well as all the involved personnel in the study has the duty to report all changes in research activity, unanticipated problems involving risks to humans and premature study end to the CEC. Further, no changes can be made to the protocol without prior Sponsor and CEC approval, except where necessary to eliminate apparent immediate hazards to study participants.

Premature study end or interruption of the study is reported within 15 days. The regular end of the study is reported to the CEC within 90 days, the final study report shall be submitted within one year after study end. Amendments are reported according to chapter 2.10.

## 2.4 Competent Authorities (CA)

As the only CA in this study is the CEC (risk category A), the section 2.3 applies.

## 2.5 Ethical Conduct of the Study

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the European Directive on medical devices 93/42/EEC and the ISO Norm 14155 and ISO 14971, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

## 2.6 Declaration of interest

The investigators certify that they have no affiliations with or involvement in any organization or entity with any financial interest (such as honoraria; educational grants; participation in speakers' bureaus; membership, employment, consultancies, stock ownership, or other equity interest; and expert testimony or patent-licensing arrangements), or non-financial interest (such as personal or professional relationships, affiliations, knowledge or beliefs) in the materials analysed in this study.

## 2.7 Patient Information and Informed Consent

The investigators will explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each participant will be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical assistance and treatment.

The participant must be informed that his/her medical records may be examined by authorised individuals other than their treating physician.

All participants for the study will be provided a participant information sheet and a consent form describing the study and providing sufficient information for participant to make an informed decision about their participation in the study. The participant is given enough time (ca. 1 week) to decide whether to participate in the study or not.

The patient information sheet and the consent form will be submitted to the CEC to be reviewed and approved. The formal consent of a participant, using the approved consent form, must be obtained before the participant is submitted to any study procedure.

The participant should read and consider the statement before signing and dating the informed consent form, and should be given a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.

## 2.8 Participant privacy and confidentiality

The investigator affirms and upholds the principle of the participant's right to privacy and that they shall comply with applicable privacy laws. Especially, anonymity of the participants shall be guaranteed when presenting the data at scientific meetings or publishing them in scientific journals.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

For data verification purposes, authorised representatives of the Sponsor (-Investigator), a competent authority (e.g. Swissmedic), or an ethics committee may require direct access to parts of the medical records relevant to the study, including participants' medical history.

## 2.9 Early termination of the study

The Sponsor-Investigator and any other competent authority may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns
- when the safety of the participants is doubtful or at risk, respectively
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise
- early evidence of harm of the experimental intervention

## 2.10 Protocol amendments

Suggestions regarding study protocol changes are allowed only to direct collaborators in the study (investigators, medical staff), and are internally approved by Pleus Michael and Dr. med. Groegli Marion before being submitted to the CEC.

Substantial amendments are only implemented after approval of the CEC.

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 CEC. Such deviations shall be documented and reported to the sponsor and the CEC as soon as possible.

All non-substantial amendments are communicated to the CEC within the Annual Safety Report (ASR).

# 3. BACKGROUND AND RATIONALE

## 3.1 Background and Rationale

It has been observed that patients subjected to amputations develop so called receptive fields (observations at Rehaklinik Bellikon and Cort X Sensorics), which time of occurrence and localization over time are yet not examined systematically.
A receptive field is defined as skin area ipsilateral to the amputation, which when stimulated by others, causes phantom sensations in the amputated extremity. Phantom Sensations are defined as sensations originating from a body part not connected through the nervous system.

Furthermore, a device has been developed and certified, which can stimulate these receptive fields, and though evoke these sensations, through conventional TENS-Electrodes.

The questions to be answered in the first part of the study are the changes in size and position over time and their timed occurrence after the amputation of these receptive fields as well as the inter-/intratester reliability in their detection.

The testing sequence is explained in sections Study Synopsis and Study Schedule. The monitoring of these fields, which entails no harms to the participants, enables the correct use of the followingly tested stimulation system (Phantom Stimulator, Cort X Sensorics, Spaichingen, Germany) and therefore entails all its benefits.

The question to be answered in the second part of the study is whether in people with lower limb amputation below the knee (prosthesis cannot entail an artificial knee) a “Phantom stimulator” (Cort X Sensorics, Spaichingen, Germany) produces a measurable effect. This effect is measured through changes in gait parameters (gait analysis with OptoGait) and a self-elaborated questionnaire concerning phantom sensations. As above, the testing sequence is described as well in the sections Study Synopsis and Study Schedule.

This treatment constitutes a supplement to the today normally used prosthetic treatment as it upgrades the patient’s normal prosthesis by adding a sensory insole, a black box and electrode patches.

Studies investigating the use of this product haven’t been done so far, yet important findings have been made regarding the reduction of phantom limb pain thanks to enhanced sensory input from the lost extremity.


- Katz J. (1991); Auricular Transcutaneous Electrical Nerve Stimulation (TENS) reduces Phantom Limb Pain; Journal of Pain and Symptom Management 6 (73-83)
- Dietrich C. (2012); Sensory feedback prosthesis reduces phantom limb pain: Proof of a principle; Neuroscience Letters 507 (97-100)
- Hu X. (2014); The effectiveness of acupuncture/TENS for phantom limb syndrome. I: A systematic review of controlled clinical trials; European Journal of Integrative Medicine 6 (355-364)
- Koller T. (2013); Zweipunktdiskriminierung bei Phantomschmerzen: Effekt einer 4-wöchigen Therapie bei einem oberarmamputierten Patienten mit Phantomschmerzen; Orthopädie 42 (449-452)

## 3.2 Investigational Product and Indication

Product name: Phantom Stimulator
Model: PST 3010
2 channel stimulator with separate outputs for heel and ball
Auto Power On and Power OFF function (sleep / wake-up function)
15 integrated setting-wide (frequency / amplitude / intensity)
Power supply: 7.4 VDC (Integrated LIPO rechargeable)
Power consumption: = 40 mA (treatment); = 30 µA (power down)
Electr. supply capacity: 760 mAh (calculated range approx. 10 hrs.)
Dimensions: 76 x 44 x 22 mm (H x B x T)
Weight: 60 g without battery
Output current: 0.5 - 6 mA (on 1 kOhm load)
Output voltage: max. 36 volts (1 kOhm load)
Pulse shape: positive rectangle with a negative share (bi-phase / mono-phase)
Frequency range: 5 - 150 Hz
Pulse width: 75µs - 100 ms

**Working conditions:**

Temperature: 5 to 40°C
Relative Humidity: 30% to 90%
Storage Temperature: -20 to 60°C
Relative Humidity: 10% to 90%

**Available Accessories/Replacement Parts**

Long life electrode pads - 25 mm round (set of 4)
Long life electrode pads - 45 mm square (set of 4)
Electrode extension cord - 0.5 meter length
Electrode extension cord - 0.75 meter length
Electrode extension cord - 1.0 meter length

Further relevant information is provided separately in the attached user manual.

The device needs a training (1000 Steps) and installation prior to use. Indications for the use of the device are the bearing of a lower limb prosthesis without artificial knee.

## 3.3 Preclinical Evidence

Not applicable.

## 3.4 Clinical Evidence to Date

To date there is no clinical research data available on the investigational product.

## 3.5 Rationale for the intended purpose in study (pre-market MD)

The device is used for a duration 1 day during the intervention. During this period, the device complementing the prosthesis is worn for at least 2x1000 steps.
These times have been selected to allow the patients enough time to adapt to the system.

The application of the system is as follows:

- For the intervention, the electrodes have to be placed on the correspondent receptive fields (heel and ball) so to allow the wanted sensory feedback.

The selected device as well as the defined timespan with the functioning device allows us to detect the positive effects on gait parameters and phantom sensations, thus providing important information for improvements of the quality of life of the target group.

## 3.6 Explanation for choice of comparator (or placebo)

As the direct effects of the system have to be measured, the natural choice for a placebo group (in our cross over design) is to use the exact same setup. Only difference being that the system remains in an unfunctional state during the whole testing period.

In this manner, we exclude the weight or the simple sight of the attached system to have any influence on our measured results.

## 3.7 Risks / Benefits

The benefit/risk relationship for our patients is very high, as there are potentially no risks coming from the device or the performed tests. This as the device is only used in its described purposes in the CE certification, and as all the performed tests are well established and safe to perform. The benefit of this study consists in a better understanding of the receptive fields and better application of such stimulation systems improving the quality of life.

Relevant information to this section is given in the attached user manual.

## 3.8 Justification of choice of study population

For the implementation of the study on the description of the receptive fields we selected a relatively wide range of people with lower limb amputation, to expand the number of participants to a maximum. We excluded people only with amputations of the upper limbs as to confine the results of this study on lower limb amputees which can also benefit from the tested stimulating system.

For the implementation of the study on the stimulating system we selected a population with lower limb amputations to apply the system on. We excluded people with an amputation site proximal the knee because of the unknown influence the several types of prosthetic knees could have on the study outcome.

We guarantee that signs and symptoms showing that a participant is unwilling to participate in the study will result in the exclusion of the participant from the study. Further we guarantee that a physician not participating in the study, safeguards the participants interests and insures proper medical care.

Finally, we do not recruit participants that are incapable of judgement, minors or under tutelage.

# 4. STUDY OBJECTIVES

## 4.1 Overall Objective

The question to be answered through this study is how the receptive fields of lower limb amputees behave in size and position over a timespan ranging from 1 day to 1 month. Further, the intra-/intertester reliability of the proposed detection method for the receptive fields should be assessed.

## 4.2 Primary Objective

The study seeks to evaluate the behaviour of the receptive fields of lower limb amputees in size and position over a timespan ranging from 1 day to 1 month.

## 4.3 Secondary Objectives

Secondary objectives are:

- Intra-/intertester reliability of the proposed detection method
- Influence of the Phantom Stimulator (Cort X Sensorics, Spaichingen, Germany) on selected gait parameters and phantom sensations

## 4.4 Safety Objectives

As the safety of the detection method is out of discussion no safety objectives are set.

As the safety of the stimulation system has already been proven for the certification with the CE label, in this study we do not analyse safety aspects related with the use of the “Phantom Stimulator” (Cort X Sensorics, Spaichingen, Germany).

# 5. STUDY OUTCOMES

## 5.1 Primary Outcome

The primary measured outcome is the evolution/difference in size and position/movement of the detected receptive fields. This is done in the unit of $cm^2$.

This is done comparing size and position of the same receptive fields between day 1, 2, 7, 14, 21, 28 and 31 of the study.

## 5.2 Secondary Outcomes

The secondary outcomes are measured as follows:

- The intratester reliability is evaluated by comparing size and position of the same receptive fields within 1 week detected by two different investigators.
- The intertester reliability is evaluated by comparing size and position of the same receptive field within 1 week detected by the same investigator.
- Influence of the stimulating system on phantom sensations and gait parameters is measured through the evaluation of a questionnaire concerning the phantom sensations, and through the analysis of a gait analysis (step width, step length, cadence, floor contact time and walking speed).

## 5.3 Other Outcomes of Interest

No other outcomes are measured and relevant to the study.

## 5.4 Safety Outcomes

As no safety objectives are planned in this study, no safety outcomes are recorded.

# 6. STUDY DESIGN

## 6.1 General study design and justification of design

The study with lower limb amputees is divided in two main parts and should incorporate 31 subjects.

The first part lasting 31 days, analyses the position and size of the receptive fields in a purely descriptive manner. Therefore, no randomisation, blinding or control group is needed.

The second part lasting 1 half-day, analyses the acute effect of a stimulation system (Phantom Stimulator, Cort X Sensorics, Spaichingen, Germany) on selected gait parameters and phantom sensations. Here the participants are randomized into two groups (AB or BA). As the design is a crossover, every subject serves as its own control and are single-blinded (unblinded investigators).

A schematic diagram can be found under 9.1 Study Flowchart.

## 6.2 Methods of minimising bias

### 6.2.1 Randomisation

The randomisation is done by block randomisation with a block size of 2 patients. This is done to ensure the same number of patients in each of the two possible sequences.

### 6.2.2 Blinding procedures

The blinding of the participants is ensured as there is no visible difference between the two groups as well as through standardised questions and talking patterns of the investigators so not to reveal any relevant information.

### 6.2.3 Other methods of minimising bias

As other methods to minimise bias we use all well-established and validated tests and measurement methods in the gait analysis. Further we analyse the selected method of receptive field detection on intra-/intertester reliability.

## 6.3 Unblinding Procedures (Code break)

The codes for the unblinding procedures are stored in sealed envelopes which can be opened only by Dr. med. Groegli Marion or Pleus Michael.

This procedure can take place in case of suspension/exclusion from the study, premature study termination, explicit requests from part of the CC or in case of individual analysation of the data because of health issues or threats to the participant.

# 7. STUDY POPULATION

## 7.1 Eligibility criteria

Participants fulfilling all the following inclusion criteria are eligible for the first part of the study:

- Informed Consent as documented by signature (Appendix Informed Consent Form)
- Lower limb amputation
- Legal age, capable of judgement

Participants fulfilling all the following inclusion criteria are eligible for the second part of the study:

- Lower limb amputation below/distal of the knee
- Presence of receptive fields for heel and forefoot at day 31 of the first part of the study

The presence of any one of the following exclusion criteria will lead to exclusion of the participant from the entire study:

- With history or suspect of non-compliance, drug or alcohol abuse
- Inability to follow the procedures of the study, e.g. due to language problems, psychological disorders, dementia, etc. of the participant
- Participation in another study with investigational drug within the 30 days preceding and during the present study
- Previous enrolment into the current study
- Enrolment of the investigator, his/her family members, employees and other dependent persons

The presence of any one of the following exclusion criteria will lead to exclusion of the participant from the second part of the study:

- Contraindications to the product under investigation (skin irritability or allergy to electrode glue)
- Women who are pregnant or breast feeding
- Intention to become pregnant during the study
- Implanted devices as pacemakers or defibrillators

## 7.2 Recruitment and screening

The study participants are preselected through a database of the Rehaklinik Bellikon and run per all in- and exclusion criteria. As a second step, the selected patients are contacted via E-Mail or personally if stationary at the Rehaklinik Bellikon. A pregnancy test is also conducted.

The preselection can be performed by every employee of the Rehaklinik Bellikon as he/she must have access to the patient information program. The second step of the contact via E-Mail, is performed through a separately created E-Mail address (Studie@rehabellikon.ch) and can therefore be performed by authorised personnel only (Dr. med. Groegli Marion and Pleus Michael). Also, the personal contact is performed directly by one of the investigators (Dr. med. Groegli Marion and Pleus Michael).

## 7.3 Assignment to study groups

The participants are assigned into the 2 possible sequences of the second part of the study in randomised order by block randomisation with a block size of 2 patients. This randomisation is performed by the principal investigator as soon as two patients are available. These are then randomized with the computer program Excel.

After this process, the assigned sequence is communicated to the responsible investigator for the patient and marked on the CRF. The patient is unaware of the study sequence until the study is terminated completely.

## 7.4 Criteria for withdrawal / discontinuation of participants

Participants can be withdrawn from the Study in case of development of one of the exclusion criteria during the intervention, the informed consent is withdrawn, in case of non-compliance or safety concerns for the patient.

The withdrawn participants do not have to be replaced.

If the participant withdrawals from the study, his/her data must be anonymized at the end of the study. This anonymization is not done if the participant gives his/her explicit consent.

For the protection of the withdrawn participant he/her has to be provided follow-up care.

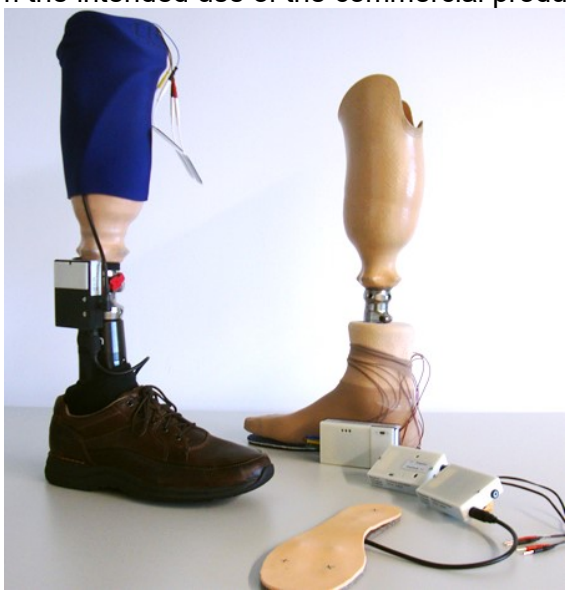
# 8. STUDY INTERVENTION

## 8.1 Identity of Investigational Products

### 8.1.1 Experimental Intervention

The investigated product is the Phantom Stimulator (Cort X Sensorics, Spaichingen, Germany). We obtain it directly from the developers (Karl-Heinz Weber, Prof. Dr. Alfred Meier-Koll). It is composed of a sensory insole (pressure) connected to a plastic box (black/white), which is than connected to conventional electrode patches. This sensory insole is placed in the shoe, the box on the prosthesis shaft and the electrodes are placed on the receptive fields for forefoot and heel (same side as amputation).

There is no deviation from the intended use of the commercial product.



### 8.1.2 Control Intervention

Same as 8.1.1 Experimental Intervention. Only difference is that during the placebo phase, the system is unfunctional (not activated).

### 8.1.3 Packaging, Labelling and Supply (re-supply)

The system is packaged in a white carton box and except of the name, not labelled. The packaging also contains an operating instruction.

The re-supply, if further material is needed (extension cables, …), is organised directly through the developers by the Rehaklinik Bellikon.

No deviation from the commercially available product is planned.

### 8.1.4 Storage Conditions

The devices are stored in a limited access storage room at climatized room temperatures of ca. 22°C and as in the box, with no exposure to sunlight. Once the products are in the hands of the participants they are informed to treat the product as described in the product information sheet.

These conditions are all according to standard procedures.

## 8.2 Administration of experimental and control interventions

### 8.2.1 Experimental Intervention

The experimental intervention concerns only the second part of the study. In the first part, a purely descriptive evaluation of the size and position of the receptive fields over the timespan of one month (31 days) is performed.

During the second part of the study, which is performed in one day, the certified medical device Phantom Stimulator (Cort X Sensorics, Spaichingen, Germany) is tested upon its effects on selected gait parameters and phantom sensations.

During the experimental intervention, the participants are setup with the device and are given an instruction. Further they are asked to walk 1000 steps with the functional device and to perform a gait analysis.

The time spent by the participants with the functional device is therefore restricted to 1000 steps and 10 times 10 meters of gait analysis.

Information on the medical device is given in section 8.1 and in the attached user manual.

#### 8.2.2 Control Intervention

Also, the control intervention applies only for the second part of the study.

The control intervention consists of performing 1000 steps and a gait analysis under the same conditions as the experimental intervention, only difference being that the tested medical device is turned off during this period.

Therefore, also in the control intervention, the time spent by the participants is restricted to 1000 steps and 10 times 10 meters of gait analysis.

## 8.3 Dose / Device modifications

The only criteria for changing the dose or routine of the intervention are:

- the malfunctioning of a device which needs repair work
- if harm is done to the participants
- after explicit request of the participant (leads to exclusion from the study)
- if condition of the participant is drastically worsened by the medical device

## 8.4 Compliance with study intervention

To ensure compliance with the intervention we monitor the performed steps with a pedometer.

In case of non-compliance the participant is alerted once, if the non-compliance proceeds he/she is excluded from the study and the data, on an individual basis, kept and used or destroyed.

As in the different interventions during the study (detection and stimulation of the receptive fields) the participant is always in one to one support with the investigator, no additional strategies are required.

## 8.5 Data Collection and Follow-up for withdrawn participants

The data from withdrawn patients is analysed on an individual basis. Depending on the motive of withdrawal and the usefulness of the collected data, the material is kept and utilised in the study or destroyed.

Once a participant has withdrawn from the study, he has no follow up treatments or check-ups directly connected with the study.

## 8.6 Trial specific preventive measures

Medications or treatments not permitted during the study are:

- Drugs or psychopharmaceutic drugs altering the sensory perception other than normally taken
- Invasive treatments to the stump or the areas of the receptive fields
- Medication affecting the skin (tolerance of electrodes)
- Painkillers others than normally taken

## 8.7 Concomitant Interventions (treatments)

Permitted during the study are all form of usual medication the participants are/were taking

before the enrolment in the study if they don't fall under those listed in 8.6. Nevertheless, their use should be documented in the CRF.

The only medications having a potential impact on the study outcome are those concerning the phantom limb pain. In this case, we will perhaps expect a weaker improvement in phantom limb pain due to an already supressed starting point.

## 8.8 Study Drug / Medical Device Accountability

The devices are ordered directly from Cort X Sensorics (Spaichingen, Germany) at the moment of inclusion into the second part of the study of one of the participants. This must be done as the soles need to be personally adapted to the participant.

These devices are then shipped by postal service to the Rehaklinik Bellikon, where they are stored according to the regulations written in the user manual.

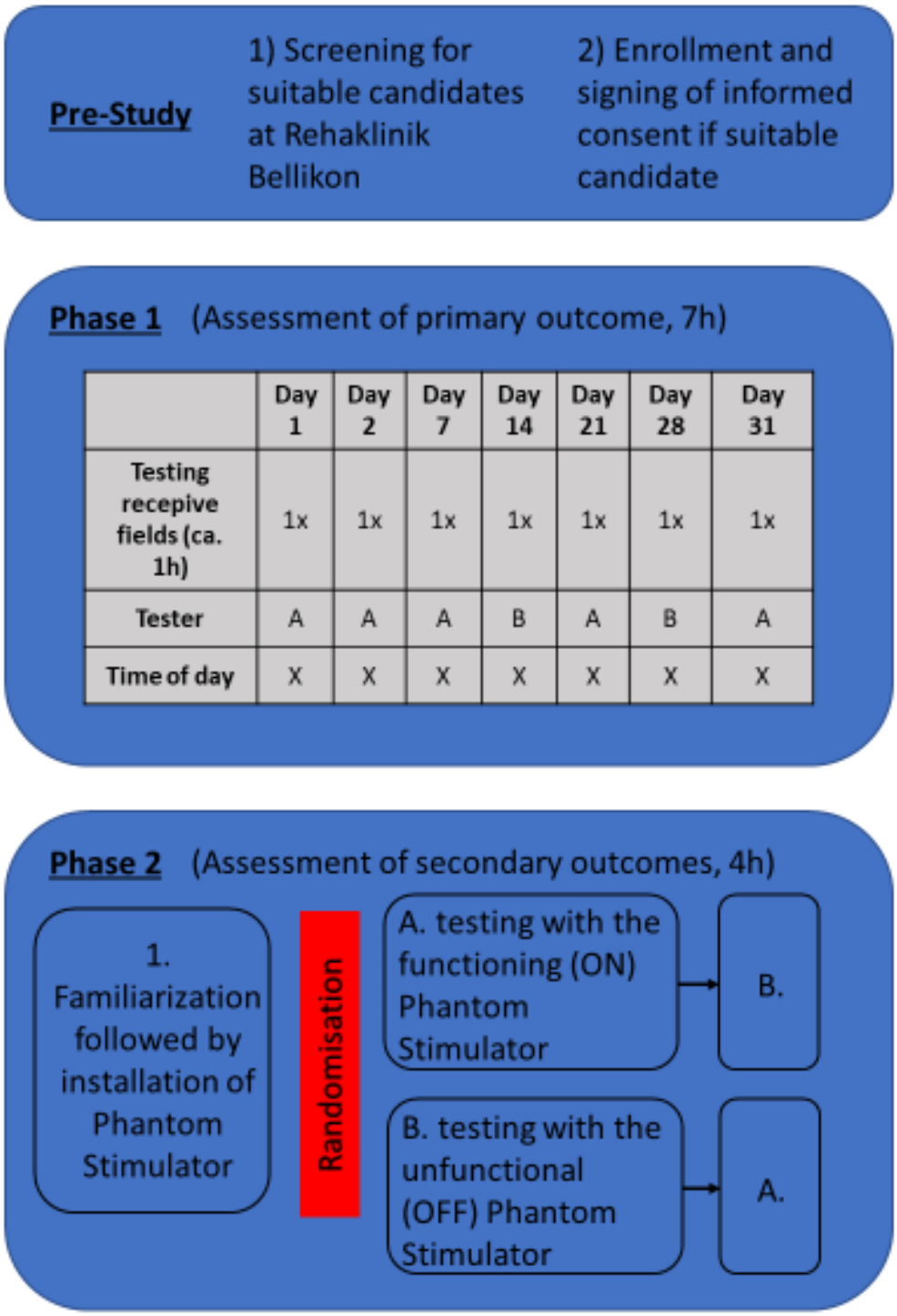
After completion of the study the used devices are returned to the manufacturer (Cort X Sensorics, Spaichingen, Germany).

## 8.9 Return or Destruction of Study Drug / Medical Device

At the end of the intervention, the used material is sent back to Cort X Sensorics (Spaichingen, Germany).

# 9. STUDY ASSESSMENTS

## 9.1 Study flow chart / table of study procedures and assessments



## 9.2 Assessments of outcomes

### 9.2.1 Assessment of primary outcome

The primary measured outcome is the evolution/difference in size and position/movement of the detected receptive fields. This is done in the unit of $cm^2$.

To record the data needed to compare the receptive fields is collected as follows:

- Day 1: detection of the receptive fields by one single tester at a self-selected time of day.
- Day 2: detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1.
- Day 7: detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1.
- Day 14: detection of the receptive fields at the same time of day as on day 1 by another tester as on day 1.
- Day 21: detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1.
- Day 28: detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 14.
- Day 31: detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1.

The expression “same time of day” stands for:
-at maximum 1-hour difference in timing between the measurements.
-similar sleeping and dietary pattern 12 hours prior the measurement (assessed through a questionnaire).

The detection of the receptive fields is planned as follows:

1. performed by two specifically trained persons
2. performed through tactile stimulation of the skin surface with a brush (mild toothbrush or similar).
3. the receptive fields are determined through the dialogue with the participant. Here he can signal the presence of a receptive field with the word “Yes”. Important in this setup is that the participant does not look at the inspected site or the tester.
4. the receptive fields are drawn on to the skin with a commercial eyeliner pencil.
5. the drawn receptive fields are photographed from different locations under standardized conditions (distance and angle).
6. this photo is imported in the program Photoshop (Adobe Photoshop Version 2017.1.1) where the respective area and position can be determined.

As a change in size is defined as a difference of more than 10% when comparing the same receptive field of two separate times.

We define as a change in position if the area of the two overlapping areas exceeds the area of the bigger of the two single areas by more than 20%. So, if the two areas overlap completely (even if different in size) we do not count it as a change in position.

As every meeting last approximatively one hour, we estimate a total duration of about 7 hours for this phase of the study.

### 9.2.2 Assessment of secondary outcomes

The Intra-/intertester reliability of the proposed detection method as secondary outcome is assessed by comparing the size and position of the detected receptive between two different testers. Here the sizes and positions are compared and the deviations calculated. The detection takes place as described in section 9.2.1.

The influence of the Phantom Stimulator on gait parameters and phantom sensations is assessed through a gait analysis (OPTOGait, Microgate S.r.I, Italy, 2010) and a self-made questionnair.

After the conclusion of the first descriptive part of the trial, the participants qualifying for the Phantom Stimulator are tested. These tests are performed in one single day.

This day is planned as follows:

- first (for familiarization): Walking for 1000 Steps with a step counter, questionnaire and 10 runs of gait analysis
- second: The Phantom Stimulator (Cort X Sensorics, Spaichingen, Germany) will be installed
- third: Participants will perform A or B in a randomized and balanced order:
    A. walking with the functioning (ON) Phantom Stimulator (1000 steps), questionnaire and 10 runs of gait analysis
    B. walking with the unfunctional (OFF) Phantom Stimulator (1000 steps), questionnaire and 10 runs of gait analysis

For gait analysis, subjects will be walking in maximally possible self-selected speed for 10 runs (both directions are analyzed).

The recorded parameters during the gait analysis are:

- Step width
- Step length
- Ground contact time
- Cadence
- Walking speed

The 1000 steps during the familiarization and testing phases are recorded/controlled through a pedometer (Omron Walking Style One 2.0, Mannheim, Germany).

The questionnaire evaluating the short-term effects of the Phantom Stimulator on phantom sensations addresses the existence of these sensations and their nature with a VAS from 0-10 and is performed directly after the 1000 steps (right before the gait analysis).

For this phase of the study we calculate approximatively 4 hours. The “Phantom Stimulator” is worn during approximatively 3 hours.

### 9.2.3 Assessment of other outcomes of interest

Not applicable.

### 9.2.4 Assessment of safety outcomes

#### *9.2.4.1 Adverse events*

In case of adverse events the event must be noted on the CRF. If the adverse event endangers the safety of the participant the testing must be stopped immediately.

In all cases the following information needs to be collected and recorded on the CRF: time of

onset, duration, action to be taken, relationship with study treatment.

#### *9.2.4.2 Laboratory parameters*

As there is no laboratory involved in this study, these parameters do not have to be assessed.

#### *9.2.4.3 Vital signs*

In this study, no vital parameters will be assessed as they are not of importance to the intervention. Further, as this study does not intend to change or affect any of these parameters, no assessment is necessary.

### 9.2.5 Assessments in participants who prematurely stop the study

After the recording of the reasons of premature withdrawal from the study (If there are any) and the rendering of the device (if in second part of the study), the participants do not receive any follow up procedures directly related to the intervention.

## 9.3 Procedures at each visit

### 9.3.1 Screening (until day 0)

- Screening done by the personnel of Rehaklinik Bellikon prior to the contact with the patients through the database of the clinic
- Afterwards an e-mail is sent to the included patients (studie@rehabellikon.ch) or they are contacted personally if stationary at the Rehaklinik Bellikon
- If the contacted patients show interest, a last interview is conducted to assess important inclusion and exclusion criteria (also pregnancy test) and if applicable sign the informed consent
- If they suit the study, they are scheduled for the meetings

### 9.3.2 Meeting 1 (day 1, 1h)

- Detection of the receptive fields by one single tester at a self-selected time of day (selected during scheduling in screening)

### 9.3.3 Meeting 2 (day 2, 1h)

- Detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1

### 9.3.4 Meeting 3 (day 7, 1h)

- Detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1

### 9.3.5 Meeting 4 (day 14, 1h)

- Detection of the receptive fields at the same time of day as on day 1 by another tester as on day 1

### 9.3.6 Meeting 5 (day 21, 1h)

- Detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1

### 9.3.7 Meeting 6 (day 28, 1h)

- detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 14

### 9.3.8 Meeting 7 (day 31, 1h)

- detection of the receptive fields at the same time of day as on day 1 by the same tester as on day 1

#### 9.3.9 Meeting 8 (second part of the study, done in 1 single half-day, 4h)

- **Phase 1:** Familiarization (1000 steps, questionnaire and gait analysis)
- **Phase 2:** Fitting of System and randomization
- **Phase 3:** AB or BA
    A. walking with the functioning (ON) Phantom Stimulator (1000 steps), questionnaire and 10 runs of gait analysis
    B. walking with the unfunctional (OFF) Phantom Stimulator (1000 steps), questionnaire and 10 runs of gait analysis

# 10. SAFETY

## 10.1 Medical Device Category A studies

### 10.1.1 Definition and Assessment of safety related events

- Health hazards that require measures
- Findings in the trial that may affect the safety of study participants and which require preventive or corrective measures intended to protect the health and safety of study participants

Findings which require preventive or corrective measures:

- All of the above
- Malfunctioning of the device
- Skin irritations related to the electrodes
- Pregnancies
- Implanted devices (pacemaker or defibrillator)

### 10.1.2 Reporting of Safety related events

Reporting to Sponsor-Investigator:

- Health hazard that require measures are reported to the Sponsor-Investigator within 24 hours upon becoming aware of the event:

Pregnancies:

- Reporting of pregnancies is mandatory within 24 hours to the investigators at Rehaklinik Bellikon. This event has the exclusion from the second part of the study as consequence.

Reporting to Authorities:

- In Category A studies it is the Investigator's responsibility to report to the local Ethics Committee
- **Health hazards** that require measures within 2 days

# 11. STATISTICAL METHODS

## 11.1 Hypothesis

Null Hypothesis:

1) Receptive fields do not change in position and size over the various measured time intervals
2) The intra-/intertester reliability concerning the proposed detection system is good and therefore no difference in detection are seen
3) The stimulating device has no effect on the participants performing a gait analysis (selected parameters) and answering a questionnaire regarding phantom sensations

Alternative Hypothesis:

1) The position and size of the detected receptive fields changes significantly over the various measured time intervals
2) The intra-/intertester reliability concerning the proposed detection system is imperfect and therefore difference in detection can be seen
3) The stimulating device has a significant effect on the participants performing a gait analysis (selected parameters) and answering a questionnaire regarding phantom sensations

## 11.2 Determination of Sample Size

As this study is a first in this field (Pilot), regarding literature is not present and different assumptions (professional guesses) must be made.

We define a change in size of the receptive field if over the 31 days the size change is of more than 10%.
We anticipate a change in size and position of 30% of the measured receptive fields between day 1 and 31 to be clinically significant for the purposes of our and further studies. In this case significant means that the attached electrodes at day 1 would not be touching the receptive field anymore at day 31.
From previous studies concerning the two-point discrimination (Catley M. J. (2014)) we know that the standard deviation (Streuung) between similar population subgroups (chronic pain patients) is of 0.27%.

Therefore, the effect size is d = 1.11 with $\mu_i = 0.3$ and SD = 0.27.

We set the significance level at 5% and the power at 0.8.

Using the paired t-test these values originate the following N´s:

| $\mu_i$ | d | N |
|---|---|---|
| 0.25 | 0.93 | 40 |
| 0.3 | 1.11 | 28 |
| 0.35 | 1.23 | 24 |

As we assume a dropout rate of 10% we aim at 31 Participants for the duration of this study.

## 11.3 Statistical criteria of termination of trial

The Sponsor-Investigator (Rehaklinik Bellikon) and any other competent authority may terminate the study prematurely according to certain circumstances, for example:

- ethical concerns
- when the safety of the participants is doubtful or at risk, respectively
- alterations in accepted clinical practice that make the continuation of a clinical trial unwise
- early evidence of harm of the experimental intervention

## 11.4 Planned Analyses

### 11.4.1 Datasets to be analysed, analysis populations

First descriptive part of the study:

The analysed population is the study population consisting of people with lower limb amputation.

Of the population only those participants completing the trial in conformity with the approved regulations are considered.

The datasets used for the analysis are as in the example on the next page. Those sheets are created for every detected field and gather the information obtained from the evaluated pictures (Photoshop).

| **Participant X,** **Field ex. Heel** | Size ($cm^2$) | Filed-position on body |
|---|---|---|
| Day 1 | | |
| Day2 | | |
| Day 7 | | |
| Day 14 | | |
| Day 21 | | |
| Day 28 | | |
| Day 31 | | |

| **Overlap for position comparison** | Overlap (%) |
|---|---|
| Day 1 with Day 2 | |
| Day 1 with Day 7 | |
| Day 1 with Day 14 | |
| Day 1 with day 21 | |
| Day 1 with day 28 | |
| Day 1 with day 31 | |
| | |

| **Comparison for intratester reliability** | Size ($cm^2$)/Position overlap (%) |
|---|---|
| Day 28 with day 31 | |
| **Comparison for intertester reliability** | |
| Day 1 with day 2 | |
| | |
| | |
| | |
| | |

Second part:

The analysed population is the study population consisting of people with lower limb amputation distal of the knee with present receptive fields for heel and forefoot at day 31 of the first part of the study. Further the participants cannot be pregnant or have any implanted electronic devices as pacemakers or defibrillators.

Of the population only those participants completing the trial in conformity with the approved regulations are considered.

The datasets used for the analysis are as in the example:

| **Participant X** | Familiarisation | Randomisation A | Randomisation B |
|---|---|---|---|
| Steph width (cm) | | | |
| Step length (cm) | | | |
| Cadence (steps/min) | | | |
| Walking speed (m/s) | | | |
| Ground contact time (s) | | | |

The questionnaire on phantom sensations has the following dataset:

| **Participant X** | Familiarisation | Randomisation A | Randomisation B |
|---|---|---|---|
| Phantomschmerzen (0-10) | | | |
| Telescoping (0-10) | | | |
| Kranmpfartig/Schnürend (0-10) | | | |
| Spont. Bewegungen (0-10) | | | |
| Druckstellen/Narben (0-10) | | | |
| Druckempfindlichkeit (0-10) | | | |
| Unwillkürliche Bewegungen (0-10) | | | |
| Brennend/Stechend (0-10) | | | |
| Einschiessend (0-10) | | | |

### 11.4.2 Primary Analysis

At the end of the 31-day period making up the first part of the study, the datasets concerning the receptive fields are evaluated by the principal investigators (Pleus Michael, Dr. med. Groegli Marion).

Here, next to the numerical tables exhibiting the monitored changes in size and position of the receptive fields, a graph will be made explaining the occurrence of these fields in relation to the time since the amputation occurred.

### 11.4.3 Secondary Analyses

A secondary analysis concerning the inter- and intratester reliability is performed by the principal investigators (Pleus Michael, Dr. med. Groegli Marion) at the end of the first part of the study (day 31). Here the days 1 and 2 are compared for intertester reliability and the days 28 and 31 are compared for the intratester reliability.
The secondary analysis concerning the intervention period (single day after day 31) is as well performed by the principal investigators (Pleus Michael, Dr. med. Groegli Marion) after completion of the last gait analysis. Here the recorded gait parameters as well as the questionnaires are evaluated on changes originating between randomization A and B.

In both cases graphs and tables will be generated showing the mean, standard deviation, change as well as all single values of the participants.

### 11.4.4 Interim analyses

Not applicable.

#### 11.4.5 Safety analysis

Not applicable.

#### 11.4.6 Deviation(s) from the original statistical plan

Any deviations from the planned analyses must be run by the PI and CEC before implementation. Reporting these changes is the duty of the PI and they must be accepted through the competent authorities before implementation.

Justification of these changes must be in accordance with:

- ethical concerns
- when the safety of the participants is doubtful or at risk, respectively
- when the privacy and confidentiality of the participant is at risk

### 11.5 Handling of missing data and drop-outs

Missing data concerning one of the participants will lead to:

- Exclusion from the trial analysis if more than 10% of the data is unavailable or if one entire meeting is missing for the analysis
- Admonition but retention in the trial analysis if less than 10% of the data is missing or if only one test or part of a test of one meeting is missing (all meetings have to be attended)

If the data has to be excluded from the trial, an analysis concerning the dropout causes has to be made (what is the reason for discontinuation?).

Dropouts do not have to be replaced.

# 12. QUALITY ASSURANCE AND CONTROL

## 12.1 Data handling and record keeping / archiving

### 12.1.1 Case Report Forms

Study data is recorded with paper CRFs (pCRF) for each enrolled study participant and kept current to reflect subject status at each phase during the study. In the pCRF the participants are identified by coded identification (participant number and year of birth).

Entries in the pCRF are authorized by every trained investigator of Rehaklinik Bellikon and are made after leaving an identification signature at the beginning of the section.

The entry in the electronic database for the analysis is performed through an investigator at the Rehaklinik Bellikon and double checked by two additional investigators before evaluation.

### 12.1.2 Specification of source documents

Source documents are:

- Visit dates
- Participation in study and informed consent forms
- Results of examinations
- Adverse events report
- Raw data of intervention tests (gait analysis, questionnaires)

This data can be found in folders at a non-public office (Dr. med. Groegli Marion).

### 12.1.3 Record keeping / archiving

All study data must be archived for a minimum of 10 years after study termination or premature termination of the clinical trial. The data is stored in the archives of the Rehaklinik Bellikon.

## 12.2 Data management

### 12.2.1 Data Management System

Systems used:

- Excel
- OptoGait software
- Photoshop
- Handwriting on pCRF

Responsibility of functioning and testing is the principal investigators Dr. med. Groegli Marion and Pleus Michael. The software as well as the Excel sheets, Photoshop and the pCRFs are tested previously to the study.

### 12.2.2 Data security, access and back-up

The access to the data is permitted to every investigator if he/she is logged in the intranet of the Rehaklinik Bellikon. Backup systems are the raw data present on the pCRF.

### 12.2.3 Analysis and archiving

Data is extracted directly from the OptoGait system (where it is also stored), from Photoshop or from the paper questionnaires and firstly transcribed to the relevant pCRFs. These pCRFs are then stored in a non-public office of a principal investigator (Dr. med. Groegli Marion) for the duration of the study, and then moved to the archives of the Rehaklinik Bellikon where they are stored for 10 years.

### 12.2.4 Electronic and central data validation

OptoGait: through proper setup and calibration (as written in the user's manual) prior to every measurement, and presence of at least 2 different investigators while performing the analysis.

Questionnaires: through evaluation by at least 2 different investigators and comparison of the

results.

Photoshop measurements: the measurements of size and position are performed 3 times by 2 different investigators and the mean value is considered.

## 12.3 Monitoring

Prior the study one information/monitoring visit was conducted by Cort X Sensorics on the studied device. In this occasion, we had the opportunity to test the whole procedure of the tested product on 2 patients and solve/discuss study related issues.

Further, one of the heads of Cort X Sensorics (Karl-Heinz Weber, Prof. Dr. Alfred Meier-Koll) will be present during the setup and testing of the first participant to ensure right handling of the product. No additional monitoring visits are planned to date.

However, all the source data and documents are accessible to monitors and questions are answered during monitoring if any additional visits will take place.

## 12.4 Audits and Inspections

There are no planned procedures for auditing trial conduct other than the internal inspection and control of the principal investigators.

However, the study documentation and the source data and documents are accessible to auditors, inspectors and CEC and questions are answered during every planned and surprise inspection. Of course, all involved parties must keep the participant data strictly confidential.

## 12.5 Confidentiality, Data Protection

Direct access to source documents will be permitted for purposes of monitoring (12.3), audits and inspections (12.4) (ICHE6, 6.10).

During and after the study the Investigators as well as the people involved in the publication and dissemination of the study related paper will have access to protocol, dataset and statistical code.

## 12.6 Storage of biological material and related health data

Not applicable.

# 13. PUBLICATION AND DISSEMINATION POLICY

The study results are communicated to the participants after termination and evaluation of the study per E-Mail. To healthcare professionals, the public and other relevant groups not participating directly in the study, the results are being presented via publication. There is no intended use of professional writers and there is no plan of granting public access to the full protocol, participant-level dataset and statistical code.

The decision to submit the report for publication as well as the ultimate authority over any of the activities is handed to Dr. med. Tschui Felix and Dr. med. Groegli Marion.

The trade secrets of the medical device are to be protected at all times.

# 14. FUNDING AND SUPPORT

## 14.1 Funding

The only financial support for this study is provided by the Rehaklinik Bellikon.

## 14.2 Other Support

Other sources are the generous donation of the medical devices from Cort X Sensorics (Spaichingen, Germany) for the duration of the study.

# 15. INSURANCE

The insurance of this study is managed through the insurance policy of the Rehaklinik Bellikon. This is possible as this study is a risk category A study of medical devices.

# 16. REFERENCES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15. WHO, International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)

# 17. APPENDICES

The following documents are provided separately.

1. Medical Devices: IB (according to ISO 14155)
2. Medical Devices: Assurance of producer
3. Medical Devices: List of norms
4. Other:
    a. Case Report Form
    b. Patient Information and informed consent
    c. Other material to patients
        i. 2 questionnaires
        ii. 2 user manuals