TEMPLATE RESEARCH PROTOCOL

(September 2018)

- May 2015: adaptation section 11.5: text in accordance to old and new Measure regarding Compulsory Insurance for Clinical Research in Humans
- Sept 2015: adaptation section 9.1, 9.2 and 12.5: text in accordance to WMO amendment on reporting SAE and temporary halt (section 10 of WMO)
- Oct 2015: adaptation section 4.4 – comment [CCMO15], 8.2 and 10.1 with respect to methodology/statistics
- Sept 2018: adaptation section 12.1 and comment [CCMO46] due to applicability GDPR as of May, 2018

PROTOCOL TITLE

'Gait stability of transtibial and transfemoral amputees on slopes and lateral inclines.'

Protocol ID	72723
Short title	Walking with a prosthesis: ups and downs
Version	1.2
Date	April 17th 2020
Coordinating investigator	Prof.dr. J.H. van Dieën Professor of Biomechanics j.van.dieen@vu.nl +31 20 59 88501
Principal investigator	Dr. M.R. Prins Researcher MR.Prins@MRCDoorn.nl +31 343 598 593
Sponsor	Dutch Ministry of Defence
Subsidising party	Military Rehabilitation Center 'Aardenburg'
Independent expert (s)	Prof.dr. C.A.M. van Bennekom Rehabilitation Physician
Laboratory sites	CAREN-system Military Rehabilitation Center Doorn

Affiliations:

van Dieën J.H.[1], Prins M.R.[1,2,3], van der Wurff, P[2,3], Prof.dr. C.A.M. van Bennekom[4]

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2. Department of Research and Development, Military Rehabilitation Centre 'Aardenburg, Doorn, the Netherlands.
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4. Rehabilitation Center Heliomare, Wijk aan Zee, The Netherlands

The undersigned,

Prof. Dr. J.H. van Dieën is professor of biomechanics at Research Institute Move, Department of Human Movmement Sciences, van der Boechorststraat 9, Amsterdam.

He is hereinafter referred to as **"Coordinating Investor"**

M.R. Prins (Principal Investigator) is a BIG-certified physical therapist, employed at the Dutch Military Rehabilitation Centre, Doorn, Korte Molenweg 3, 3941 PW, Doorn, the Netherlands. He is also a PhD Student at the department of Humand Movement Sciences at the Vrij Universiteit Amsterdam, van der Boechorststraat 9, Amsterdam and lecturer at the University of Applied Sciences, department of physiotherapy, Heidelberglaan 7, 3584 CS Utrecht.

He is hereinafter referred to as "**Principal Investigator**"

Dr. P. van der Wurff (Local Supervisor) is head of the Research and Development Department at the Dutch Military Rehabilitation Centre, Doorn, Korte Molenweg 3, 3940 AD, Doorn, the Netherlands. He is the representative for Commander Lkol. L. Jans of the Military Rehabilitation Centre Aardenburg.

They are hereinafter referred to as "**Sponsor**"

Together they are referred to as "**Parties**"

PROTOCOL SIGNATURE SHEET

Name	Signature	Date
Sponsor: Dr. P. van der Wurff Head Research and Development Military Rehabilitation Center		
Coordinating Investigator: Prof. Dr. J.H. van Dieën Professor of Biomechanics Research Institute MOVE		
Principal Investigator: Dr. M.R. Prins Researcher Military Rehabilitation Center		

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	General Assessment and Registration form (ABR form), the application form that is required for submission to the accredited Ethics Committee; in Dutch: Algemeen Beoordelings- en Registratieformulier (ABR-formulier)
CAREN	Computer Assisted Rehabilitation ENvironment
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
EU	European Union
IC	Informed Consent
METC	Medical research ethics committee (MREC); in Dutch: medisch-ethische toetsingscommissie (METC)
MRC	Military Rehabilitation Center
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
WMO	Medical Research Involving Human Subjects Act; in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen

SUMMARY

Rationale: This study is part of the Dutch UDBenchmark-project, which is part of the European EUROBENCH-framework (eurobench2020.eu). EUROBENCH aims to create the first framework for the application of benchmarking methodology on robotic systems. The UDBenchmark-project aims to deliver a measurement protocol, data analysis software and a reference database to assess how exoskeletons and humanoids perform while walking on slopes and lateral inclines. This particular research proposal concerns the assessment of the gait pattern and gait stability of people with lower limb prosthesis as part of the EUROBENCH-framework.

Objective: To deliver data to be used as part of a reference database for the EUROBENCH-framework, to gain insight in standing and walking stability of transtibial and transfemoral amputees and to evaluate the effect of different prostethic components on these outcomes.

Study design: Quasi Experimental

Study population: 20 Healthy controls (have already been measured), 10 unilateral transtibial amputees (TT) 5 unilateral transfemoral amputees (TF)

Intervention (if applicable): Standing and walking on a treadmill on a series of slopes and lateral inclines to a maximum of 15 degrees. Performing these tasks on a carbon fibre foot and a glass fibre foot (transtibial amputees only).

Main study parameters/endpoints: Standing and walking stability measures.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The participants will walk on a treadmill with several slopes and inclines at moderate speed of 2.1 km/h for 40 (TF) to 60 (TT) min. The amplitudes of imposed slopes could be larger than the maximal capacity of transtibial amputees and probably is larger than the maximal capacity of transfemoral amputees, which could result in a fall if the subject or researcher does not decide to stop in time. To prevent negative consequences as a result of a fall, all subjects will wear a safety harness. The results of this study will complement the EUROBENCH data base and will inform clinicians on potential problems of people with a lower limb amputation while walking on slopes and inclines.

1. INTRODUCTION AND RATIONALE

This study is part of the Dutch UDBenchmark-project, which is part of the European EUROBENCH-framework (eurobench2020.eu).

EUROBENCH aims to create the first framework for the application of benchmarking methodology on robotic systems. The framework, specifically focused on bipedal robotic technologies (humanoïds and exoskeletons), will include methods and tools to measure System Ability Levels on a rigorous, quantitative and replicable way, both during stance and during gait.

The UDBenchmark-project is a collaboration between the VU University, Amsterdam, The Netherlands, Military Rehabilitation Center 'Aardenburg', Doorn, The Netherlands and Heliomare, Wijk aan Zee, the Netherlands. The goals of this project are to deliver:
(1) a measurement protocol, ...
(2) data analysis software, ...
(3) a reference database ...
to assess how exoskeletons and humanoids perform while walking on slopes and lateral inclines.

Using this protocol, we measured 20 healthy controls over a range of walking speeds, slopes and lateral inclines, both with and without an extension limiting knee brace or mobility limiting ankle brace. The protocol of this study was evaluated and approved by the Scientific and Ethical Review Board of the Faculty of Behavioral and Movement Sciences from the VU University, Amsterdam, The Netherlands.

The current proposal concerns measurements of transfemoral and transtibial amputees to be added to the reference database. Moreover, this data can be used to gain more insight in balance strategies of amputees and the effect of prosthetic components on standing and walking balance. Walking ability of people with a lower limb amputation is most often assessed on flat level surfaces. While it has been shown that transfemoral and transtibial amputees experience difficulties maintaining balance during standing and walking on flat surfaces (Hak et al. 2013; Prinsen et al. 2017), likely such difficulties will be amplified when walking on slopes or lateral inclines. Prosthetic components, that differ in the degree of flexibility and therefore their ability to accommodate to different surfaces, can affect their gait pattern (Jonkergouw et al. 2019, 2016). However, to what extent these patients are able to maintain balance on difference slopes and lateral inclines and how prosthetic

componentry affects this remains unknown. The EUROBENCH protocol allows quantitative assessment of the gait pattern and gait stability of these patients in a safe and controlled manner and will hence contribute to insight in their capacity to negotiate non-level surfaces and guide prosthetic manufacturers to optimize prosthetic design.

2. OBJECTIVES

Primary Objectives:

To deliver data to be used as part of a reference database for the EUROBENCH-framework

Secondary Objectives:

To assess:

- to what extent transfemoral and transtibial amputees are able to adapt to standing and walking on slopes and laterally inclined surfaces in terms of standing and walking stability.
- how this stability is related to different prosthetic components.

3. STUDY DESIGN

Design: Quasi Experimental

3.1 Equipment

Patients will be tested in a Computer Assisted Rehabilitation Environment (CAREN, MOTEK Forcelink, Amsterdam, The Netherlands, Figure 1). The CAREN system consists of an instrumented treadmill. During the experiment, subjects stand or walk on the treadmill at a pace of 2.1 kilometres per hour (km/h). During the trials the slope or lateral incline of the treadmill will increase, in steps of 3 degrees, to a maximum of 15 degrees. Ten high resolution infra-red cameras (Vicon, Oxford, UK) and a modified Full Body PlugIn Gait marker setup (figure 2) will be used to capture kinematic data. A safety harness system suspended overhead will prevent the subjects from falling. Although the harness is attached to an overhead suspension system, no weight support will be provided.

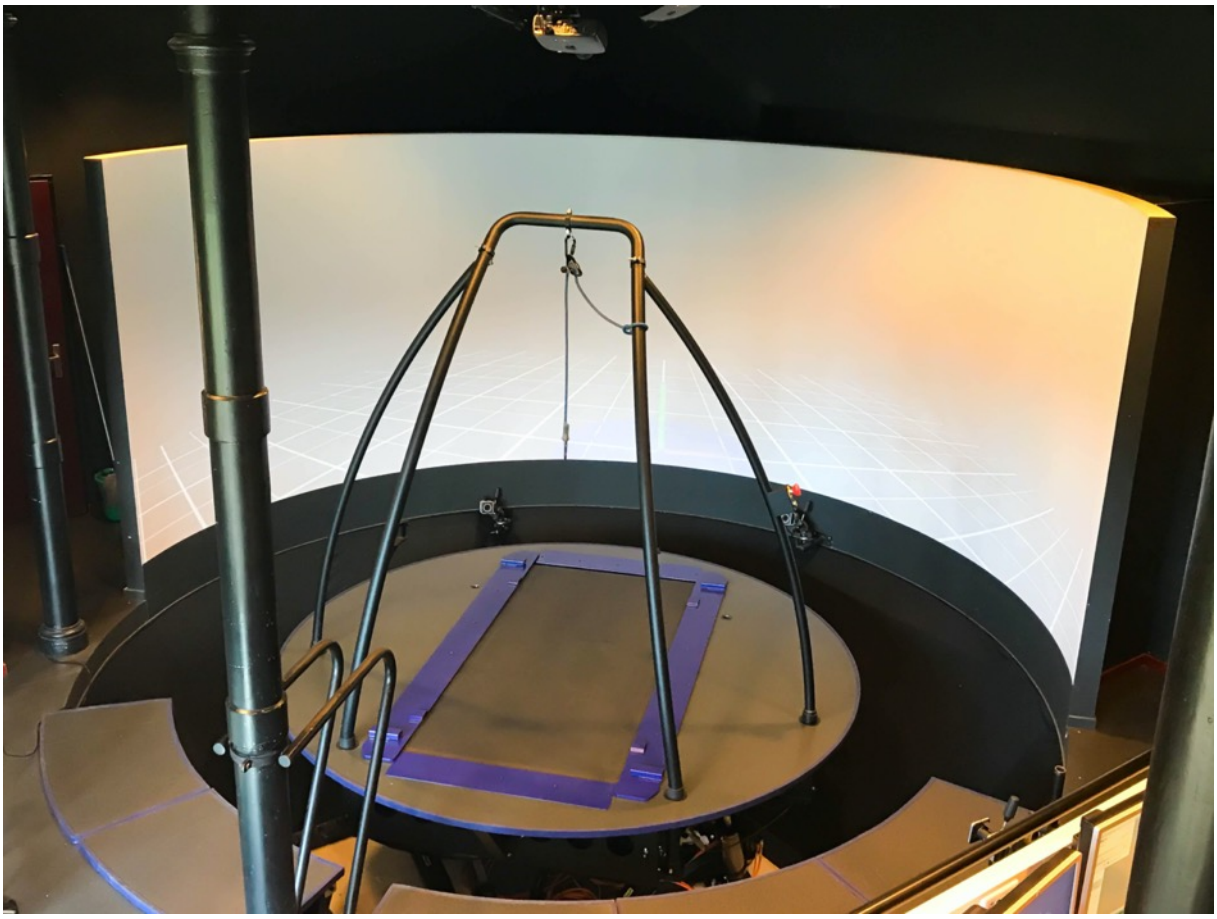

Figure 1. The CAREN-system at the MRC

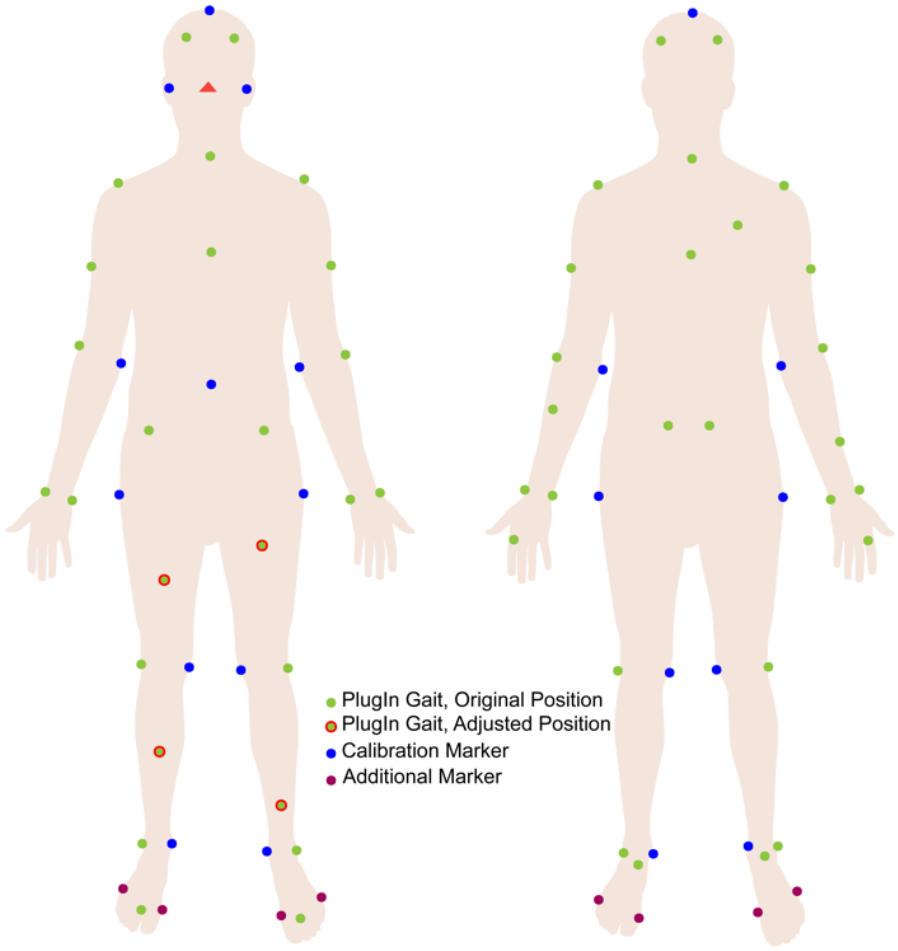

Figure 2. The modified Full Body PlugIn Gait marker setup

3.1 Protocol

The maximum duration of the protocol is 120 minutes for transfemoral amputees and 180 minutes for transtibial amputees. Subjects will be walking for a maximum duration of 40 (transfemoral amputees) or 60 (transtibial amputees) minutes. In figure 3 the duration of each step in in the protocol is visualized.

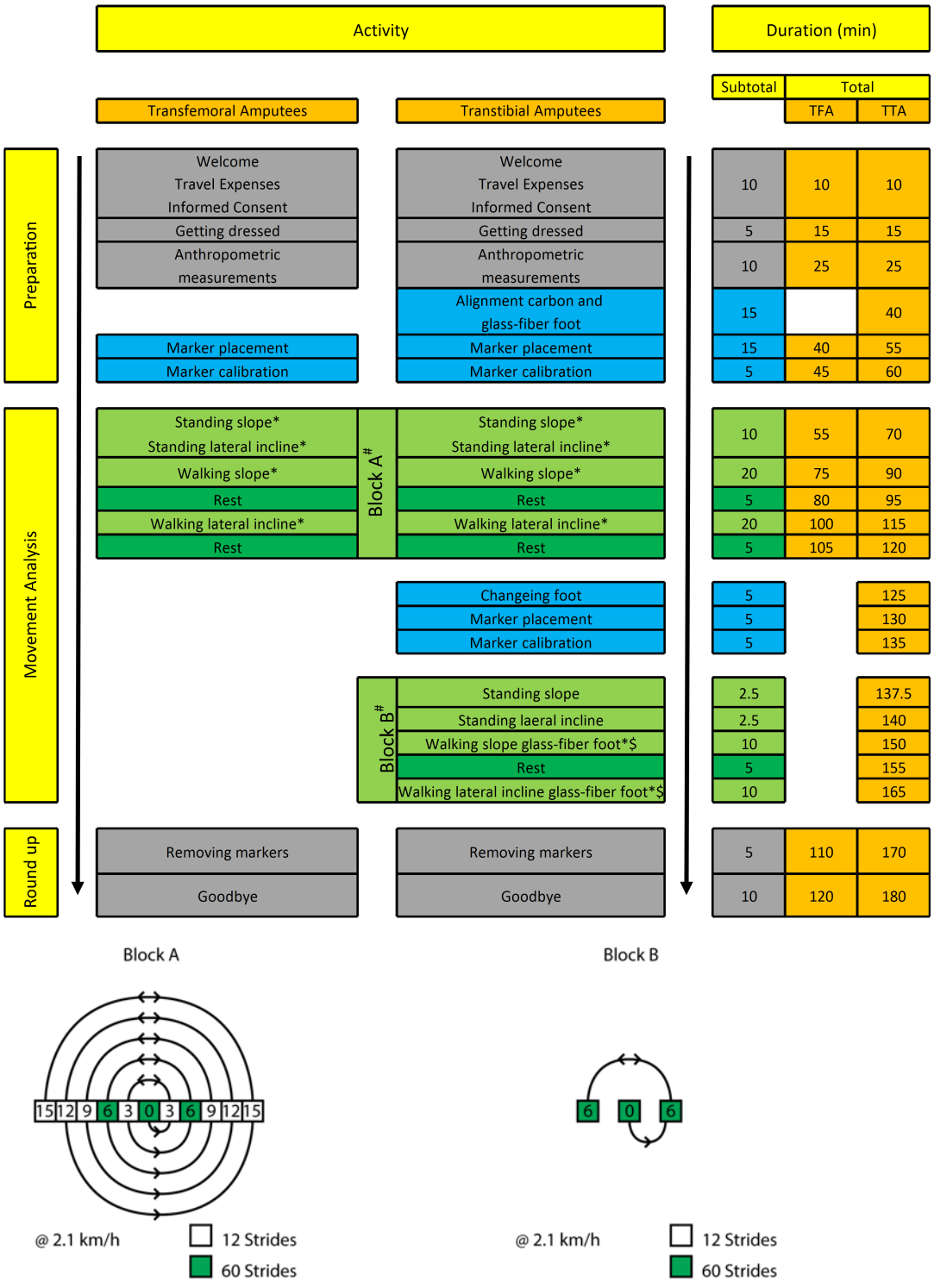

Figure 3. Protocol visualization

Top: Flow through the protocol with each activity (left side) and corresponding duration (right side)
Bottom left: Platform angles throughout the gait trials of Block A. After 60 strides on a flat surface, the platform will move to 3 degrees in one direction (i.e., uphill), after 12 strides the platform will move to 3 degrees in the other direction, after another 12 strides, the platform will move to 6 degrees, and so forth. In the standing trials the order of angles is the same, buth the angle will change after 7 seconds instead of a number of strides. Bottom right: In block B the subjects will only stand and walk on 0 and 6 degrees.

4. STUDY POPULATION

4.1 Population

Amputees will be recruited via an advertisement on the website of the national patient association (https://kortmaarkrachtig.com), directly via the rehabilitation physician at the military rehabilitation center or via the prosthetists of OIM orthopedie. Multiple studies with amputee patients have been performed at the Military Rehabilitation Center, both with transfemoral (Prinsen et al. 2017) and transtibial (Hak et al. 2013; Jonkergouw et al. 2019) amputees, with similar numbers of participants. We therefor expect no considerable difficulties with recruitment.

4.2 Inclusion criteria

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Uni-lateral transtibial (n=10) or transfemoral (n=5) amputation;
- Wearing a prosthesis for at least 1 year;
- Able to walk without assistive walking aid on flat surfaces and mild slopes (3 degrees)
- At least 18 years old;

4.3 Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Use of a computer assisted foot;
- Stump problems;
- Cognitive or communicative disorders;
- Visual impairments.
- Any condition (other than leg amputation) that might interfere with gait (e.g. neurodegenerative disease, peripheral vascular disease)
- Any condition that renders unfit to be tested (e.g. severe cardiovascular conditions)

4.4 Sample size calculation

For our main aim, that is, building a database, which is observational, the standard error of measurement of our main outcomes (margins of stability) of each slope and group (controls / transtibial amputees / transfemoral amputees) should be sufficiently small to represent the effect of these factors in the normative database. If gait stability measures differ

significantly between slopes and groups, this implies that the difference between the observed means of that outcome in these slopes/groups is sufficiently large, and the standard error of measurement sufficiently small, to represent an actual effect. The required number subjects required to significantly demonstrate an effect of slope or group is described below.

The effect of slope (within subjects):
With no pilot estimates, normal practice is to use Cohen's d as a means of estimating an appropriate sample size i.e. based upon the ratio of the mean difference and standard deviation being small, medium or large. To significantly demonstrate the effect of slope (0 vs 6 degrees) within groups, using a large d of 0.8 and a two-tailed paired design, at a 5% level of significance, a power of 80% should be achievable from a sample of size 10 for each group.

The effect of amputation (between subjects):
Stability measures have been evaluated during treadmill walking without slopes in transtibial amputees and healthy controls in previous research (Hak et al. 2013). The difference in mediolateral and backwards margins of stability between groups was 1.2 (Cohen's d). Using a Cohen's d of 1.2 and a one tailed test for the difference between two independent means (transtibial amputation vs control) at a 5% level of significance a power of 80% should be achievable from a sample size of 10 in each group. A similar design would require 13 participants per group for a 90% power. Given this information and the logistic of this study, a convenience sample of 10 uni-lateral amputees is proposed thus aiming for an 80% power.

Transfemoral amputees:
Since transfemoral amputees experience considerably more difficulty maintaining balance during stance and gait, we propose a sample of 5 transfemoral amputees. This would require an effect size of 1.7 to demonstrate an effect of slope, and an effect size of 1.8 to achieve a power of 80% to demonstrate an effect of amputation. This is to be expected, based on previous findings of differences in the gait pattern between transfemoral amputees and able bodied controls (Sturk et al. 2019).

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Standing and walking on a treadmill at 2.1 km/h at imposed slopes and lateral inclines to a maximum of 15 degrees.

Standing and walking on two types of prosthetic feet (transtibial amputees).

6. INVESTIGATIONAL PRODUCT

6.1 Name and description of investigational product(s)

For the assessment of the effect of type prosthetic foot on walking ability on slopes and inclines, two different commercially available types of feet will be used: a carbon-fibre foot the Aeris Performance 2, and as glass-fibre foot the RUSH HiPro (Figure 4).

The Aeris Performance 2 is used as carbon-fibre foot. This foot is suitable for moderate to high activity and contains multiple parallel springs for increased energy return. The foot consists of a split keel and pylon design, allowing the two sides of the foot to move independently that is beneficial on uneven ground, during turns and to provide enhanced stability. In addition, the carbon fibre material improves flexibility, absorption of shock and reduce of stress on the residual limb. Furthermore, due to the stacked, parallel structure of these carbon fibre springs, a higher energy return is provided. Each spring independently absorbs energy before working together, enhancing the energy return.

The RUSH HiPro foot is used as glass-fibre foot. This foot is suitable for moderate to high activity and maintains or achieves a higher level of activity, giving even high activity amputees the comfort, flexibility and freedom during any type of activity. The foot provides a realistic and responsive foot and ankle motion with a high energy return. This enables users to easily transverse the most aggressive terrains. The glass composite material is twice as flexible and more durable than carbon and produces a more natural gait.

Additional information is provided in documents D1a, D1b, D1c and D1d. These prosthetic feet will be borrowed to parties free of charge by OrthoEurope.

Aeris Performance 2

RUSH HiPro

Figure 4. Provided prosthetic feet

7. METHODS

7.1 Study parameters/endpoints

7.1.1 Main study parameter/endpoint

Standing stability measures for each slope (Doyle et al. 2007):
- mean center of pressure (COP) velocity
- COP anteroposterior sway
- COP mediolateral sway

Gait stability measures for each slope (Bruijn et al. 2013):
- local divergence exponents
- foot placement coordination
- margins of stability (mediolateral and backward) (Hak et al. 2013)

7.1.2 Secondary study parameters/endpoints (if applicable)

Spatiotemporal gait parameters: step length, step width and step frequency.
Hip, knee and ankle joint kinematics (movements) and kinetics (moments).

7.1.3 Other study parameters (if applicable)

Anthropometric data (height, weight, age, segmental circumferences).

7.2 Randomisation, blinding and treatment allocation

The order of slopes and inclines will be varied in a fixed order as depicted in figure 3. Transtibial amputees will not be informed which kind of foot they are wearing during measurements. The order in which the feet will be provided will be quasi-randomized between subjects. The investigators will be informed which prosthetic foot is being measured.

7.3 Study procedures

Figure 3 gives an overview of all procedures that subjects undergo. Transfemoral amputees perform all condition with their own prosthetic foot. For the transtibial amputees, the fitting of both prosthetic feet will be performed by a certified prosthetist. During all measurements on the CAREN system a physiotherapist with more than 10 years of experience in using the system will be present (M.R. Prins). During rest-periods in the protocol, subjects are offered water and are allowed to visit the toilet.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

If a participant withdraws or if the investigator decides to withdraw a participant from the research, a replacement will be sought by the same criteria as the individuals have been recruited at the start of the research.

7.6 Follow-up of subjects withdrawn from treatment

The follow-up on withdraws will be used as mentioned in: 8.3 Follow-up of adverse events.

7.7 Premature termination of the study

The research will be terminated if unforeseen problems arise which are in contradiction with the permission of the Brabant METC or when an event occurs as stated below, commencing on March 1, 2020 and shall continue in force until the earlier of October 1, 2020 at:

- Completion of the measurements of the study;
- Termination in accordance with the following agreements between the Sponsor, Coordinating Researcher and the Principal Researcher.

Termination of the Clinical Trial on other grounds than mutually agreed completion would not terminate this Agreement or any obligations arising from it. Either Party may terminate this Agreement upon written notice to the other party with immediate effect in the following events:

- If one of the Parties is dissolved;
- If one of the Parties becomes or is declared insolvent or a petition in bankruptcy has been filed against it;
- If the purpose of the Clinical Trial, as confirmed by the Ethics Committee, becomes obsolete;
- If, through no fault of the Parties, the Clinical Trial does not receive official approval from the Ethics Committee and/or competent authorities, or this approval is permanently revoked;
- If the Clinical Trial ceases to be in the interests of the health of the Clinical Trial Subjects as determined by the Ethics Committee or Competent Authority;

- If one of the Parties fails to comply with the obligations arising from the Agreement and, provided compliance is not permanently impossible, this compliance has not taken place within thirty (30) days of the defaulting party receiving a written request to comply, unless failure to comply is not in reasonable proportion to the premature termination of the Clinical Trial;
- If circumstances beyond the control of the Sponsor, Principal Investigator or Funder make it unreasonable to require the continuation of the Clinical Trial.

Parties may terminate this Agreement if the Principal Investigator is no longer able (for whatever reason) to act as Principal Investigator and no mutually acceptable replacement can be found.

If the Agreement is terminated by the Sponsor for one of the reasons in clauses, the Sponsor shall pay all costs incurred and falling due for payment by Institution up to the date of termination, and also all expenditure falling due for payment after the date of termination which arises from commitments reasonably and necessarily incurred by the Institution for the performance of the Clinical Trial.

8. SAFETY REPORTING

8.1 Temporary halt for reasons of subject safety

In accordance to section 10, subsection 4, of the WMO, the sponsor will suspend the study if there is sufficient ground that continuation of the study will jeopardise subject health or safety. The sponsor will notify the accredited METC without undue delay of a temporary halt including the reason for such an action. The study will be suspended pending a further positive decision by the accredited METC. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to the trial procedure. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect; or
- any other important medical event that did not result in any of the outcomes listed above due to medical or surgical intervention but could have been based upon appropriate judgement by the investigator.

An elective hospital admission will not be considered as a serious adverse event.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 7 days of first knowledge for SAEs that result in death or are life threatening followed by a period of maximum of 8 days to complete the initial preliminary report. All other SAEs will be reported within a period of maximum 15 days after the sponsor has first knowledge of the serious adverse events.

8.3 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

9. STATISTICAL ANALYSIS

All statistics will be performed using Matlab 2016b (The Mathworks, USA).

9.1 Descriptive statistics (secondary outcomes)

The following data will be presented quantitatively:

- The mean (SD) age, weight, height, body mass index per group.
- The type of prosthetic fitting (socket with or without pin-system, osseo-integration)

9.2 ANOVAs (primary outcomes)

To determine the effect of condition on standing and walking stability, Factorial ANOVA with within-subject factor slope angle and between-subject factor condition (healthy/transtibial amputation/transfemoral amputation) will be calculated for each of the dependent main study parameters described in 7.1. For the transtibial amputees only the carbon foot trials will be used for these analyses. To determine the effect of prosthetic feet on the primary outcomes a repeated measures ANOVA will be performed for each trial and slope direction with foot (carbon-fibre / glass-fibre) and slope (Flat / 6 degrees) as within-subject factors

9.3 Study parameter(s)

All primary study outcomes will be calculated using a custom-made MATLAB algorithm. The same algorithm will be used for each participant to avoid subjective choices during the analysis.

10. ETHICAL CONSIDERATIONS

10.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki and in accordance with the Medical Research Involving Human Subjects Act (WMO) and by the Good clinical Practice (GCP) guidelines.

Article 458 of the Wet Geneeskundige Behandelings Overeenkomst (WGBO) and The Algemene Verordening Gegevensbescherming (AVG) and Gedrag Gezondheidszorg (2005) will be working on the personal data. The Principal Researcher will ask the participants for permission, by informed consent (IC), to permit sharing the pseudonymized data with the Eurobench Consortium. All data will be stored for 10 years, after which the data traceable to the person (name, phone, e-mail, address) will be destroyed. The participants will be informed about what the research team will be doing during the research. All rights of the clients will be stated to the client on paper as well as orally. Thereby, a participant will explicitly be asked to sign an IC form. During the study the participant may withdraw at any time, see 4.3.

10.2 Recruitment and consent

Amputees will be recruited via an advertisement on the website of the national patient association (https://kortmaarkrachtig.com), directly via the rehabilitation physician at the military rehabilitation center or via the prosthetists of OIM orthopedie. In all cases, the information letter will be handed over. Permission to participate in the study will be requested at least 48 ours later by the principal investigator. This decision will be asked at least 48 ours before the measurements will take place. Healthy control subjects have already been measured.

10.3 Benefits and risks assessment, group relatedness

A benefit for the participants is that they will receive insight in their own functional capacities.

The tests will be performed in an unfamiliar virtual reality laboratory, that can be somewhat intimidating to the subjects. The amplitudes of imposed slopes could be larger than the maximal capacity of transtibial amputees and probably is larger than the maximal capacity of transfemoral amputees, which could result in a fall if the subject or researcher does not decide to stop in time. To prevent negative consequences as a result of a fall, all subjects will wear a safety harness. The gait lab (CAREN: Computer Assisted Rehabilitation ENvironment) of the military rehabilitation center is used on a daily basis to improve

patients' ability to walk on varying slopes as part of a multidisciplinary rehabilitation program. These patients include transtibial and transfemoral amputees.
The military rehabilitation center has worked with this system for more than 10 years. Dr. M.R. Prins, who will be present at all the measurements, is registered in the BIG-registry as a physiotherapist and has been working fulltime at the VR rehabilitation department of the rehabilitation center for 10 years (and
still works there fulltime). Therefore, we estimate the chance of unforeseen risks as 'low'.

10.4 Compensation for injury

The sponsor has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.
The sponsor has an insurance which is in accordance with the legal requirements in the Netherlands (Article 7 WMO and the Measure regarding Compulsory Insurance for Clinical Research in Humans of 23th June 2003). This insurance provides cover for damage to research subjects through injury or death caused by the study.

- € 450.000,-- (i.e. four hundred and fifty thousand Euro) for death or injury for each subject who participates in the Research;
- € 3.500.000,-- (i.e. three million five hundred thousand Euro) for death or injury for all subjects who participate in the Research;
- € 5.000.000,-- (i.e. five million Euro) for the total damage incurred by the organisation for all damage disclosed by scientific research for the Sponsor as ‘verrichter’ in the meaning of said Act in each year of insurance coverage.

The insurance applies to the damage that becomes apparent during the study or within 4 years after the end of the study.

10.5 Incentives (if applicable)

The participants time invested is compensated by a voucher of €20,- and is provided to all participants.

11. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

11.1 Handling and storage of data and documents

Data will be handled anonymously and confidentially. A code list will be used to couple data to an individual subject. The code will consist of 3 numbers. The first number will identify the group (control, transfemoral amputee or transtibial amputee) and the second and third number will be a unique combination for each subject. Only the principal investigator (M.R. Prins) and coordinating investigator (P. van der Wurff) will have access to data traceable to the person (name, e-mail, phone number, address, with subject code). This data is stored on an encrypted USB disk stored in a safe at the military rehabilitation center.

11.2 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

11.3 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

11.4 Temporary halt and (prematurely) end of study report

The investigator/sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC.

11.5 Public disclosure and publication policy

The Sponsor acknowledges the importance of public publication of information collected or generated by the Principal Investigator, under the condition that public publication takes place under the provisions of this article 8.7.

Upon completion of the Study (whether prematurely or otherwise) the Principal Investigator and Sponsor shall co-operate in producing a report of the Study detailing the methodology, results and containing an analysis of the results and drawing appropriate conclusions. The Principal Investigator will be authorized to publish the results, subject to the provisions set forth under this section.

The Sponsor agrees that the Principal Investigator and his institution shall be permitted to present at symposia, national or regional professional meetings, and to publish in journals, theses or dissertations.

Upon completion of the Study, the Principal Investigator may prepare the data derived from the Study for publication. In order to ensure that the Sponsor will be able to make comments and suggestions where pertinent, material for public dissemination will be submitted to the Sponsor for review at least ninety (90) days prior to submission for publication, public dissemination, or review by a publication committee.

The Institution and the Principal Investigator agree that all reasonable comments made by the Sponsor in relation to a proposed publication will be incorporated into the publication.

13. REFERENCES

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