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Complete List of Authors:	Lendaro, Eva; Chalmers tekniska hogskola, Electrical Engineering Hermansson, Liselotte; University Health Care Research Centre, Faculty of Medicine and Health, Örebro University; Department of Prosthetics and Orthotics, Faculty of Medicine and Health, Örebro University Hospital, Burger, Helena; University Rehabilitation Institute; University of Ljubljana, Faculty of Medicine Van der Sluis, Corry; University of Groningen, University Medical Center Groningen, Rehabilitation Medicine McGuire, Brian; National University of Ireland, Galway, Ireland, School of Psychology & Centre for Pain Research Pilch, Monika; National University of Ireland, Galway, Ireland, School of Psychology & Centre for Pain Research Bunketorp-Käll, Lina; Sahlgrenska University Hospital, Centre for Advanced Reconstruction of Extremities Kulbacka-Ortiz, Katarzyna; Sahlgrenska University Hospital, Centre for Advanced Reconstruction of Extremities Rignér, Ingrid ; Sahlgrenska universitetssjukhuset, Gåskolan/Ortopedteknik Stockselius, Anita; Rehabcenter Sfären,Bräcke Diakoni Gudmundson, Lena; Rehabcenter Sfären,Bräcke Diakoni Widehammar, Cathrine; University Health Care Research Centre, Faculty of Medicine and Health, Örebro University Hill, Wendy; University of New Brunswick, Institute of Biomedical Engineering Geers, Sybille; Fysische Geneeskunde en Revalidatie, University Hospital Gent Ortiz-Catalan, Max; Chalmers tekniska hogskola, Electrical Engineering; Integrum AB
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Phantom Motor Execution as a treatment for Phantom Limb Pain: Protocol of an international, double-blind, randomised, controlled clinical trial.

Eva Lendaro[1], Liselotte Hermanson[2,3], Helena Burger[4,5], Corry van der Sluis[6], Brian E. McGuire[7], Monika Pilch[7], Lina Bunketorp-Käll[8], Katarzyna Kulbacka-Ortiz[8], Ingrid Rignér[9], Anita Stockselius[10], Lena Gudmundson[10], Cathrine Widehammar[3], Wendy Hill[11], Sybille Geers[12], and Max Ortiz-Catalan[1,13]

[1] Biomechatronics and Neurorehabilitation Laboratory, Department of Electrical Engineering, Chalmers University of Technology, Gothenburg, Sweden
[2] Department of Prosthetics and Orthotics, Faculty of Medicine and Health, Örebro University Hospital, Örebro, Sweden
[3] Faculty of Medicine and Health, University Health Care Research Centre, Örebro University, Örebro, Sweden
[4] University Rehabilitation Institute, Ljubljana, Slovenia
[5] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[6] University of Groningen, University Medical Centre Groningen, Department of Rehabilitation Medicine, Groningen, Netherlands
[7] School of Psychology & Centre for Pain Research, National University of Ireland, Galway, Ireland.
[8] Centre for Advanced Reconstruction of Extremities, Sahlgrenska University Hospital, Gothenburg, Sweden.
[9] Gåskolan/Ortopedteknik, Sahlgrenska University Hospital, Gothenburg, Sweden.
[10] Rehabcenter Sfären, Bräcke Diakoni, Stockholm, Sweden.
[11] Institute of Biomedical Engineering, University of New Brunswick, New Brunswick, Canada.
[12] Fysische Geneeskunde en Revalidatie, University Hospital Gent, Gent, Belgium.
[13] Integrum AB, Mölndal, Sweden.

Correspondence to: Dr. Max Ortiz-Catalan maxo@chalmers.se

Abstract

Introduction: Phantom limb pain (PLP) is a chronic condition that can greatly diminish quality of life. Control over the phantom limb and exercise of such control have been hypothesized to reverse maladaptive brain changes correlated to PLP. Preliminary investigations have shown that decoding motor volition using myoelectric pattern recognition, while providing real-time feedback via virtual and augmented reality (VR-AR), facilitates phantom motor execution (PME) and reduces PLP.

Here we present the study protocol for an international (seven countries), multicentre (nine clinics), double-blind, randomized, controlled clinical trial to assess the effectiveness of PME in alleviating PLP.

Methods and analysis: Sixty-seven subjects suffering from PLP in upper or lower limbs are randomly assigned to PME or Phantom Motor Imagery (PMI) interventions. Subjects allocated to either treatment receive 15 interventions and are exposed to the same VR-AR environments using the same device. The only difference between interventions is whether phantom movements are actually performed (PME) or just imagined (PMI). Complete evaluations are conducted at baseline and at intervention completion, as well as 1, 3 and 6 months later using an intention to treat approach. Changes in PLP measured using the Pain Rating Index between the first and last session are the primary measure of efficacy. Secondary outcomes include: frequency, duration, quality of pain, intrusion of pain in activities of daily living and sleep, disability associated to pain, pain self-efficacy, frequency of depressed mood, presence of

catastrophizing thinking, health-related quality of life and clinically significant change as patient's own impression. Follow-up interviews are conducted up to six months after the treatment.

Ethics and dissemination: The study is performed in agreement with the Declaration of Helsinki, and under approval by the governing ethical committees of each participating clinic. The results will be published according to the CONSORT guidelines in a peer-reviewed journal.

Strengths and limitations of this study

Strengths

- This study involves a large number of participants (>60) with upper and lower limb amputations and thus can provide sufficient power to draw clinically meaningful conclusions
- This study is double-blinded, randomized, and conducted in geographically different locations which enhances generalizability.
- The choice of the comparator allows controlling in a stringent manner for the effect of the key factor hypothesized as the cause of pain reduction, namely, the execution of phantom limb movements.

Limitations

- Treatment is limited to 15 sessions, which might not be enough to alleviate pain in all participants.
- The nature of the experimental treatment (PME) does not allow inclusion of individuals from which myoelectric signals cannot be recorded from the muscles in their residual limbs.

Trial Registration

DATA CATEGORY	**INFORMATION**
Primary registry and trial identifying number	ClinicalTrials.gov NCT03112928
Date of registration in primary registry	April 10, 2017
Source(s) of monetary or material support	Promobilia foundation (F16501), VINNOVA (Medtech4Health 2016-02290), EFIC Grünenthal Grant (358041552) and Integrum AB (sponsor).
Coordinator	Chalmers University of Technology, Sweden
Investigational sites	Sahlgrenska University Hospital, Sweden Örebro University, Sweden Bräcke Diakoni, Sweden

DATA CATEGORY	INFORMATION
	University Rehabilitation Institute, Slovenia Ghent University Hospital, Belgium University Medical Center Groningen, The Netherlands The University of New Brunswick, Canada National University of Ireland, Galway, Ireland Ruhr-University Bochum, Germany
Sponsor	Integrum AB
Contact for public queries	Eva Lendaro, MSc, +46704231352 lendaro@chalmers.se
Contact for scientific queries	Max Ortiz Catalan, PhD, +46708461065 maxo@chalmers.se
Public title	*Phantom Motor Execution as a Treatment of Phantom Limb Pain*
Scientific title	*Phantom Motor Execution Via Myoelectric Pattern Recognition, Virtual and Augmented Reality, and Serious Gaming as a Treatment of Phantom Limb Pain*
Countries of recruitment	Sweden, Slovenia, Netherlands, Belgium, Ireland, Canada, Germany
Health condition(s) or problem(s) studied	Phantom Limb Pain
Intervention(s)	Experimental: Phantom Motor Execution Control: Phantom Motor Imagery
Key eligibility criteria	• The participants must be older than 18 years with chronic PLP • People with acute PLP are non-eligible. At least six months should have passed since

DATA CATEGORY	INFORMATION
	amputation • In case of pharmacological treatments, the dosage must have been stable for the last month • Any previous PLP treatment must have terminated at least 3 months prior to commencing the study • Any pain reduction potentially attributable to previous PLP treatments must have occurred at least 3 months prior to commencing the study • Voluntary control over at least a portion of biceps and triceps muscles in case of upper limb amputation, or quadriceps and hamstrings in case of lower limb amputation. • Stable prosthetic situation (i.e. satisfaction with the fitting of the prosthesis) or being a non-user. • The participant should not have cognitive impairment that prevents them from following instructions. • No abundant soft tissue on the stump that prevents sufficient myoelectric signals from being recorded. • No presence of pain > 2 on a numeric rating scale (NRS) upon contact with the skin or muscle contraction in the stump • The PLP must not be aggravated (NRS > 4) by the execution or imagination of phantom movements • No condition associated with risk of poor protocol compliance • No injury, disease or addiction that would render the individual unsuitable for the trial • Pain Rating Index > 0 as assessed in the Q-PLP at Visit 0
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: double-blind (participant, evaluator) Primary purpose: treatment

DATA CATEGORY	INFORMATION
Date of first enrolment	May 8th, 2017
Target sample size	67
Recruitment status	Recruiting
Primary outcome	Change in Phantom Limb Pain as measured by the Pain Rating Index.

Protocol version

Clinical investigation plan code 007 733, version 02, 2017-05-24.

Sponsor contact information

Trial Sponsor: Integrum AB
Contact name: Malin Ling
Address: Krokslätts Fabriker 50, SE-431 37, Mölndal, Sweden
Telephone: +46723198311
Email: malin.ling@Integrum.se

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Role of study sponsor and funders

The sponsor (Integrum AB) provided the devices and materials used in this study. Neither the sponsor nor the funders (Promobilia, VINNOVA, EGG) had a role in the design of the present protocol.

Roles and responsibilities

MO-C is the coordinating investigator of the study and endpoint adjudication evaluator. EL is the monitor of the trial, independent from the sponsor, and responsible for data management. Each site is constituted by at least a principal investigator, a therapist, and a blinded-evaluator. Investigational sites are independent from each other and from the sponsor.

Authors' contributions

MO-C conceived the PME treatment. MO-C and EL reviewed the literature and designed the study. All authors provided feedback on the design of the trial. BMG and MP assisted in the selection of psychological measure. LB-K and KK-O coordinated the ethical applications. EL and MO-C drafted the

manuscript. EL, LH, HB, CS, BMG, MP, LB-K, KK-O, IR, AS, LG, CW, WH, SG and MO-C revised the study protocol and approved the final manuscript.

Competing interests

The sponsor of this study (Integrum AB) is a for-profit organization that might commercialize the device used in this study (PME and PMI). MO-C was partially funded by Integrum AB. The core technology used in this study has been made freely available as open source by MO-C (machine learning, virtual reality and electronics). All the other authors declare no competing interests.

Introduction

Phantom limb pain (PLP) is a chronic condition commonly suffered by amputees (Clark et al., 2013; Dijkstra et al., 2002). Although more than 60 different treatments to alleviate PLP have been described in the literature (Nikolajsen and Jensen, 2001), controlled clinical trials on such treatments are scarce. The clinical investigation presented in this protocol aims to evaluate the efficacy of Phantom Motor Execution (PME) in reducing Phantom Limb Pain (PLP) in an international, multi-centre, double blind, randomized, controlled clinical trial. PME is accomplished by using a system (Neuromotus, Integrum AB, Sweden) that employs myoelectric pattern recognition to predict motor volition (movements of the phantom limb), while providing real-time feedback to the patient in virtual and augmented reality (VR/AR) environments. This technology allows the application of serious gaming in the therapy. PME is a non-invasive, non-pharmacological, and engaging treatment with no identified side effects at present (Ortiz-Catalan *et al*., 2014, 2016).

The effectiveness of PME was initially explored in a single upper limb amputee, with satisfactory results reported (Ortiz-Catalan *et al*., 2014). Prior to the pilot study, the patient had shown resistance to a variety of treatments for 48 years (including mirror therapy). After PME, the sustained level of pain reported by the patient was gradually reduced to pain-free periods. He and his family also reported less intrusion of PLP in sleep and activities of daily living (ADL). Finally, the patient also acquired the ability to freely move his phantom arm and hand, consistent with a recent study by Raffin and colleagues where they found that reduced capability of phantom movement was correlated with more severe PLP (Raffin 2016).

In the light of the findings in the case study, a non-randomized clinical investigation on PME was conducted in subjects with chronic intractable upper limb PLP (Ortiz-Catalan et al., 2016). Fourteen patients, for whom conventional PLP treatments failed and who suffered from PLP for an average of 10 years, received 12 treatment sessions of PME, each of 1.5 hours' duration. At the end of the treatment period, patients showed statistically and clinically significant improvements (approx. 50% reduction of PLP). Intrusion of PLP during sleep and ADL was also reduced by a similar degree. These improvements were still present up to 6 months' post-treatment (Ortiz-Catalan *et al*., 2016). More recently, PME was also proven to be a viable treatment for PLP in lower limb amputations (Lendaro et al., 2017).

Strong evidence shows that PLP is related to neuroplastic changes in the primary somatosensory cortex, suggesting that central maladaptive plasticity is responsible for its maintenance. Neuroplasticity-based approaches for the relief of PLP, such as motor imagery and mirror therapy, ultimately aim to regain brain circuitry from pain processing. Nonetheless, these approaches have been shown to be limited in their effectiveness.

Although the practice of motor imagery has been shown to normalize previously altered cortical maps and reduce PLP (MacIver et al., 2008), evidence from randomized clinical studies has also suggested that it can increase pain (Chan et al., 2007). These seemingly contradictory findings suggest that motor imagery should not be used alone but combined with other interventions, such as graded motor imagery (Moseley, 2006) or mirror therapy (Bowering et al., 2013).

Mirror therapy has demonstrated higher effectiveness than motor imagery in reducing pain (Chan et al., 2007), however, it still cannot ensure that the patient performs movements with the phantom limb. For instance, it is enough for the patient to move their healthy arm to produce movement in the reflected limb. Whether a patient is actually engaging in execution of phantom limb movements is unknown. PME overcomes some of the methodological limitations of previous treatments by ensuring that central and peripheral mechanisms in motor control are activated during therapy.

Study objective

This paper presents the study protocol for a RCT in which upper and lower limb amputees are treated. The investigation primarily aims at assessing the efficacy of PME aided by myoelectric pattern recognition, augmented and virtual reality, and serious gaming to reduce Phantom Limb Pain (PLP). In order to isolate the contribution of PME in alleviating PLP over potential placebo effects, Phantom Motor Imagery (PMI) is used in this study as an active control treatment.

The working hypothesis of PME is that execution of phantom limb movements would exploit competitive neuroplasticity and provide a more integral normalization of cortical, sub-cortical, and spinal circuits compared to interventions that do not enable integration of sensory and motor information. Therefore, in this superiority trial, we expect the participants receiving the experimental treatment (PME) to obtain a larger reduction in PLP levels than those randomized to the control treatment.

Trial design

This clinical study is an international, multicentre, double-blind, randomised controlled trial. The study takes place in seven counties and involves nine clinics, which are listed in Table 1. Participants are randomly assigned to receive either the experimental or the control treatment in a 2:1 allocation ratio. The choice of the allocation ration was made in order to collect more data on the intervention of interest and deemed superior. Each patient is followed up for a period of six months, at the end of

Table 1: List of the investigational sites, divided by countries taking part to the international, multicenter randomized clinical trial.

Country	**Investigational site**
Sweden	Sahlgrenska University Hospital, Gothenburg
	Örebro University Hospital, Örebro
	Rehabcenter Sfären, Bräcke Diakoni, Stockholm
Slovenia	University Rehabilitation Institute, Ljubljana
Belgium	Fysische Geneeskunde en Revalidatie University Hospital Gent, Gent
Netherlands	Department of Rehabilitation Medicine, University Medical Centre Groningen, Groningen
Canada	Institute of Biomedical Engineering, University of New Brunswick, New Brunswick
Ireland	Centre for Pain Research, National University of Ireland, Galway
Germany	Department of Psychosomatic Medicine and Psychotherapy, LWL University Hospital, Ruhr-University Bochum, Bochum

which they are given the choice to undergo the alternative treatment. The total duration of the study is expected to be approximately three years.

Methods: Participants, interventions, and outcomes

A procedural overview of the trial is provided by the flow diagram of Figure 1. Recruitment of the participants is conducted via advertisements at local investigation clinics, on social media, and in local newspapers. People who are interested in taking part in the trial are invited to contact the principal investigator of the site, or a person appointed by the principal investigator, via phone or email.

Eligibility criteria

Interested people are invited to a pre-assessment visit (Visit 0). On this occasion, the therapist (clinical investigator) explains the study in detail and answers all the questions that might arise. Afterwards, the participants are asked to provide written informed consent (see Appendix A). If consent is granted, eligibility to the study is assessed according to the criteria presented below:

- The participants must be older than 18 years with chronic PLP
- Participants must have chronic PLP - at least six months should have passed since amputation. Participants with acute PLP are non-eligible.
- In case of pharmacological treatments, the dosage must have been stable for the previous month
- Any previous PLP treatments must have terminated at least 3 months prior to entering the study
- Any pain reduction potentially attributable to previous PLP treatments must have occurred at least 3 months prior to entering the study
- Voluntary control over at least a portion of biceps and triceps muscles in case of upper limb amputation, or quadriceps and hamstrings in case of lower limb amputation.
- Stable prosthetic situation (i.e. satisfaction with the fitting of the prosthesis) or being a non-user.
- The subject should not have a cognitive impairment that prevents them from following instructions.
- No abundant soft tissue on the stump that prevents sufficient myoelectric signals from being recorded.
- No presence of pain > 2 on NRS upon contact with the skin or muscle contraction in the stump
- The PLP must not be aggravated (NRS > 4) by the execution or imagination of phantom movements
- No condition associated with risk of poor protocol compliance
- No injury, disease or addiction that would render the individual unsuitable for the trial
- Pain Rating Index (PRI) > 0 as assessed in the Questionnaire for Phantom Limb Pain (Q-PLP) at Visit 0

Concomitant medications

Any co-intervention aiming to reduce PLP is prohibited during the trial. However, in the design of the trial it is acknowledged that there is a large possibility for patients with PLP to be high consumers of analgesic medicines. Therefore, the use of concomitant medications is allowed provided that at the time of inclusion, the patient has stable consumption for at least one month before entering the study and any pain reduction potentially attributable to the drug occurred at least three months before entering the study. Intake of pain medication in patients who show considerable improvement can be gradually reduced at the discretion of the responsible physician, given that the patient is followed up regularly.

Medication intake is thus monitored as an outcome variable called “need of concomitant medication”, which is used to describe and compare the amount of co-medication in the treatment groups.

Interventions

All of the therapists at the clinics are introduced to the technology with at least one practical demonstration by the first (EL) and/or last author (MO-C). The therapists conduct the interventions independently, and periodically the first author monitors the correct execution of the protocol. Participants in both intervention groups receive 15 treatment sessions of 2 hours’ duration, including system setup and a blinded outcome assessment. The frequency of the sessions is chosen by the participant and can be once, twice (advised frequency), or five times per week, yielding a total patient duration that ranges between 28 and 40 weeks. Both treatment groups use the same device and set up, which are sketched in Figure 2. The only difference between the two groups is the type of interaction with the virtual environments (active: motor execution; or passive: motor imagery). Allocated interventions for a given trial participant cannot be modified. Dates of the treatment sessions are recorded.

Experimental Treatment

In the PME intervention, motor volition is decoded by interpreting the signals from the stump muscles via myoelectric pattern recognition (Ortiz-catalan et al., 2014; Ortiz-Catalan et al., 2013). The decoded movement is visualized in the virtual environments (i.e. virtual limb or serious gaming). The end result is that the user, by training with the system, can achieve control over the virtual environments by performing phantom limb movements associated with kinetic sensations analogous to the ones pertaining to the limb prior to amputation.

A treatment session consists of the following steps:

1. Placement of the electrodes and fiducial marker;
2. Treatment cycles
    - Recording session
    - Practice of PME with VR/AR
    - Serious gaming using phantom movements
    - Practice of PME by matching random target postures of a virtual arm in VR (TAC Test (Simon et al., 2011)).
3. Pain evaluation (Q-PLP, see Outcomes section)

Different treatment cycles (step 2) are repeated during a treatment session in order to execute various phantom limb movements or combinations of movements. The level of difficulty gradually increases during the treatment phase from 1 to 5 by adding degrees of freedom to be trained within the same treatment cycle. In this context, a degree of freedom is any pair of movements performing opposite actions such as opening and closing of the hand, or extension and flexion of the knee.

Clinicians are instructed to advance the level of difficulty once the previous level is accomplished successfully, and revert to the previous level if the patient shows considerable difficulty accomplishing the tasks. More details on the acquisition of myoelectric signals, prediction of motor volition, the various parts of the treatment session, and the different levels of difficulty are presented in Appendix B.

Control Treatment

In the control treatment (PMI), patients are not allowed to produce/execute phantom movements, but must imagine performing such movements while observing them executed autonomously by the VR/AR environments. The device is identical to the one used in the experimental treatment, but here the myoelectric signals are used to monitor that the patient does not produce muscular contractions, rather than decoding motor volition.

The control treatment session is conducted using the same step-wise procedure as the experimental group with the addition of a calibration step at the beginning of the treatment cycle. Calibration is necessary to set the threshold for myoelectric signals above which the system alerts the user that a muscular contraction is performed. As in PME, the treatment cycle is repeated for different imaginary phantom limb movements or a set of imaginary movements following the same levels of difficulty. In the game format, the participants control the game using the keyboard with an able limb. Bilateral upper limb amputees use a joystick with any able limb. Details on the methods are presented in Appendix B.

Withdrawal or termination of individual participants

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event, clinical abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant no longer meets the eligibility criteria because of a condition newly developed or not previously recognized.

The main analysis will be conducted using the intention to treat (ITT) methodology. Missing data due to withdrawal or termination will be imputed using the 'last observation carried forward' method. From previous studies, the dropout rate is estimated at approximately 10% and this was taken into account for the calculation of the sample size.

Outcomes

Outcomes will be evaluated at every treatment session and three follow-up assessments at one, three, and six months' post-treatment. The outcomes are measured by the evaluators following the participant treatment schedule presented in Table 2.

Primary outcome measure

The primary outcome of the study is the change in PLP intensity measured by the difference in Pain Rating Index (PRI) between baseline (Visit 0) and at the post-treatment assessment (Visit 15). The PRI is computed as the sum of the scores for all descriptors of the Short Form of the McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987).

Secondary outcome measures

Secondary outcomes consider different aspects related to PLP such as pain frequency, pain duration, quality of pain, intrusion of pain in activities of daily living and sleep, disability associated with pain, pain self-efficacy, mood, presence of catastrophizing thinking, health-related quality of life and the patient's own impression about the effect of treatment. The secondary outcome measures are:

Pain Disability Index (PDI)

Pain Disability Index, a 7-item questionnaire designed to investigate the extent to which chronic pain interferes with a person's ability to engage in various life activities (Pollard, 1984). An overall pain disability index score is obtained by summing the numerical ratings of the questionnaire's single items.

Questionnaire for Phantom Limb Pain (Q-PLP)

The Q-PLP is a 16-item questionnaire based on a combination of the SF-MPQ (Melzack 1987) and study-specific questions use in previous studies ((Lendaro et al., 2017; Ortiz-Catalan et al., 2014, 2016)). The part containing the SF-MPQ is used for the calculation of the Pain Rating Index (primary outcome measure).

The Q-PLP assesses intensity, quality, duration, and frequency of phantom limb pain using the following metrics: the numeric rating scale (scale range 0 - 10) to assess the intensity of pain at present; the weighted pain distribution (scale range 0 - 5) to capture the time-varying nature of chronic pain by adding the contributions of weighted portions of time spent in six pain levels (present pain intensity scale (Melzack, 1975)); and a study-specific descriptive scale of seven steps: "never", "once per month", "once per week", "few times per week", "once per day", "few times per day", and "always" to measure the frequency of pain.

In addition, the Q-PLP is used to monitor the intensity of stump pain, phantom limb sensations, phantom motor ability, intrusion of phantom limb pain in activities of daily living and sleep, by one question each using a numeric rating scale. Changes in prosthetic hardware, medication, presence of telescoping (feeling that the phantom limb is gradually shortening over time), and location of pain are also monitored by the Q-PLP.

Euroqol-5D-5L (EQ-5D-5L)

The EQ-5D-5L is a standardised questionnaire used to investigate health-related quality of life which is constituted by two components: health status and health evaluation (Herdman et al., 2011). Health status is measured in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on a five-point scale (no problems, slight problems, moderate problems, severe problems and extreme problems). In the health evaluation part, the EQ Visual Analogue Scale (EQ VAS) records the respondent's health on a vertical VAS where the end points are labelled 'best imaginable health state' and 'worst imaginable health state'.

Pain Self-Efficacy Questionnaire (PSEQ-2)

The PSEQ-2 is a 2-item questionnaire that measures pain self-efficacy, which is the belief held by people with chronic pain that they can carry out certain activities and enjoy life, despite experiencing pain (Nicholas, 2007; Nicholas et al., 2015). The items of the questionnaire are rated on a numeric rating scale from 0 to 6.

Pain Catastrophizing Scale – 6 (PCS-6)

The PCS-6 is a 6-item questionnaire that investigates catastrophizing thinking in a range from 0 to 4 (McWilliams et al., 2015; Sullivan et al., 1995). Pain catastrophizing denotes a negative cognitive-affective response to pain and is associated to increased pain severity, disability and depressive symptoms and is associated with poor adjustment to chronic pain (Sullivan et al., 2001).

Patient Health Questionnaire-2 (PHQ-2)

The PHQ-2 is a screening instrument consisting of two items assessing the presence of a depressed mood and a loss of interest or pleasure in routine activities (Kroenke et al., 2003; Spitzer et al., 1999). The items of the questionnaire are rated on a numerical scale from 0 to 3.

Patients' Global Impression of Change (PGIC)

The PGIC is a single question used to identify clinically significant change by rating the patient's belief about the efficacy of treatment on a 7-point scale, ranging from 'no change (or condition has got worse)' to 'a great deal better' (Hurst and Bolton, 2004).

Additional measurements

Participants are asked to supply details regarding background information such as age, gender, height, weight, type and use of the prosthesis, level of embodiment of the prosthesis, onset of PLP, details about previous and ongoing intervention for PLP and side, level and date of amputation. Additionally, we also survey: patients' expectancy of benefit using the Expectations for Complementary and Alternative Medicine Treatments (EXPECT-SF) (Jones et al., 2016); patients' judgment about the credibility of the treatment using the Opinion About Treatment (OAT) (Mooney et al., 2015) and patients' perception of therapists' supportive behaviour using the short form of the 6-item Health Care Climate Questionnaire (HCCQ) (Williams et al., 1998).

Sample size

The calculation of the sample size was based on our primary hypothesis and informed by our previous clinical trial with no control group (Ortiz-Catalan et al., 2016). In order to find a mean difference of 4 between the two randomised groups in the primary outcome measure (PRI), with power of 80% resulting from a two-sided Fisher's non-parametric permutation test at 5% significance level, is estimated that at least 60 participants are required. As a drop-out rate of 10% is expected, a total of 67 patients will be randomised.

Methods: Assignment of intervention

Randomization

Participants are assigned to the experimental or control group according to the optimal allocation scheme of minimization, aimed at reducing the imbalance between the number of patients allocated to each treatment group. The randomization proportion is 2:1, with twice as many subjects assigned to the experimental treatment. The allocation ratio was chosen because we predict with high confidence that the experimental treatment will outperform the control treatment, and because of the possibility to collect more information on important variables regarding the intervention of interest. The allocation aims to minimize the imbalance of the following factors:

- Level of amputation (upper and lower)
- Baseline PLP based on the NRS (low 1 to 4, and high 5 to 10)
- Investigation site (9 centres)

The minimisation process is conducted using the open source desktop application MinimPy (Saghaei, 2011), operated by the monitor of the clinical trial. Every time a research team at a particular investigational site recruits a new participant, they assess the person's eligibility for the study (Visit 0). Afterwards, if the participant is deemed eligible, the research team sends the minimization factors

relative to the enrolled participant to the monitor, who runs the randomisation, and informs the research team of the allocation.

Blinding

This investigation has been designed in such a way that participants of the two treatment groups use the same device under the same circumstances.

Even though the patients are necessarily aware of the treatment they are receiving, they do not have an expectation of superiority of the experimental over the control treatment (or vice versa), since the trial is framed as a comparison between two different interventions previously described in the literature. It is worth noting that the distinction between motor execution and motor imagery is often imperceptible, even for professionals in the field, who have often described voluntary movements of the missing limb as imaginary movements (Ersland et al., 1996; Hugdahl et al., 2001; Lotze et al., 2001; MacIver et al., 2008; Rosén et al., 2001; Roux et al., 2001, 2003). We take this fact as a corroborant of our assumption that there are no differences at baseline with respect to expectations and opinions about the assigned treatment among participants. Nevertheless, individuals' expectations regarding outcomes and credibility of the assigned treatment are assessed with the EXPECT-SF and the OAT questionnaires respectively.

The nature of the investigation does not allow the masking of the treatment for the therapists. However, it is still important to check for possible differences between the two groups concerning the therapists' supportive behaviour. For this reason, the HCCQ, is included as a measure of the extent to which a health care provider (or the staff) interacts with their patient in a supportive manner.

The outcome assessments are conducted by independent persons who are blinded to the group allocation, making the trial double blind. In order to keep group allocation confidential, participants are requested prior to each assessment not to reveal allocation or therapy content to the evaluators.

The raw data resulting from the outcome assessment has the same structure for both interventions, making it impossible to tell the group assignment without being in possession of the documents containing links between participant's identity and their code number.

Table 2: Summary of the different items (intervention, forms and questionnaires) to be completed at each evaluation appointment. Questionnaire for Phantom Limb Pain (Q-PLP), Pain Disability Index (PDI), 2-item Pain Self-Efficacy Questionnaire (PSEQ-2), Euroqol-5D-5L (EQ-5D-5L), Pain Catastrophizing Scale Short Form (PCS-SF), 2-item Patient Health Questionnaire (PHQ-2), Patients' Global Impression of Change (PGIC), Opinion About Treatment (OAT), Health Care Climate Questionnaire (HCCQ) and Expectations for Complementary and Alternative Medicine Treatments Short Form (EXPECT-SF).

Session	**Summary of content**
Visit 0	• Patient Information (T/E) • Study Consent (T/E) • Pre-Assessment (T/E) • Background Information (T/E) • Q-PLP (T/E) • PDI (T/E) • EQ5D-5L (T/E) • PSEQ-2 (T/E) • PCS-SF (T/E) • PHQ-2 (T/E) • EXPECT-SF (T/E)
Randomization	
Visit 1	• Treatment session (T) • Q-PLP (E) • OAT (E) • EXPECT-SF (E) • HCCQ-SF (E)
Visit 2-14	• Treatment session (T) • Q-PLP (E)
Visit 15	• Treatment session (T) • Q-PLP (E) • PDI (E) • EQ5D-5L (E) • PSEQ-2 (E) • PCS-SF (E) • PHQ-2 (E) • PGIC (E) • HCCQ-SF (E)
1-month follow-up	• Q-PLP (E) • PDI (E) • EQ5D-5L (E) • PSEQ-2 (E) • PCS-SF (E) • PHQ-2 (E)
3-month follow-up	
6-month follow-up	

Methods: Data collection, management and analysis

Data collection and management

The monitor of the study (EL) is in charge of overseeing the progress of the RCT and ensuring that it is conducted, recorded, and reported in accordance with the protocol, Good Clinical Practice (GCP), and regulatory requirements.

The monitor supplies Case Report Forms (CRFs), which are filled in by the evaluator at each site. The evaluator is responsible to document all data obtained during the study which is identified by participant code number. This also applies to data for patients who, after having consented to participate, undergo the baseline examinations required for inclusion in the study, but who are not included. No items in the CRF are to be left unattended: if data are missing or are impossible to obtain, these should be documented as "not available" (NA) and the reasons for missing data must be noted in the document.

All data are recorded and stored in digital form on encrypted electronic devices. Documents containing links between a participant's identity and their code number exist only in paper form and are kept in locked file cabinets with limited access at the investigation site where the participants have been treated. In accordance with the regulations issued by The Swedish Data Protection Authority, a personal register will be established.

The clinical investigators are responsible to probe, via discussion with the participant, for the occurrence of adverse events during each visit and record the information in the patient CRF. Adverse events must be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study device, or if unrelated, the cause. The investigator must report any reportable event to the monitor in acceptable timely conditions, but not later than three working days after the occurrence of the event. The sponsor must report to the Medical Products Agency (Läkemedelsverket) any serious adverse event which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients, users or other persons immediately, but not later than two working days after becoming aware of a new reportable event or of new information in relation to an already reported event.

Once all the data are collected, checked, and corrected, the database is closed and analyses performed. All data transfer, processing and analyses are done using depersonalised data and all the data sets are protected by password. In order to promote data quality, the evaluators are trained on all the data collection and management procedures and are provided with written instructions by the first (EL) and last (MO-C) authors.

To incentivise the completion of the follow-up, the patients are given the choice to participate in these assessments at the clinic or via a phone interview with the evaluators. When possible, follow-up assessments are also conducted with participants that had discontinued the treatment or withdrew from the study.

Statistical methods

The main analysis will be performed in terms of change from baseline to the measurement at treatment completion using the ITT population. Complementary analyses will be performed on the Per Protocol (PP) population with respect to the change from baseline to the follow up assessments at 1,3 and 6 months after completion. Both the ITT population and the PP population will be specified in detail at the

Clean file meeting before the database lock and before breaking the code. The PP population will be restricted to the participants who successfully complete all 15 treatment sessions.

Suitable graphical and numerical summaries will be provided for all the variables measured and for corresponding changes in scores.

For the main unadjusted comparison between two groups, Fisher's non-parametric permutation test will be used for continuous variables, Mantel-Haenszel chi-square test for ordered categorical variables, Fisher's exact test for dichotomous variables and Pearson's chi-square test for non-ordered categorical variables. Confidence intervals at 95% for the mean differences between two groups will be given when appropriate. If significant differences exist between the two randomised groups between baseline variables that could influence the outcome variables, a complementary adjusted analysis will be performed for these baseline variables.

For adjusted comparison between two groups, analysis of covariance (ANCOVA) will be used for continuous outcome variables not obviously non-normally distributed with intervention/control as independent variable and all confounders as covariates.

For analysis of change within groups, Wilcoxon Signed rank test will be used for continuous variables and Sign test for ordered categorical and dichotomous variables. A complementary mixed model analysis between the two treatments regarding the primary efficacy variable with centre as random effect will be used to correct for the centre-effect in the statistical models.

All correlations will be performed with Spearman's correlation coefficient. The distribution of continuous variables will be given as mean, standard deviation, median, minimum and maximum, and distribution of categorical variables will be given as numbers and percentages. All statistical tests will be two-sided and conducted at the 5% significance level. The theory of sequential multiple test procedures will be applied for the primary analysis and for secondary analyses. If a test gives a significant result at the 5% significance level, the total test mass will be transferred to the following number in the test sequence until a non-significant result is achieved. All these significant tests will be considered confirmative. A Statistical Analysis Plan (SAP) will be written with all detailed statistical analyses specified.

Ethics and dissemination

Research ethics approval

There are no known risks associated with the experimental or control treatments and clinically significant deterioration is rare. Possible individual benefits include reduced phantom limb pain, reduced disability associated with pain, and improvement in various aspects related to quality of life. This trial has been approved by the governing ethical committees of each participating country. Important protocol modifications will be reported in a timely manner to all the relevant parties.

Access to data

The principal investigator, MO-C, has full access to all of the data in the study except the documents containing the link between patient's identity and their code number, which will be accessible only after the completion of the data analyses. MO-C takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dissemination Policy

Regardless of the significance, direction, or magnitude of effect, the consortium will publish the findings of this study in scientific, peer-reviewed journals and conferences following the CONSORT guidelines. All the clinical investigators will author the scientific article reporting the results of the trial. No professional writers external to the study will be used aside from conventional English proof reading. Access to the detailed clinical investigation plan, participant-level dataset, and statistical code will be granted based on reasonable requests after the publication of the study.

Trial status

This clinical trial is currently in the participant enrolment phase. Fourteen patients have been randomized and are under treatment at November 2017. It is anticipated that full analysis will be finalised in April 2020.

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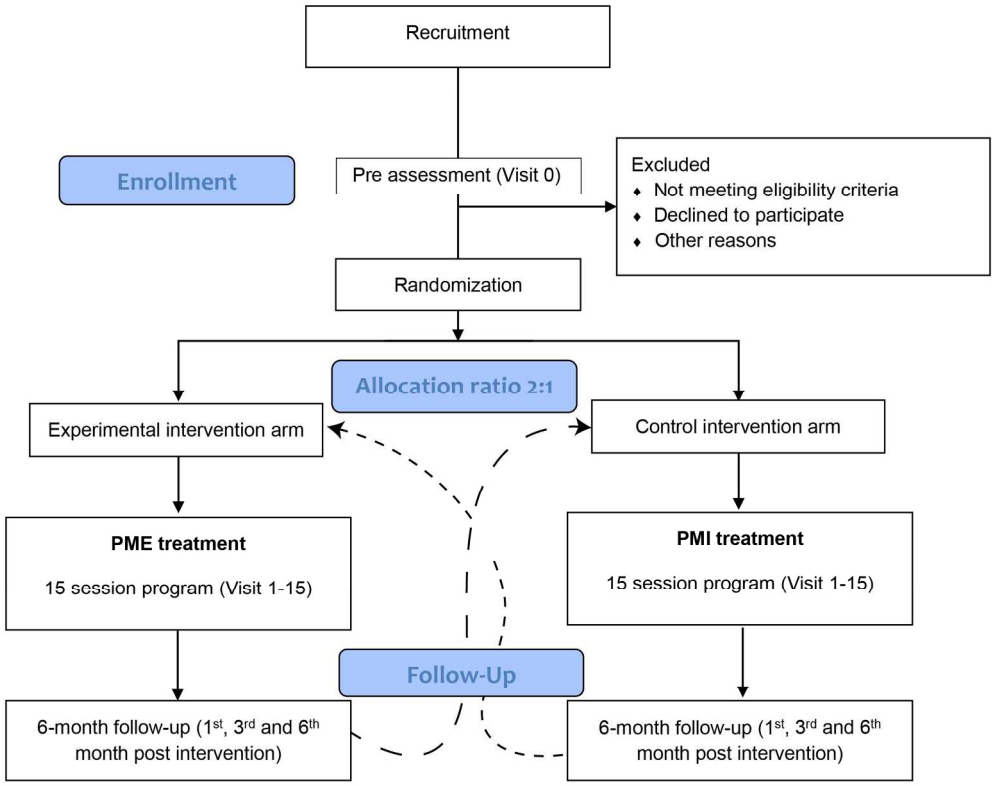
Figure legends

Figure 1: Flow diagram for the randomized controlled clinical trial. At least sixty-seven patients are recruited and randomly allocated to either Phantom Motor Execution (PME) or Phantom Motor Imagery (PMI) interventions in allocation ratio 2:1. Following the completion of the treatment protocol and wash-out period of six months it is possible for the patient to cross over to the parallel interventional arm, according to their will.

Figure 2: Schematic illustration of the clinical investigation device with all its components. Myoelectric signals are acquired though surface electrodes (A) by a myoelectric amplifier (B), electrically isolated (C). The signals are then processed by the software installed on the computer (D). The camera (E) films the participant and the recorded image is displayed on the monitor (F) with a virtual limb superimposed where the marker (G) is detected. Figure courtesy of Jason Millenaar.



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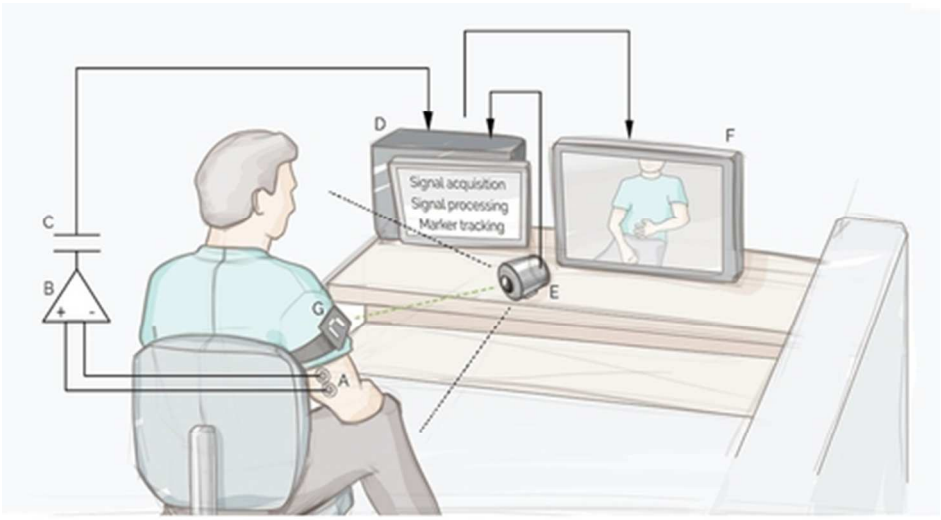

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PARTICIPANT INFORMATION SHEET

1. Introduction

Title of Project: Virtual Reality as a Treatment for Phantom Limb Pain – A Randomised Controlled Trial

2 Invitation

You are being invited to take part in a research study investigating the effect of two different forms of virtual motor training as a treatment for phantom pain. Before you decide, it is important for you to understand why the research is being done and what it will involve. This *Participant Information Sheet* will tell you about the purpose, risks and benefits of this research study. If you agree to take part, we will ask you to sign a Consent Form. If there is anything that you are not clear about, we will be happy to explain it to you. Please take as much time as you need to read it. You should only consent to participate in this research study when you feel that you understand what is being asked of you, and you have had enough time to think about your decision. Thank you for reading this.

3 Purpose of the Study

Phantom pain occurs in about 70-80% of all amputees and many continue to feel the lost body part which is called phantom arm or phantom leg. Some individuals feel that they can move their phantom arms or legs while others feel that the phantom limb is immobile and very painful. Although there are many different ways to treat phantom limb pain, there is still no satisfactory treatment to help all patients. During the last decade, TENS and mirror therapy have started to be used to treat phantom limb pain. A further development has taken place with the help of modern computer technology which enables the training of the amputated body part in a virtual reality. The method involves performing virtual motor training exercises i.e. patients learn to move an image of their phantom arm or leg and this is believed to stimulate repair mechanisms in the brain. We aim to investigate whether two different variants of this new technology effectively reduce phantom pain in amputees.

4 Study Design

The study is a randomized, controlled clinical trial. This means that the you have been randomly assigned to one of two groups that will receive different treatments for phantom limb. Both treatment methods are believed to be effective but we will examine if there is something in one of the two methods more effective than the other. If the current treatment does not give you any improvement, you'll be able to undergo the second form of treatment, if you wish, after completion of the first programme.

5 Taking part – what it involves

What will happen to me if I take part?

In the treatment, adhesive electrodes will be used: these will be attached to the skin on your stump. With these electrodes, signals from the stump muscles can be recorded. When the virtual arm or leg on the screen moves, you should either imagine or perform the same movements with your own phantom arm or leg. Activity in the stump muscles is recorded via the adhesive pads. The training also includes various computer games that are controlled by the system.

There are several possible explanatory mechanisms for the analgesic effect that can be achieved with virtual motor training. It is believed that the areas of the brain required for movements in the amputated arm are partially reactivated. The patient receives visual feedback that tricks the brain into thinking that there is an arm that receives the brain's movement commands. After each treatment, you will be asked to answer questions about how you experience phantom pain. At the first and last treatment session, you will also answer questions about how you experience your health overall. Individual interviews will be conducted on a sample of the study participants after treatment. The objective of the qualitative part is to explore how individuals experienced the treatment, and if and how this is perceived to have affected their health in general. To investigate whether the treatment has a lasting effect, you will be called for examination 1, 3 and 6 months after treatment.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, a copy of which you can also keep. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your rights in any way.

How long will my part in the study last?

There will be a total of 15 treatment sessions that last about 2 hours each. You can choose to receive the treatment one, two or five times a week.

What are the possible benefits in taking part?

If the treatment has the effect we expect, your phantom pain is likely to decrease. In the unlikely event that the treatment does not produce results, you will get the opportunity to try the other treatment option after the completion of the long-term follow-up.

What are the possible disadvantages and risks of taking part?

All elements of the study are done under safe conditions by trained and skilled staff and you will not be exposed to any risks associated with either treatment or evaluation. If you come into the treatment group that uses the stump muscles during exercise, you may experience tiredness in your muscles at the beginning of treatment. This, however, is transient.

What happens at the end of the study?

When the long-term follow-up is completed, you will have the opportunity to have a copy of your own results. On request, you can also get information about the overall results of the study. The study and its results will be announced by publication in international scientific journals.

What happens if I change my mind during the study?

You are entitled to change your mind about participating in this at any time without disadvantage or penalty. If you decide to withdraw, all your data will be destroyed and will not be used in the study.

6 Confidentiality

All information that is collected about you during the course of the research will be kept strictly confidential and will not be shared with anyone else. The information collected in this research study will be stored in a way that protects your identity.

Information obtained during this study will be compiled with the help of a computer to analyze the results. The information is treated as confidential and will be stored for 10 years. All data processing

will be done with coded identity (individuals cannot be recognized from their data) and the results will be presented in a way in which no individual can be identified. Your personal information is securely protected and cannot be accessed by unauthorized persons. The identity code concerning research participants will be kept securely at the project leader's site.

7 Responsible for the investigations

Coordinating Investigator:
Max Ortiz Catalan, Chalmers University of Technology, Institution for Electrical Engineering, 412 96 Gothenburg.
E-mail: maxo@chalmers.se
Tel: + 46 (0) 708 46 10 65

Thank you for taking the time to read this information sheet.

Appendix B – Extended Methods

Interventions

Possible phantom movement for upper limb amputees are hand open and close, pronation and supination, wrist flexion and extension, elbow flexion and extension, flexion and extension of the individual fingers. Possible movements for lower limb amputees are knee extension and flexion, femoral rotation outwards and inwards, ankle plantar flexion and dorsiflexion, tibial rotation outwards and inwards, ankle eversion and inversion, flexion and extension of the toes. Upper and lower limb movements can be performed individually and simultaneously (more than two movements at the same time). Depending on the level of amputation, some movements are omitted from the treatment because they involve the residual rather than the phantom limb: e.g. elbow movements in transradial amputees. According to whether the subjects are assigned to the control or experimental intervention, they are asked to either imagine or execute these phantom movements as naturally and intuitively as possible.

Experimental Treatment

A Phantom Motor Execution (PME) treatment session consists of the following components:

1. **Placement of electrodes and fiducial marker.** To place the electrode in an appropriate way, subjects are asked to execute different phantom movements while the stump is palpated to localize the muscles. Areas with excess of soft-tissue between muscles and skin are avoided. Four to eight bipolar superficial electrodes (pre-gelled, adhesive, Ag/AgCl, one cm diameter, and two cm inter-electrode distance) are then placed along the muscle fibres where possible, else one electrode is placed on the target muscle while the other is placed on a more electrically neutral area. In the case of transfemoral amputations, electrodes are placed according to the *targeted monopolar configuration* described in detail in reference: (Lendaro et al., 2017).
2. **PME training cycle** (see Figure B1)
    a. **Recording session.** The subjects are asked to perform three repetitions of the movements as shown by a virtual limb alternated by rest periods. The standard contraction time is set to three seconds followed by three seconds of relaxation. However, this time might be increased in case longer time is required to complete the phantom movement. This step is necessary to collect myoelectric data used to train the motor volition decoding algorithms. The movements performed are dictated by the current level of difficulty (see “Levels of difficulty”).
    b. **Phantom motor execution in augmented reality (AR).** The subjects are then asked to control the virtual limb by performing the movements previously trained.
    c. **Serious gaming.** Each phantom movement trained during the recording session is then paired to activate a specific key on the computer keyboard. Computer games that would normally be controlled by those keys can then be controlled by the phantom movements, enabling the control of the game through *phantom motor execution*.
    d. **Target achievement control (TAC) test.** In this part of the training cycle the subjects are asked to move a virtual limb aiming to match a target posture determined by the movements previously trained. The target posture is considered achieved when the subject is able to position the virtual limb within ±5 degrees range in less than 20 seconds, and hold it for a two-second dwell interval. The trained movements are randomly requested six times each. This test was originally designed to evaluate control strategies for multi-functional prosthetic devices represented in virtual reality (Simon et al., 2011) In this study, the TAC test is used only for rehabilitation purposes and it is used as implemented in our open source platform named BioPatRec (Ortiz-Catalan et al., 2013).

3. **Outcomes evaluation.** Depending on the specific visit different outcome measures are recorded by blind evaluators at the end of the treatment, as reported in Table 2.

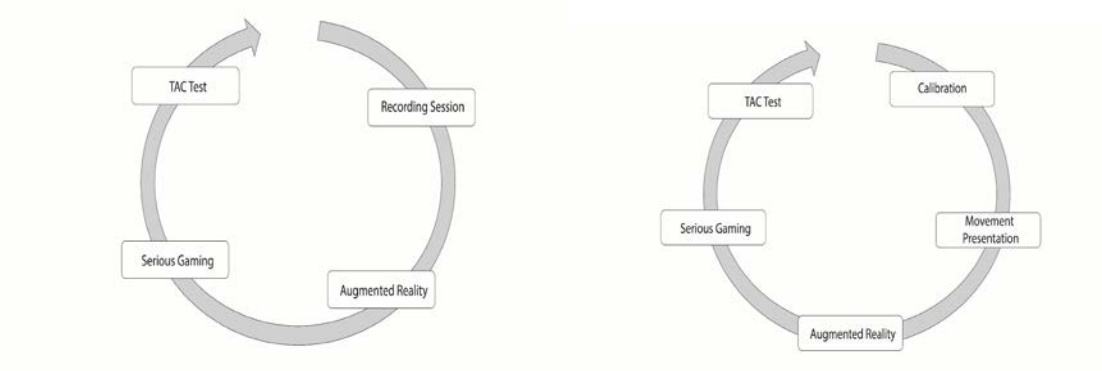

Figure B1: Training cycle for the Phantom Motor Execution (PME) intervention (left) and Phantom Motor Imagery (PMI) intervention(right)

Control Treatment

A Phantom Motor Imagery (PMI) treatment session consists of the same components as the experimental intervention, however there are some differences in the treatment cycle (see Figure B1), which are listed below:

- **Calibration.** The training cycle starts with the calibration. During this step, the patient is asked to relax the muscles completely and stay still. This phase is required in order to set the relaxation or "non-activity" level and enable the detection of contractions associated with unwanted motor execution.
- **Movement presentation.** This step is the analogue of the recording session in the experimental treatment and is meant to present a sequence of selected movements to the subject. The movements are chosen based on an increasing level of difficulty (see "Levels of difficulty"). Every movement is presented three times, for a period of three seconds in each repetition, and alternated by rest periods of equal length. During this phase the subject is asked to practice the imagination of the movements.
- **Serious gaming.** In the gaming step, the subjects will control the game using the keyboard with an able limb. No imagination is required for this step. However, the patient is expected to engage in an entertaining activity and divert cognitive resources that would be otherwise devoted to pain processing. Bilateral upper limb amputees will use a joystick with any able limb.
- **Phantom motor execution in augmented reality (AR) and TAC test.** The subjects are asked to imagine being in control of the movements autonomously performed by the virtual limb in both AR and VR environments.

Levels of difficulty

Interventions can be performed at five levels of difficulty. Subjects start at the easiest level and advance to the next level following different modalities depending on their intervention group. Subjects assigned to the PME group move to the next level when they achieve 85%-100% completion rate in the TAC test. If subjects are unable to achieve over 30% of completion rate in the new level, they are advised to move back to the previous level. On the other hand, subjects assigned to the PMI group are instructed on the specific amount of time to spend in each level, which increases with the number of degrees of freedom (DoF) exercised within the same treatment cycle.

- Level 1: Individual movements (1 DoF).

- Level 2: Individual movements (2 DoF). In the second level more than two movements are requested within the same training cycle while keeping each movement independent.
- Level 3: Simultaneous movements (2 DoF). Subjects are required to combine more than one DoF, i.e. pronation while opening or closing the hand, or supination while opening or closing the hand.
- Level 4: Individual movements (3 DoF).
- Level 5: Simultaneous movements (3 DoF).

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	3-5
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	5
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	5
	5b	Name and contact information for the trial sponsor	5
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5, 17
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6,7
	6b	Explanation for choice of comparators	7

Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9, Appendix B
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10,16

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	17
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17,18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17,18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12, 17,18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	6
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17,18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix A

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Phantom Motor Execution as a treatment for Phantom Limb Pain: Protocol of an international, double-blind, randomised, controlled clinical trial.

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Research methods, Occupational and environmental medicine, Sports and exercise medicine
Keywords:	Neurological pain < NEUROLOGY, Clinical trials < THERAPEUTICS, REHABILITATION MEDICINE

Phantom Motor Execution as a treatment for Phantom Limb Pain: Protocol of an international, double-blind, randomised, controlled clinical trial.

Eva Lendaro[1], Liselotte Hermanson[2,3], Helena Burger[4,5], Corry van der Sluis[6], Brian E. McGuire[7], Monika Pilch[7], Lina Bunketorp-Käll[8], Katarzyna Kulbacka-Ortiz[8], Ingrid Rignér[9], Anita Stockselius[10], Lena Gudmundson[10], Cathrine Widehammar[3], Wendy Hill[11], Sybille Geers[12], and Max Ortiz-Catalan[1,13]

[1] Biomechatronics and Neurorehabilitation Laboratory, Department of Electrical Engineering, Chalmers University of Technology, Gothenburg, Sweden
[2] Department of Prosthetics and Orthotics, Faculty of Medicine and Health, Örebro University Hospital, Örebro, Sweden
[3] Faculty of Medicine and Health, University Health Care Research Centre, Örebro University, Örebro, Sweden
[4] University Rehabilitation Institute, Ljubljana, Slovenia
[5] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[6] University of Groningen, University Medical Centre Groningen, Department of Rehabilitation Medicine, Groningen, Netherlands
[7] School of Psychology & Centre for Pain Research, National University of Ireland, Galway, Ireland.
[8] Centre for Advanced Reconstruction of Extremities, Sahlgrenska University Hospital, Gothenburg, Sweden.
[9] Gåskolan/Ortopedteknik, Sahlgrenska University Hospital, Gothenburg, Sweden.
[10] Rehabcenter Sfären, Bräcke Diakoni, Stockholm, Sweden.
[11] Institute of Biomedical Engineering, University of New Brunswick, New Brunswick, Canada.
[12] Fysische Geneeskunde en Revalidatie, University Hospital Gent, Gent, Belgium.
[13] Integrum AB, Mölndal, Sweden.

Correspondence to: Dr. Max Ortiz-Catalan maxo@chalmers.se

Abstract

Introduction: Phantom limb pain (PLP) is a chronic condition that can greatly diminish quality of life. Control over the phantom limb and exercise of such control have been hypothesized to reverse maladaptive brain changes correlated to PLP. Preliminary investigations have shown that decoding motor volition using myoelectric pattern recognition, while providing real-time feedback via virtual and augmented reality (VR-AR), facilitates phantom motor execution (PME) and reduces PLP.

Here we present the study protocol for an international (seven countries), multicentre (nine clinics), double-blind, randomized, controlled clinical trial to assess the effectiveness of PME in alleviating PLP.

Methods and analysis: Sixty-seven subjects suffering from PLP in upper or lower limbs are randomly assigned to PME or Phantom Motor Imagery (PMI) interventions. Subjects allocated to either treatment receive 15 interventions and are exposed to the same VR-AR environments using the same device. The only difference between interventions is whether phantom movements are actually performed (PME) or just imagined (PMI). Complete evaluations are conducted at baseline and at intervention completion, as well as 1, 3 and 6 months later using an intention to treat approach. Changes in PLP measured using the Pain Rating Index between the first and last session are the primary measure of efficacy. Secondary outcomes include: frequency, duration, quality of pain, intrusion of pain in activities of daily living and sleep, disability associated to pain, pain self-efficacy, frequency of depressed mood, presence of

catastrophizing thinking, health-related quality of life and clinically significant change as patient's own impression. Follow-up interviews are conducted up to six months after the treatment.

Ethics and dissemination: The study is performed in agreement with the Declaration of Helsinki, and under approval by the governing ethical committees of each participating clinic. The results will be published according to the CONSORT guidelines in a peer-reviewed journal.

Strengths and limitations of this study

Strengths

- This study involves a number of participants (>60) such to provide appropriate power to draw meaningful conclusions.
- This study is double-blinded, randomized, conducted in geographically different locations and involves subjects with both upper and lower limb amputations, thus enhancing generalizability.
- The choice of the comparator allows controlling in a stringent manner for the effect of the key factor hypothesized as the cause of pain reduction, namely, the execution of phantom limb movements.

Limitations

- Treatment is limited to 15 sessions, which might not be enough to alleviate pain in all participants.
- The nature of the experimental treatment (PME) does not allow inclusion of individuals from which myoelectric signals cannot be recorded from the muscles in their residual limbs.

Trial Registration

DATA CATEGORY	**INFORMATION**
Primary registry and trial identifying number	ClinicalTrials.gov NCT03112928
Date of registration in primary registry	April 10, 2017
Source(s) of monetary or material support	Promobilia foundation (F16501), VINNOVA (Medtech4Health 2016-02290), EFIC Grünenthal Grant (358041552) and Integrum AB (sponsor).
Coordinator	Chalmers University of Technology, Sweden
Investigational sites	Sahlgrenska University Hospital, Sweden Örebro University, Sweden Bräcke Diakoni, Sweden

DATA CATEGORY	INFORMATION
	University Rehabilitation Institute, Slovenia Ghent University Hospital, Belgium University Medical Center Groningen, The Netherlands The University of New Brunswick, Canada National University of Ireland, Galway, Ireland Ruhr-University Bochum, Germany
Sponsor	Integrum AB
Contact for public queries	Eva Lendaro, MSc, +46704231352 lendaro@chalmers.se
Contact for scientific queries	Max Ortiz Catalan, PhD, +46708461065 maxo@chalmers.se
Public title	*Phantom Motor Execution as a Treatment of Phantom Limb Pain*
Scientific title	*Phantom Motor Execution Via Myoelectric Pattern Recognition, Virtual and Augmented Reality, and Serious Gaming as a Treatment of Phantom Limb Pain*
Countries of recruitment	Sweden, Slovenia, Netherlands, Belgium, Ireland, Canada, Germany
Health condition(s) or problem(s) studied	Phantom Limb Pain
Intervention(s)	Experimental: Phantom Motor Execution Control: Phantom Motor Imagery
Key eligibility criteria	• The participants must be older than 18 years with chronic PLP • People with acute PLP are non-eligible. At least six months should have passed since

DATA CATEGORY	INFORMATION
	amputation • In case of pharmacological treatments, the dosage must have been stable for the last month • Any previous PLP treatment must have terminated at least 3 months prior to commencing the study • Any pain reduction potentially attributable to previous PLP treatments must have occurred at least 3 months prior to commencing the study • Voluntary control over at least a portion of biceps and triceps muscles in case of upper limb amputation, or quadriceps and hamstrings in case of lower limb amputation. • Stable prosthetic situation (i.e. satisfaction with the fitting of the prosthesis) or being a non-user. • The participant should not have cognitive impairment that prevents them from following instructions. • No abundant soft tissue on the stump that prevents sufficient myoelectric signals from being recorded. • No presence of pain > 2 on a numeric rating scale (NRS) upon contact with the skin or muscle contraction in the stump • The PLP must not be aggravated (NRS > 4) by the execution or imagination of phantom movements • No condition associated with risk of poor protocol compliance • No injury, disease or addiction that would render the individual unsuitable for the trial • Pain Rating Index > 0 as assessed in the Q-PLP at Visit 0
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: double-blind (participant, evaluator) Primary purpose: treatment

DATA CATEGORY	INFORMATION
Date of first enrolment	May 8th, 2017
Target sample size	67
Recruitment status	Recruiting
Primary outcome	Change in Phantom Limb Pain as measured by the Pain Rating Index.

Protocol version

Clinical investigation plan code 007 733, version 02, 2017-05-24.

Sponsor contact information

Trial Sponsor: Integrum AB
Contact name: Anna Borglin
Address: Krokslätts Fabriker 50, SE-431 37, Mölndal, Sweden
Telephone: +46 (0)31-760 10 60
Email: info@Integrum.se

Funding

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Role of study sponsor and funders

The sponsor (Integrum AB) provided the devices and materials used in this study. Neither the sponsor nor the funders (Promobilia, VINNOVA, EGG) had a role in the design of the present protocol.

Roles and responsibilities

MO-C is the coordinating investigator of the study and endpoint adjudication evaluator. EL is the monitor of the trial, independent from the sponsor, and responsible for data management. Each site is constituted by at least a principal investigator, a therapist, and a blinded-evaluator. Investigational sites are independent from each other and from the sponsor.

Authors' contributions

MO-C conceived the PME treatment. MO-C and EL reviewed the literature and designed the study. All authors provided feedback on the design of the trial. BMG and MP assisted in the selection of psychological measure. LB-K and KK-O coordinated the ethical applications. EL and MO-C drafted the manuscript. EL, LH, HB, CS, BMG, MP, LB-K, KK-O, IR, AS, LG, CW, WH, SG and MO-C revised the study

protocol and approved the final manuscript. The authors thank the patients that with their feedback helped to define the research questions, outcome measures and the patient advisers.

Competing interests

The sponsor of this study (Integrum AB) is a for-profit organization that might commercialize the device used in this study (PME and PMI). MO-C was partially funded by Integrum AB. The core technology used in this study has been made freely available as open source by MO-C (machine learning, virtual reality and electronics). All the other authors declare no competing interests.

Introduction

Phantom limb pain (PLP) is a chronic condition commonly suffered by amputees.(1,2) Although more than 60 different treatments to alleviate PLP have been described in the literature,(3) controlled clinical trials on such treatments are scarce and tend to be of poor quality.(4) The clinical investigation presented in this protocol aims to evaluate the efficacy of Phantom Motor Execution (PME) in reducing Phantom Limb Pain (PLP) in an international, multi-centre, double blind, randomized, controlled clinical trial. PME is accomplished by using a system (Neuromotus, Integrum AB, Sweden) that employs myoelectric pattern recognition to predict motor volition (movements of the phantom limb), while providing real-time feedback to the patient in virtual and augmented reality (VR/AR) environments. This technology allows the application of serious gaming in the therapy. PME is a non-invasive, non-pharmacological, and engaging treatment with no identified side effects at present.(5,6)

The effectiveness of PME was initially explored in a single upper limb amputee, with satisfactory results reported.(5) Prior to the pilot study, the patient had shown resistance to a variety of treatments for 48 years (including mirror therapy). After PME, the sustained level of pain reported by the patient was gradually reduced to pain-free periods. He and his family also reported less intrusion of PLP in sleep and activities of daily living (ADL). Finally, the patient also acquired the ability to freely move his phantom arm and hand, consistent with a recent study by Raffin and colleagues where they found that reduced capability of phantom movement was correlated with more severe PLP.(7)

In the light of the findings in the case study, a non-randomized clinical investigation on PME was conducted in subjects with chronic intractable upper limb PLP.(6) Fourteen patients, for whom conventional PLP treatments failed and who suffered from PLP for an average of 10 years, received 12 treatment sessions of PME, each of 1.5 hours' duration. At the end of the treatment period, patients showed statistically and clinically significant improvements (approx. 50% reduction of PLP). Intrusion of PLP during sleep and ADL was also reduced by a similar degree. These improvements were still present up to 6 months' post-treatment.(6) More recently, PME was also demonstrated to be a viable treatment for PLP in lower limb amputations.(8)

Strong evidence shows that PLP is related to neuroplastic changes in the primary somatosensory cortex, suggesting that central maladaptive plasticity is responsible for its maintenance. Neuroplasticity-based approaches for the relief of PLP, such as motor imagery and mirror therapy, ultimately aim to regain brain circuitry from pain processing. Nonetheless, these approaches have been shown to be limited in their effectiveness.

Although the practice of motor imagery has been shown to normalize previously altered cortical maps and reduce PLP,(9) evidence from randomized clinical studies has also suggested that it can increase

pain.(10) These seemingly contradictory findings suggest that motor imagery should not be used alone but combined with other interventions, such as graded motor imagery (11) or mirror therapy.(12)

Mirror therapy has demonstrated higher effectiveness than motor imagery in reducing pain,(10) however, it still cannot ensure that the patient performs movements with the phantom limb. For instance, it is enough for the patient to move their healthy arm to produce movement in the reflected limb. Whether a patient is actually engaging in execution of phantom limb movements is unknown. PME overcomes some of the methodological limitations of previous treatments by ensuring that central and peripheral mechanisms in motor control are activated during therapy.

Study objective

This paper presents the study protocol for a RCT in which upper and lower limb amputees are treated. The investigation primarily aims at assessing the efficacy of PME aided by myoelectric pattern recognition, augmented and virtual reality, and serious gaming to reduce Phantom Limb Pain (PLP). In order to isolate the contribution of PME in alleviating PLP over potential placebo effects, Phantom Motor Imagery (PMI) is used in this study as an active control treatment.

The working hypothesis of PME is that execution of phantom limb movements would exploit competitive neuroplasticity and provide a more integral normalization of cortical, sub-cortical, and spinal circuits compared to interventions that do not enable integration of sensory and motor information. Therefore, in this superiority trial, we hypothesise that the participants receiving the experimental treatment (PME) to obtain a larger reduction in PLP levels than those randomized to the control treatment.

Trial design

This clinical study is an international, multicentre, double-blind, randomised controlled trial. The study takes place in seven counties and involves nine clinics, which are listed in Table 1. Participants are randomly assigned to receive either the experimental or the control treatment in a 2:1 allocation ratio. The choice of the allocation ration was made in order to collect more data on the intervention of interest. Each patient is followed up for a period of six months, at the end of which they are given the choice to undergo the alternative treatment. The total duration of the study is expected to be

Table 1: List of the investigational sites, divided by countries taking part to the international, multicenter randomized clinical trial.

Country	**Investigational site**
Sweden	Sahlgrenska University Hospital, Gothenburg
	Örebro University Hospital, Örebro
	Rehabcenter Sfären, Bräcke Diakoni, Stockholm
Slovenia	University Rehabilitation Institute, Ljubljana
Belgium	Fysische Geneeskunde en Revalidatie University Hospital Gent, Gent
Netherlands	Department of Rehabilitation Medicine, University Medical Centre Groningen, Groningen
Canada	Institute of Biomedical Engineering, University of New Brunswick, New Brunswick
Ireland	Centre for Pain Research, National University of Ireland, Galway
Germany	Department of Psychosomatic Medicine and Psychotherapy, LWL University Hospital, Ruhr-University Bochum, Bochum

approximately three years.

Methods: Participants, interventions, and outcomes

A procedural overview of the trial is provided by the flow diagram of Figure 1. Recruitment of the participants is conducted via advertisements at local investigation clinics, on social media, and in local newspapers. People who are interested in taking part in the trial are invited to contact the principal investigator of the site, or a person appointed by the principal investigator, via phone or email.

Eligibility criteria

Interested people are invited to a pre-assessment visit (Visit 0). On this occasion, the therapist (clinical investigator) explains the study in detail and answers all the questions that might arise. Afterwards, the participants are asked to provide written informed consent (see Appendix A). If consent is granted, eligibility to the study is assessed according to the criteria presented below:

- The participants must be older than 18 years with chronic PLP
- Participants must have chronic PLP - at least six months should have passed since amputation. Participants with acute PLP are non-eligible.
- In case of pharmacological treatments, the dosage must have been stable for the previous month
- Any previous PLP treatments must have terminated at least 3 months prior to entering the study
- Any pain reduction potentially attributable to previous PLP treatments must have occurred at least 3 months prior to entering the study
- Voluntary control over at least a portion of biceps and triceps muscles in case of upper limb amputation, or quadriceps and hamstrings in case of lower limb amputation.
- Stable prosthetic situation (i.e. satisfaction with the fitting of the prosthesis) or being a non-user.
- The subject should not have a cognitive impairment that prevents them from following instructions.
- No abundant soft tissue on the stump that prevents sufficient myoelectric signals from being recorded.
- No presence of pain > 2 on NRS upon contact with the skin or muscle contraction in the stump
- The PLP must not be aggravated (NRS > 4) by the execution or imagination of phantom movements
- No condition associated with risk of poor protocol compliance
- No injury, disease or addiction that would render the individual unsuitable for the trial
- Pain Rating Index (PRI) > 0 as assessed in the Questionnaire for Phantom Limb Pain (Q-PLP) at Visit 0

Concomitant medications

Any co-intervention aiming to reduce PLP is prohibited during the trial. However, in the design of the trial it is acknowledged that there is a large possibility for patients with PLP to be high consumers of analgesic medicines. Therefore, the use of concomitant medications is allowed provided that at the time of inclusion, the patient has stable consumption for at least one month before entering the study and any pain reduction potentially attributable to the drug occurred at least three months before entering the study. Intake of pain medication in patients who show considerable improvement can be gradually reduced at the discretion of the responsible physician, given that the patient is followed up regularly. Medication intake is thus monitored as an outcome variable called “need of concomitant medication”, which is used to describe and compare the amount of co-medication in the treatment groups.

Interventions

All of the therapists at the clinics are introduced to the technology with at least one practical demonstration by the first (EL) and/or last author (MO-C). The therapists conduct the interventions independently, and periodically the first author monitors the correct execution of the protocol. Participants in both intervention groups receive 15 treatment sessions of 2 hours' duration, including system setup and a blinded outcome assessment. The frequency of the sessions is chosen by the participant and can be once, twice (advised frequency), or five times per week, yielding a total patient duration that ranges between 28 and 40 weeks. Both treatment groups use the same device and set up, which are sketched in Figure 2. The only difference between the two groups is the type of interaction with the virtual environments (active: motor execution; or passive: motor imagery). Allocated interventions for a given trial participant cannot be modified. Dates of the treatment sessions are recorded.

Experimental Treatment

In the PME intervention, motor volition is decoded by interpreting the signals from the stump muscles via myoelectric pattern recognition.(13,14) The decoded movement is visualized in the virtual environments (i.e. virtual limb or serious gaming). The end result is that the user, by training with the system, can achieve control over the virtual environments by performing phantom limb movements associated with kinetic sensations analogous to the ones pertaining to the limb prior to amputation.

A treatment session consists of the following steps:

1. Placement of the electrodes and fiducial marker;
2. Treatment cycles
    - Recording session
    - Practice of PME with VR/AR
    - Serious gaming using phantom movements
    - Practice of PME by matching random target postures of a virtual arm in VR (TAC Test,(15)).
3. Pain evaluation (Q-PLP, see Outcomes section)

Different treatment cycles (step 2) are repeated during a treatment session in order to execute various phantom limb movements or combinations of movements. The level of difficulty gradually increases during the treatment phase from 1 to 5 by adding degrees of freedom to be trained within the same treatment cycle. In this context, a degree of freedom is any pair of movements performing opposite actions such as opening and closing of the hand, or extension and flexion of the knee.

Clinicians are instructed to advance the level of difficulty once the previous level is accomplished successfully, and revert to the previous level if the patient shows considerable difficulty accomplishing the tasks. More details on the acquisition of myoelectric signals, prediction of motor volition, the various parts of the treatment session, and the different levels of difficulty are presented in Appendix B.

Control Treatment

In the control treatment (PMI), patients are not allowed to produce/execute phantom movements, but must imagine performing such movements while observing them executed autonomously by the VR/AR environments. The device is identical to the one used in the experimental treatment, but here the

myoelectric signals are used to monitor that the patient does not produce muscular contractions, rather than decoding motor volition.

The control treatment session is conducted using the same step-wise procedure as the experimental group with the addition of a calibration step at the beginning of the treatment cycle. Calibration is necessary to set the threshold for myoelectric signals above which the system alerts the user that a muscular contraction is performed. As in PME, the treatment cycle is repeated for different imaginary phantom limb movements or a set of imaginary movements following the same levels of difficulty. In the game format, the participants control the game using the keyboard with an able limb. Bilateral upper limb amputees use a joystick with any able limb. Details on the methods are presented in Appendix B.

Withdrawal or termination of individual participants

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event, clinical abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant no longer meets the eligibility criteria because of a condition newly developed or not previously recognized.

The main analysis will be conducted using the intention to treat (ITT) methodology. Missing data due to withdrawal or termination will be imputed using the 'last observation carried forward' method. From previous studies, the dropout rate is estimated at approximately 10% and this was taken into account for the calculation of the sample size.

Outcomes

Outcomes will be evaluated at every treatment session and three follow-up assessments at one, three, and six months' post-treatment. The outcomes are measured by the evaluators following the participant treatment schedule presented in Table 2.

Primary outcome measure

The primary outcome of the study is the change in PLP intensity measured by the difference in Pain Rating Index (PRI) between baseline (Visit 0) and at the post-treatment assessment (Visit 15). The PRI is computed as the sum of the scores for all descriptors of the Short Form of the McGill Pain Questionnaire (SF-MPQ).(16) Within this study, the SF-MPQ is included in one more extensive survey named Questionnaire for Phantom Limb Pain (Q-PLP), which is described below in the secondary outcome measures.

Secondary outcome measures

Secondary outcomes consider different aspects related to PLP such as pain frequency, pain duration, quality of pain, intrusion of pain in activities of daily living and sleep, disability associated with pain, pain self-efficacy, mood, presence of catastrophizing thinking, health-related quality of life and the patient's own impression about the effect of treatment. The secondary outcome measures are:

Pain Disability Index (PDI)

Pain Disability Index, a 7-item questionnaire designed to investigate the extent to which chronic pain interferes with a person's ability to engage in various life activities.(17) An over-all pain disability index score is obtained by summing the numerical ratings of the questionnaire's single items.

Questionnaire for Phantom Limb Pain (Q-PLP)

The Q-PLP is a 16-item questionnaire based on a combination of the SF-MPQ (Melzack 1987) and study-specific questions use in previous studies ((6,8,5)). The part containing the SF-MPQ is used for the calculation of the Pain Rating Index (primary outcome measure).

The Q-PLP assesses intensity, quality, duration, and frequency of phantom limb pain using the following metrics: the numeric rating scale (scale range 0 - 10) to assess the intensity of pain at present; the weighted pain distribution (scale range 0 - 5) to capture the time-varying nature of chronic pain by adding the contributions of weighted portions of time spent in six pain levels (present pain intensity scale,(18)); and a study-specific descriptive scale of seven steps: "never", "once per month", "once per week", "few times per week", "once per day", "few times per day", and "always" to measure the frequency of pain.

In addition, the Q-PLP is used to monitor the intensity of stump pain, phantom limb sensations, phantom motor ability, intrusion of phantom limb pain in activities of daily living and sleep, by one question each using a numeric rating scale. Changes in prosthetic hardware, medication, presence of telescoping (feeling that the phantom limb is gradually shortening over time), and location of pain are also monitored by the Q-PLP.

Euroqol-5D-5L (EQ-5D-5L)

The EQ-5D-5L is a standardised questionnaire used to investigate health-related quality of life which is constituted by two components: health status and health evaluation.(19) Health status is measured in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on a five-point scale (no problems, slight problems, moderate problems, severe problems and extreme problems). In the health evaluation part, the EQ Visual Analogue Scale (EQ VAS) records the respondent's health on a vertical VAS where the end points are labelled 'best imaginable health state' and 'worst imaginable health state'.

Pain Self-Efficacy Questionnaire (PSEQ-2)

The PSEQ-2 is a 2-item questionnaire that measures pain self-efficacy, which is the belief held by people with chronic pain that they can carry out certain activities and enjoy life, despite experiencing pain.(20,21) The items of the questionnaire are rated on a numeric rating scale from 0 to 6.

Pain Catastrophizing Scale – 6 (PCS-6)

The PCS-6 is a 6-item questionnaire that investigates catastrophizing thinking in a range from 0 to 4.(22,23) Pain catastrophizing denotes a negative cognitive-affective response to pain and is associated to increased pain severity, disability and depressive symptoms and is associated with poor adjustment to chronic pain.(24)

Patient Health Questionnaire-2 (PHQ-2)

The PHQ-2 is a screening instrument consisting of two items assessing the presence of a depressed mood and a loss of interest or pleasure in routine activities.(25,26) The items of the questionnaire are rated on a numerical scale from 0 to 3.

Patients' Global Impression of Change (PGIC)

The PGIC is a single question used to identify clinically significant change by rating the patient's belief about the efficacy of treatment on a 7-point scale, ranging from 'no change (or condition has got worse)' to 'a great deal better'.(27)

Additional measurements

Participants are asked to supply details regarding background information such as age, gender, height, weight, type and use of the prosthesis, level of embodiment of the prosthesis, onset of PLP, details about previous and ongoing intervention for PLP and side, level and date of amputation. Additionally, we also survey: patients' expectancy of benefit using the Expectations for Complementary and Alternative Medicine Treatments (EXPECT-SF);(28) patients' judgment about the credibility of the treatment using the Opinion About Treatment (OAT)(29) and patients' perception of therapists' supportive behaviour using the short form of the 6-item Health Care Climate Questionnaire (HCCQ).(30)

Sample size

The calculation of the sample size was based on our primary hypothesis and informed by our previous clinical trial with no control group.(6) In order to find a mean difference of 4 between the two randomised groups in the primary outcome measure (PRI), with power of 80% resulting from a two-sided Fisher's non-parametric permutation test at 5% significance level, is estimated that at least 60 participants are required. As a drop-out rate of 10% is expected, a total of 67 patients will be randomised.

Methods: Assignment of intervention

Randomization

Participants are assigned to the experimental or control group according to the optimal allocation scheme of minimization, aimed at reducing the imbalance between the number of patients allocated to each treatment group. The randomization proportion is 2:1, with twice as many subjects assigned to the experimental treatment. The allocation ratio was chosen to collect more information on important variables regarding the intervention of interest. The allocation aims to minimize the imbalance of the following factors:

- Level of amputation (upper and lower)
- Baseline PLP based on the NRS (low 1 to 4, and high 5 to 10)
- Investigation site (9 centres)

The minimisation process is conducted using the open source desktop application MinimPy,(31) operated by the monitor of the clinical trial. Every time a research team at a particular investigational site recruits a new participant, they assess the person's eligibility for the study (Visit 0). Afterwards, if the participant is deemed eligible, the research team sends the minimization factors relative to the enrolled participant to the monitor, who runs the randomisation, and informs the research team of the allocation.

Blinding

This investigation has been designed in such a way that participants of the two treatment groups use the same device under the same circumstances.

Even though the patients are necessarily aware of the treatment they are receiving, they do not have an expectation of superiority of the experimental over the control treatment (or vice versa), since the trial is framed as a comparison between two different interventions previously described in the literature. It is worth noting that the distinction between motor execution and motor imagery is often imperceptible, even for professionals in the field, who have often described voluntary movements of the missing limb as imaginary movements.(9,32–37) We take this fact as a corroborant of our assumption that there are no differences at baseline with respect to expectations and opinions about the assigned treatment among participants. Nevertheless, individuals' expectations regarding outcomes and credibility of the assigned treatment are assessed with the EXPECT-SF and the OAT questionnaires respectively.

The nature of the investigation does not allow the masking of the treatment for the therapists. However, it is still important to check for possible differences between the two groups concerning the therapists' supportive behaviour. For this reason, the HCCQ, is included as a measure of the extent to which a health care provider (or the staff) interacts with their patient in a supportive manner.

The outcome assessments are conducted by independent persons who are blinded to the group allocation, making the trial double blind. In order to keep group allocation confidential, participants are requested prior to each assessment not to reveal allocation or therapy content to the evaluators.

The raw data resulting from the outcome assessment has the same structure for both interventions, making it impossible to tell the group assignment without being in possession of the documents containing links between participant's identity and their code number.

Table 2: Summary of the different items (intervention, forms and questionnaires) to be completed at each evaluation appointment. Questionnaire for Phantom Limb Pain (Q-PLP), Pain Disability Index (PDI), 2-item Pain Self-Efficacy Questionnaire (PSEQ-2), Euroqol-5D-5L (EQ-5D-5L), Pain Catastrophizing Scale Short Form (PCS-SF), 2-item Patient Health Questionnaire (PHQ-2), Patients' Global Impression of Change (PGIC), Opinion About Treatment (OAT), Health Care Climate Questionnaire (HCCQ) and Expectations for Complementary and Alternative Medicine Treatments Short Form (EXPECT-SF). In brackets the indication of whether the therapist (T) or the evaluator (E) is responsible of conducting a particular item is

Session	**Summary of content**
Visit 0	• Patient Information (T) • Study Consent (T) • Pre-Assessment (T) • Background Information (T) • Q-PLP (T) • PDI (T) • EQ5D-5L (T) • PSEQ-2 (T) • PCS-SF (T) • PHQ-2 (T) • EXPECT-SF (T)
Randomization	
Visit 1	• Treatment session (T) • Q-PLP (E) • OAT (E) • EXPECT-SF (E) • HCCQ-SF (E)
Visit 2-14	• Treatment session (T) • Q-PLP (E)
Visit 15	• Treatment session (T) • Q-PLP (E) • PDI (E) • EQ5D-5L (E) • PSEQ-2 (E) • PCS-SF (E) • PHQ-2 (E) • PGIC (E) • HCCQ-SF (E)
1-month follow-up	• Q-PLP (E) • PDI (E) • EQ5D-5L (E) • PSEQ-2 (E) • PCS-SF (E) • PHQ-2 (E)
3-month follow-up	
6-month follow-up	

Methods: Data collection, management and analysis

Data collection and management

The monitor of the study (EL) is in charge of overseeing the progress of the RCT and ensuring that it is conducted, recorded, and reported in accordance with the protocol, Good Clinical Practice (GCP), and regulatory requirements.

The monitor supplies Case Report Forms (CRFs), which are filled in by the evaluator at each site. The evaluator is responsible to document all data obtained during the study which is identified by participant code number. This also applies to data for patients who, after having consented to participate, undergo the baseline examinations required for inclusion in the study, but who are not included. No items in the CRF are to be left unattended: if data are missing or are impossible to obtain, these should be documented as "not available" (NA) and the reasons for missing data must be noted in the document.

All data are recorded and stored in digital form on encrypted electronic devices. Documents containing links between a participant's identity and their code number exist only in paper form and are kept in locked file cabinets with limited access at the investigation site where the participants have been treated. In accordance with the regulations issued by The Swedish Data Protection Authority, a personal register will be established.

The clinical investigators are responsible to probe, via discussion with the participant, for the occurrence of adverse events during each visit and record the information in the patient CRF. Adverse events must be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study device, or if unrelated, the cause. The investigator must report any reportable event to the monitor in acceptable timely conditions, but not later than three working days after the occurrence of the event. The sponsor must report to the Medical Products Agency (Läkemedelsverket) any serious adverse event which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients, users or other persons immediately, but not later than two working days after becoming aware of a new reportable event or of new information in relation to an already reported event.

Once all the data are collected, checked, and corrected, the database is closed and analyses performed. All data transfer, processing and analyses are done using depersonalised data and all the data sets are protected by password. In order to promote data quality, the evaluators are trained on all the data collection and management procedures and are provided with written instructions by the first (EL) and last (MO-C) authors.

To incentivise the completion of the follow-up, the patients are given the choice to participate in these assessments at the clinic or via a phone interview with the evaluators. When possible, follow-up assessments are also conducted with participants that had discontinued the treatment or withdrew from the study.

Statistical methods

The main analysis will be performed in terms of change from baseline to the measurement at treatment completion using the ITT population. Complementary analyses will be performed on the Per Protocol (PP) population with respect to the change from baseline to the follow up assessments at 1,3 and 6

months after completion. These complementary analyses will include also the data coming from patients that after appropriate washout period to exclude carry-over, have crossed over to the alternative treatment. Both the ITT population and the PP population will be specified in detail at the Clean file meeting before the database lock and before breaking the code. The PP population will be restricted to the participants who successfully complete all 15 treatment sessions.

Suitable graphical and numerical summaries will be provided for all the variables measured and for corresponding changes in scores.

For the main unadjusted comparison between two groups, Fisher's non-parametric permutation test will be used for continuous variables, Mantel-Haenszel chi-square test for ordered categorical variables, Fisher's exact test for dichotomous variables and Pearson's chi-square test for non-ordered categorical variables. Confidence intervals at 95% for the mean differences between two groups will be given when appropriate. If differences exist between the two randomised groups between baseline variables that could influence the outcome variables, a complementary adjusted analysis will be performed for these baseline variables.

For adjusted comparison between two groups, analysis of covariance (ANCOVA) will be used for continuous outcome variables not obviously non-normally distributed with intervention/control as independent variable and all confounders as covariates.

For analysis of change within groups, Wilcoxon Signed rank test will be used for continuous variables and Sign test for ordered categorical and dichotomous variables. A complementary mixed model analysis between the two treatments regarding the primary efficacy variable with centre as random effect will be used to correct for the centre-effect in the statistical models.

All correlations will be performed with Spearman's correlation coefficient. The distribution of continuous variables will be given as mean, standard deviation, median, minimum and maximum, and distribution of categorical variables will be given as numbers and percentages. All statistical tests will be two-sided and conducted at the 5% significance level. The theory of sequential multiple test procedures will be applied for the primary analysis and for secondary analyses. If a test gives a significant result at the 5% significance level, the total test mass will be transferred to the following number in the test sequence until a non-significant result is achieved. All these significant tests will be considered confirmative. A Statistical Analysis Plan (SAP) will be written with all detailed statistical analyses specified.

Patient and Public Involvement

The design of the study was informed by the experience with our previous clinical investigation, (6) thanks to which patients' priorities, experience, and preferences were identified and used for the development of the research question and outcome measures of the current RCT. The burden of the control intervention was assessed with a pilot study on volunteers with past experience with the experimental intervention.

Ethics and dissemination

Research ethics approval

There are no known risks associated with the experimental or control treatments and clinically significant deterioration is rare. Possible individual benefits include reduced phantom limb pain, reduced disability associated with pain, and improvement in various aspects related to quality of life. This trial has been approved by the governing ethical committees of each participating country. Important protocol modifications will be reported in a timely manner to all the relevant parties.

Access to data

The principal investigator, MO-C, has full access to all of the data in the study except the documents containing the link between patient's identity and their code number, which will be accessible only after the completion of the data analyses. MO-C takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dissemination Policy

Regardless of the significance, direction, or magnitude of effect, the consortium will publish the findings of this study in scientific, peer-reviewed journals and conferences following the CONSORT guidelines. All the clinical investigators will author the scientific article reporting the results of the trial. Results will be also disseminated to all the participants of the study with a report. No professional writers external to the study will be used aside from conventional English proof reading. Access to the detailed clinical investigation plan, participant-level dataset, and statistical code will be granted based on reasonable requests after the publication of the study.

Trial status

This clinical trial is currently in the participant enrolment phase. Fourteen patients have been randomized and are under treatment at November 2017. It is anticipated that full analysis will be finalised in April 2020.

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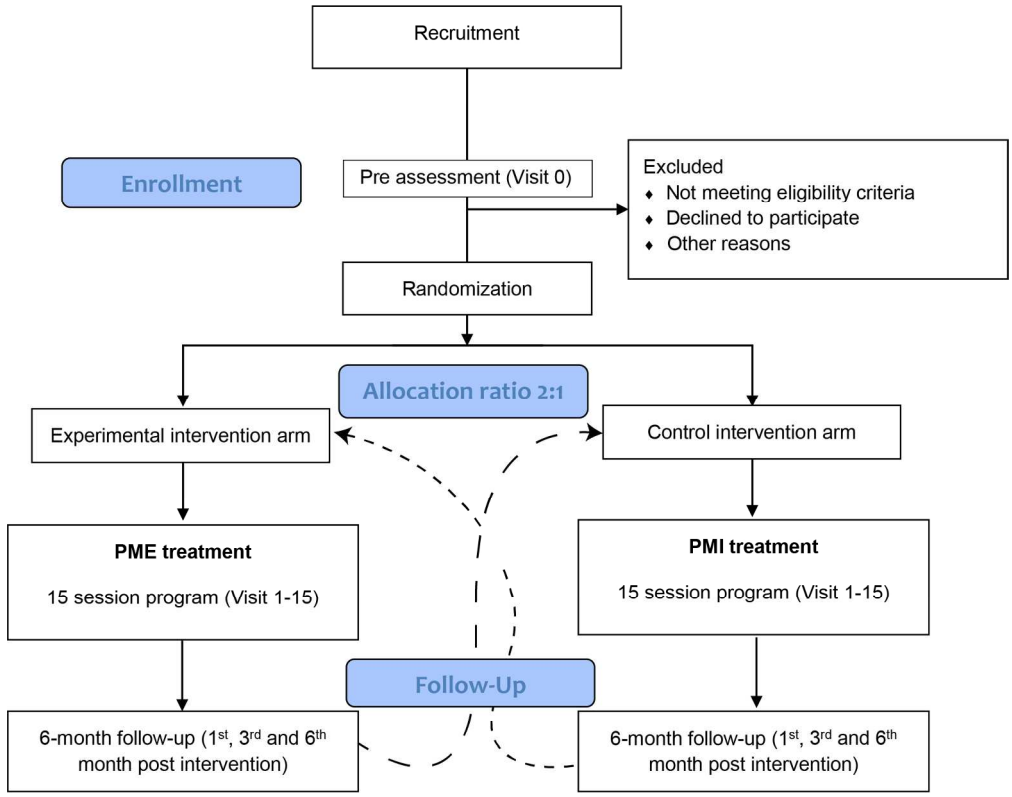
Figure legends

Figure 1: Flow diagram for the randomized controlled clinical trial. At least sixty-seven patients are recruited and randomly allocated to either Phantom Motor Execution (PME) or Phantom Motor Imagery (PMI) interventions in allocation ratio 2:1. Following the completion of the treatment protocol and wash-out period of six months it is possible for the patient to cross over to the parallel interventional arm, according to their will.

Figure 2: Schematic illustration of the clinical investigation device with all its components. Myoelectric signals are acquired though surface electrodes (A) by a myoelectric amplifier (B), electrically isolated (C). The signals are then processed by the software installed on the computer (D). The camera (E) films the participant and the recorded image is displayed on the monitor (F) with a virtual limb superimposed where the marker (G) is detected. Figure courtesy of Jason Millenaar.



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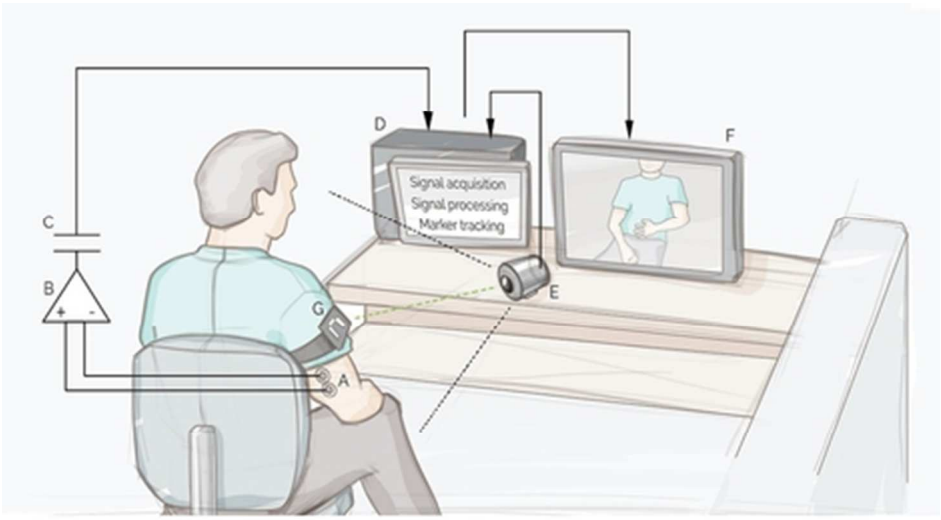

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39x22mm (300 x 300 DPI)

PARTICIPANT INFORMATION SHEET

1. Introduction

Title of Project: Virtual Reality as a Treatment for Phantom Limb Pain – A Randomised Controlled Trial

2 Invitation

You are being invited to take part in a research study investigating the effect of two different forms of virtual motor training as a treatment for phantom pain. Before you decide, it is important for you to understand why the research is being done and what it will involve. This *Participant Information Sheet* will tell you about the purpose, risks and benefits of this research study. If you agree to take part, we will ask you to sign a Consent Form. If there is anything that you are not clear about, we will be happy to explain it to you. Please take as much time as you need to read it. You should only consent to participate in this research study when you feel that you understand what is being asked of you, and you have had enough time to think about your decision. Thank you for reading this.

3 Purpose of the Study

Phantom pain occurs in about 70-80% of all amputees and many continue to feel the lost body part which is called phantom arm or phantom leg. Some individuals feel that they can move their phantom arms or legs while others feel that the phantom limb is immobile and very painful. Although there are many different ways to treat phantom limb pain, there is still no satisfactory treatment to help all patients. During the last decade, TENS and mirror therapy have started to be used to treat phantom limb pain. A further development has taken place with the help of modern computer technology which enables the training of the amputated body part in a virtual reality. The method involves performing virtual motor training exercises i.e. patients learn to move an image of their phantom arm or leg and this is believed to stimulate repair mechanisms in the brain. We aim to investigate whether two different variants of this new technology effectively reduce phantom pain in amputees.

4 Study Design

The study is a randomized, controlled clinical trial. This means that the you have been randomly assigned to one of two groups that will receive different treatments for phantom limb. Both treatment methods are believed to be effective but we will examine if there is something in one of the two methods more effective than the other. If the current treatment does not give you any improvement, you'll be able to undergo the second form of treatment, if you wish, after completion of the first programme.

5 Taking part – what it involves

What will happen to me if I take part?

In the treatment, adhesive electrodes will be used: these will be attached to the skin on your stump. With these electrodes, signals from the stump muscles can be recorded. When the virtual arm or leg on the screen moves, you should either imagine or perform the same movements with your own phantom arm or leg. Activity in the stump muscles is recorded via the adhesive pads. The training also includes various computer games that are controlled by the system.

There are several possible explanatory mechanisms for the analgesic effect that can be achieved with virtual motor training. It is believed that the areas of the brain required for movements in the amputated arm are partially reactivated. The patient receives visual feedback that tricks the brain into thinking that there is an arm that receives the brain's movement commands. After each treatment, you will be asked to answer questions about how you experience phantom pain. At the first and last treatment session, you will also answer questions about how you experience your health overall. Individual interviews will be conducted on a sample of the study participants after treatment. The objective of the qualitative part is to explore how individuals experienced the treatment, and if and how this is perceived to have affected their health in general. To investigate whether the treatment has a lasting effect, you will be called for examination 1, 3 and 6 months after treatment.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, a copy of which you can also keep. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your rights in any way.

How long will my part in the study last?

There will be a total of 15 treatment sessions that last about 2 hours each. You can choose to receive the treatment one, two or five times a week.

What are the possible benefits in taking part?

If the treatment has the effect we expect, your phantom pain is likely to decrease. In the unlikely event that the treatment does not produce results, you will get the opportunity to try the other treatment option after the completion of the long-term follow-up.

What are the possible disadvantages and risks of taking part?

All elements of the study are done under safe conditions by trained and skilled staff and you will not be exposed to any risks associated with either treatment or evaluation. If you come into the treatment group that uses the stump muscles during exercise, you may experience tiredness in your muscles at the beginning of treatment. This, however, is transient.

What happens at the end of the study?

When the long-term follow-up is completed, you will have the opportunity to have a copy of your own results. On request, you can also get information about the overall results of the study. The study and its results will be announced by publication in international scientific journals.

What happens if I change my mind during the study?

You are entitled to change your mind about participating in this at any time without disadvantage or penalty. If you decide to withdraw, all your data will be destroyed and will not be used in the study.

6 Confidentiality

All information that is collected about you during the course of the research will be kept strictly confidential and will not be shared with anyone else. The information collected in this research study will be stored in a way that protects your identity.

Information obtained during this study will be compiled with the help of a computer to analyze the results. The information is treated as confidential and will be stored for 10 years. All data processing

will be done with coded identity (individuals cannot be recognized from their data) and the results will be presented in a way in which no individual can be identified. Your personal information is securely protected and cannot be accessed by unauthorized persons. The identity code concerning research participants will be kept securely at the project leader's site.

7 Responsible for the investigations

Coordinating Investigator:
Max Ortiz Catalan, Chalmers University of Technology, Institution for Electrical Engineering, 412 96 Gothenburg.
E-mail: maxo@chalmers.se
Tel: + 46 (0) 708 46 10 65

Thank you for taking the time to read this information sheet.

Appendix B – Extended Methods

Interventions

Possible phantom movement for upper limb amputees are hand open and close, pronation and supination, wrist flexion and extension, elbow flexion and extension, flexion and extension of the individual fingers. Possible movements for lower limb amputees are knee extension and flexion, femoral rotation outwards and inwards, ankle plantar flexion and dorsiflexion, tibial rotation outwards and inwards, ankle eversion and inversion, flexion and extension of the toes. Upper and lower limb movements can be performed individually and simultaneously (more than two movements at the same time). Depending on the level of amputation, some movements are omitted from the treatment because they involve the residual rather than the phantom limb: e.g. elbow movements in transradial amputees. According to whether the subjects are assigned to the control or experimental intervention, they are asked to either imagine or execute these phantom movements as naturally and intuitively as possible.

Experimental Treatment

A Phantom Motor Execution (PME) treatment session consists of the following components:

1. **Placement of electrodes and fiducial marker.** To place the electrode in an appropriate way, subjects are asked to execute different phantom movements while the stump is palpated to localize the muscles. Areas with excess of soft-tissue between muscles and skin are avoided. Four to eight bipolar superficial electrodes (pre-gelled, adhesive, Ag/AgCl, one cm diameter, and two cm inter-electrode distance) are then placed along the muscle fibres where possible, else one electrode is placed on the target muscle while the other is placed on a more electrically neutral area. In the case of transfemoral amputations, electrodes are placed according to the *targeted monopolar configuration* described in detail in reference: (Lendaro et al., 2017).
2. **PME training cycle** (see Figure B1)
    a. **Recording session.** The subjects are asked to perform three repetitions of the movements as shown by a virtual limb alternated by rest periods. The standard contraction time is set to three seconds followed by three seconds of relaxation. However, this time might be increased in case longer time is required to complete the phantom movement. This step is necessary to collect myoelectric data used to train the motor volition decoding algorithms. The movements performed are dictated by the current level of difficulty (see “Levels of difficulty”).
    b. **Phantom motor execution in augmented reality (AR).** The subjects are then asked to control the virtual limb by performing the movements previously trained.
    c. **Serious gaming.** Each phantom movement trained during the recording session is then paired to activate a specific key on the computer keyboard. Computer games that would normally be controlled by those keys can then be controlled by the phantom movements, enabling the control of the game through *phantom motor execution*.
    d. **Target achievement control (TAC) test.** In this part of the training cycle the subjects are asked to move a virtual limb aiming to match a target posture determined by the movements previously trained. The target posture is considered achieved when the subject is able to position the virtual limb within ±5 degrees range in less than 20 seconds, and hold it for a two-second dwell interval. The trained movements are randomly requested six times each. This test was originally designed to evaluate control strategies for multi-functional prosthetic devices represented in virtual reality (Simon et al., 2011) In this study, the TAC test is used only for rehabilitation purposes and it is used as implemented in our open source platform named BioPatRec (Ortiz-Catalan et al., 2013).

3. **Outcomes evaluation.** Depending on the specific visit different outcome measures are recorded by blind evaluators at the end of the treatment, as reported in Table 2.

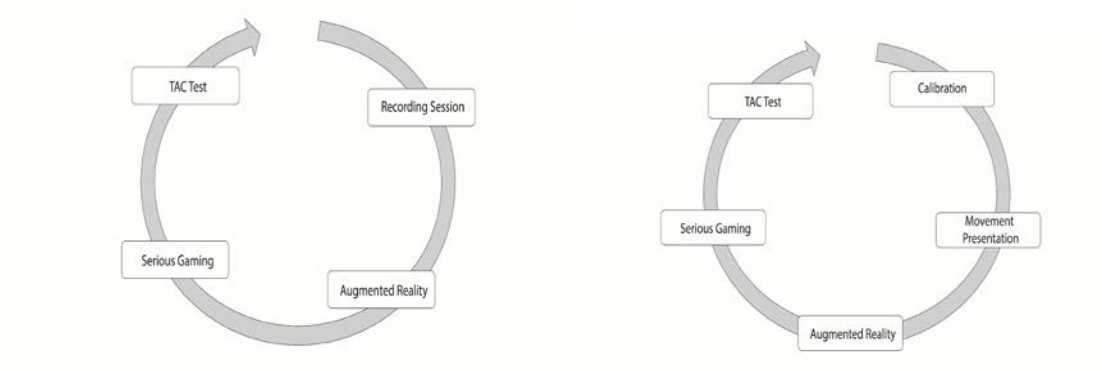

Figure B1: Training cycle for the Phantom Motor Execution (PME) intervention (left) and Phantom Motor Imagery (PMI) intervention(right)

Control Treatment

A Phantom Motor Imagery (PMI) treatment session consists of the same components as the experimental intervention, however there are some differences in the treatment cycle (see Figure B1), which are listed below:

- **Calibration.** The training cycle starts with the calibration. During this step, the patient is asked to relax the muscles completely and stay still. This phase is required in order to set the relaxation or "non-activity" level and enable the detection of contractions associated with unwanted motor execution.
- **Movement presentation.** This step is the analogue of the recording session in the experimental treatment and is meant to present a sequence of selected movements to the subject. The movements are chosen based on an increasing level of difficulty (see "Levels of difficulty"). Every movement is presented three times, for a period of three seconds in each repetition, and alternated by rest periods of equal length. During this phase the subject is asked to practice the imagination of the movements.
- **Serious gaming.** In the gaming step, the subjects will control the game using the keyboard with an able limb. No imagination is required for this step. However, the patient is expected to engage in an entertaining activity and divert cognitive resources that would be otherwise devoted to pain processing. Bilateral upper limb amputees will use a joystick with any able limb.
- **Phantom motor execution in augmented reality (AR) and TAC test.** The subjects are asked to imagine being in control of the movements autonomously performed by the virtual limb in both AR and VR environments.

Levels of difficulty

Interventions can be performed at five levels of difficulty. Subjects start at the easiest level and advance to the next level following different modalities depending on their intervention group. Subjects assigned to the PME group move to the next level when they achieve 85%-100% completion rate in the TAC test. If subjects are unable to achieve over 30% of completion rate in the new level, they are advised to move back to the previous level. On the other hand, subjects assigned to the PMI group are instructed on the specific amount of time to spend in each level, which increases with the number of degrees of freedom (DoF) exercised within the same treatment cycle.

- Level 1: Individual movements (1 DoF).

- Level 2: Individual movements (2 DoF). In the second level more than two movements are requested within the same training cycle while keeping each movement independent.
- Level 3: Simultaneous movements (2 DoF). Subjects are required to combine more than one DoF, i.e. pronation while opening or closing the hand, or supination while opening or closing the hand.
- Level 4: Individual movements (3 DoF).
- Level 5: Simultaneous movements (3 DoF).

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	3-5
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	5
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	5
	5b	Name and contact information for the trial sponsor	5
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5, 17
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6,7
	6b	Explanation for choice of comparators	7

Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9, Appendix B
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10,16

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	17
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17,18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17,18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12, 17,18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	6
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17,18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix A

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.

BMJ Open

Phantom Motor Execution as a treatment for Phantom Limb Pain: Protocol of an international, double-blind, randomised, controlled clinical trial.

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Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Research methods, Occupational and environmental medicine, Sports and exercise medicine
Keywords:	Neurological pain < NEUROLOGY, Clinical trials < THERAPEUTICS, REHABILITATION MEDICINE

Phantom Motor Execution as a treatment for Phantom Limb Pain: Protocol of an international, double-blind, randomised, controlled clinical trial.

Eva Lendaro[1], Liselotte Hermanson[2,3], Helena Burger[4,5], Corry van der Sluis[6], Brian E. McGuire[7], Monika Pilch[7], Lina Bunketorp-Käll[8], Katarzyna Kulbacka-Ortiz[8], Ingrid Rignér[9], Anita Stockselius[10], Lena Gudmundson[10], Cathrine Widehammar[3], Wendy Hill[11], Sybille Geers[12], and Max Ortiz-Catalan[1,13]

[1] Biomechatronics and Neurorehabilitation Laboratory, Department of Electrical Engineering, Chalmers University of Technology, Gothenburg, Sweden
[2] Department of Prosthetics and Orthotics, Faculty of Medicine and Health, Örebro University Hospital, Örebro, Sweden
[3] Faculty of Medicine and Health, University Health Care Research Centre, Örebro University, Örebro, Sweden
[4] University Rehabilitation Institute, Ljubljana, Slovenia
[5] Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia
[6] University of Groningen, University Medical Centre Groningen, Department of Rehabilitation Medicine, Groningen, Netherlands
[7] School of Psychology & Centre for Pain Research, National University of Ireland, Galway, Ireland.
[8] Centre for Advanced Reconstruction of Extremities, Sahlgrenska University Hospital, Gothenburg, Sweden.
[9] Gåskolan/Ortopedteknik, Sahlgrenska University Hospital, Gothenburg, Sweden.
[10] Rehabcenter Sfären, Bräcke Diakoni, Stockholm, Sweden.
[11] Institute of Biomedical Engineering, University of New Brunswick, New Brunswick, Canada.
[12] Fysische Geneeskunde en Revalidatie, University Hospital Gent, Gent, Belgium.
[13] Integrum AB, Mölndal, Sweden.

Correspondence to: Dr. Max Ortiz-Catalan maxo@chalmers.se

Abstract

Introduction: Phantom limb pain (PLP) is a chronic condition that can greatly diminish quality of life. Control over the phantom limb and exercise of such control have been hypothesized to reverse maladaptive brain changes correlated to PLP. Preliminary investigations have shown that decoding motor volition using myoelectric pattern recognition, while providing real-time feedback via virtual and augmented reality (VR-AR), facilitates phantom motor execution (PME) and reduces PLP.

Here we present the study protocol for an international (seven countries), multicentre (nine clinics), double-blind, randomized, controlled clinical trial to assess the effectiveness of PME in alleviating PLP.

Methods and analysis: Sixty-seven subjects suffering from PLP in upper or lower limbs are randomly assigned to PME or Phantom Motor Imagery (PMI) interventions. Subjects allocated to either treatment receive 15 interventions and are exposed to the same VR-AR environments using the same device. The only difference between interventions is whether phantom movements are actually performed (PME) or just imagined (PMI). Complete evaluations are conducted at baseline and at intervention completion, as well as 1, 3 and 6 months later using an intention to treat approach. Changes in PLP measured using the Pain Rating Index between the first and last session are the primary measure of efficacy. Secondary outcomes include: frequency, duration, quality of pain, intrusion of pain in activities of daily living and sleep, disability associated to pain, pain self-efficacy, frequency of depressed mood, presence of

catastrophizing thinking, health-related quality of life and clinically significant change as patient's own impression. Follow-up interviews are conducted up to six months after the treatment.

Ethics and dissemination: The study is performed in agreement with the Declaration of Helsinki, and under approval by the governing ethical committees of each participating clinic. The results will be published according to the CONSORT guidelines in a peer-reviewed journal.

Strengths and limitations of this study

Strengths

- This study involves a number of participants (>60) such to provide appropriate power to draw meaningful conclusions.
- This study is double-blinded, randomized, conducted in geographically different locations and involves subjects with both upper and lower limb amputations, thus enhancing generalizability.
- The choice of the comparator allows controlling in a stringent manner for the effect of the key factor hypothesized as the cause of pain reduction, namely, the execution of phantom limb movements.

Limitations

- Treatment is limited to 15 sessions, which might not be enough to alleviate pain in all participants.
- The nature of the experimental treatment (PME) does not allow inclusion of individuals from which myoelectric signals cannot be recorded from the muscles in their residual limbs.

Trial Registration

DATA CATEGORY	**INFORMATION**
Primary registry and trial identifying number	ClinicalTrials.gov NCT03112928
Source(s) of monetary or material support	Promobilia foundation (F16501), VINNOVA (Medtech4Health 2016-02290), EFIC Grünenthal Grant (358041552) and Integrum AB (sponsor).
Coordinator	Chalmers University of Technology, Sweden
Investigational sites	Sahlgrenska University Hospital, Sweden Örebro University, Sweden Bräcke Diakoni, Sweden University Rehabilitation Institute, Slovenia Ghent University Hospital, Belgium

DATA CATEGORY	INFORMATION
	University Medical Center Groningen, The Netherlands The University of New Brunswick, Canada National University of Ireland, Galway, Ireland Ruhr-University Bochum, Germany
Sponsor	Integrum AB
Contact for public queries	Eva Lendaro, MSc, +46704231352 lendaro@chalmers.se
Contact for scientific queries	Max Ortiz Catalan, PhD, +46708461065 maxo@chalmers.se
Public title	*Phantom Motor Execution as a Treatment of Phantom Limb Pain*
Scientific title	*Phantom Motor Execution Via Myoelectric Pattern Recognition, Virtual and Augmented Reality, and Serious Gaming as a Treatment of Phantom Limb Pain*
Countries of recruitment	Sweden, Slovenia, Netherlands, Belgium, Ireland, Canada, Germany
Health condition(s) or problem(s) studied	Phantom Limb Pain
Intervention(s)	Experimental: Phantom Motor Execution Control: Phantom Motor Imagery
Key eligibility criteria	• The participants must be older than 18 years with chronic PLP • People with acute PLP are non-eligible. At least six months should have passed since amputation • In case of pharmacological treatments, the

DATA CATEGORY	INFORMATION
	dosage must have been stable for the last month • Any previous PLP treatment must have terminated at least 3 months prior to commencing the study • Any pain reduction potentially attributable to previous PLP treatments must have occurred at least 3 months prior to commencing the study • Voluntary control over at least a portion of biceps and triceps muscles in case of upper limb amputation, or quadriceps and hamstrings in case of lower limb amputation. • Stable prosthetic situation (i.e. satisfaction with the fitting of the prosthesis) or being a non-user. • The participant should not have cognitive impairment that prevents them from following instructions. • No abundant soft tissue on the stump that prevents sufficient myoelectric signals from being recorded. • No presence of pain > 2 on a numeric rating scale (NRS) upon contact with the skin or muscle contraction in the stump • The PLP must not be aggravated (NRS > 4) by the execution or imagination of phantom movements • No condition associated with risk of poor protocol compliance • No injury, disease or addiction that would render the individual unsuitable for the trial • Pain Rating Index > 0 as assessed in the Q-PLP at Visit 0
Study type	Interventional Allocation: randomized Intervention model: parallel assignment Masking: double-blind (participant, evaluator) Primary purpose: treatment

DATA CATEGORY	INFORMATION
Date of first enrolment	May 8th, 2017
Target sample size	67
Recruitment status	Recruiting
Primary outcome	Change in Phantom Limb Pain as measured by the Pain Rating Index.

Protocol version

Clinical investigation plan code 007 733, version 02, 2017-05-24.

Sponsor contact information

Trial Sponsor: Integrum AB
Contact name: Anna Borglin
Address: Krokslätts Fabriker 50, SE-431 37, Mölndal, Sweden
Telephone: +46 (0)31-760 10 60
Email: info@Integrum.se

Funding

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Role of study sponsor and funders

The sponsor (Integrum AB) provided the devices and materials used in this study. Neither the sponsor nor the funders (Promobilia, VINNOVA, EGG) had a role in the design of the present protocol.

Roles and responsibilities

MO-C is the coordinating investigator of the study and endpoint adjudication evaluator. EL is the monitor of the trial, independent from the sponsor, and responsible for data management. Each site is constituted by at least a principal investigator, a therapist, and a blinded-evaluator. Investigational sites are independent from each other and from the sponsor.

Authors' contributions

MO-C conceived the PME treatment. MO-C and EL reviewed the literature and designed the study. All authors provided feedback on the design of the trial. BMG and MP assisted in the selection of psychological measure. LB-K and KK-O coordinated the ethical applications. EL and MO-C drafted the manuscript. EL, LH, HB, CS, BMG, MP, LB-K, KK-O, IR, AS, LG, CW, WH, SG and MO-C revised the study

protocol and approved the final manuscript. The authors thank the patients that with their feedback helped to define the research questions, outcome measures and the patient advisers.

Competing interests

The sponsor of this study (Integrum AB) is a for-profit organization that might commercialize the device used in this study (PME and PMI). MO-C was partially funded by Integrum AB. The core technology used in this study has been made freely available as open source by MO-C (machine learning, virtual reality and electronics). All the other authors declare no competing interests.

Introduction

Phantom limb pain (PLP) is a chronic condition commonly suffered by amputees.(1,2) Although more than 60 different treatments to alleviate PLP have been described in the literature,(3) controlled clinical trials on such treatments are scarce and tend to be of poor quality.(4) The clinical investigation presented in this protocol aims to evaluate the efficacy of Phantom Motor Execution (PME) in reducing Phantom Limb Pain (PLP) in an international, multi-centre, double blind, randomized, controlled clinical trial. PME is accomplished by using a system (Neuromotus, Integrum AB, Sweden) that employs myoelectric pattern recognition to predict motor volition (movements of the phantom limb), while providing real-time feedback to the patient in virtual and augmented reality (VR/AR) environments. This technology allows the application of serious gaming in the therapy. PME is a non-invasive, non-pharmacological, and engaging treatment with no identified side effects at present.(5,6)

The effectiveness of PME was initially explored in a single upper limb amputee, with satisfactory results reported.(5) Prior to the pilot study, the patient had shown resistance to a variety of treatments for 48 years (including mirror therapy). After PME, the sustained level of pain reported by the patient was gradually reduced to pain-free periods. He and his family also reported less intrusion of PLP in sleep and activities of daily living (ADL). Finally, the patient also acquired the ability to freely move his phantom arm and hand, consistent with a recent study by Raffin and colleagues where they found that reduced capability of phantom movement was correlated with more severe PLP.(7)

In the light of the findings in the case study, a non-randomized clinical investigation on PME was conducted in subjects with chronic intractable upper limb PLP.(6) Fourteen patients, for whom conventional PLP treatments failed and who suffered from PLP for an average of 10 years, received 12 treatment sessions of PME, each of 1.5 hours' duration. At the end of the treatment period, patients showed statistically and clinically significant improvements (approx. 50% reduction of PLP). Intrusion of PLP during sleep and ADL was also reduced by a similar degree. These improvements were still present up to 6 months' post-treatment.(6) More recently, PME was also demonstrated to be a viable treatment for PLP in lower limb amputations.(8)

Strong evidence shows that PLP is related to neuroplastic changes in the primary somatosensory cortex, suggesting that central maladaptive plasticity is responsible for its maintenance. Neuroplasticity-based approaches for the relief of PLP, such as motor imagery and mirror therapy, ultimately aim to regain brain circuitry from pain processing. Nonetheless, these approaches have been shown to be limited in their effectiveness.

Although the practice of motor imagery has been shown to normalize previously altered cortical maps and reduce PLP,(9) evidence from randomized clinical studies has also suggested that it can increase

pain.(10) These seemingly contradictory findings suggest that motor imagery should not be used alone but combined with other interventions, such as graded motor imagery (11) or mirror therapy.(12)

Mirror therapy has demonstrated higher effectiveness than motor imagery in reducing pain,(10) however, it still cannot ensure that the patient performs movements with the phantom limb. For instance, it is enough for the patient to move their healthy arm to produce movement in the reflected limb. Whether a patient is actually engaging in execution of phantom limb movements is unknown. PME overcomes some of the methodological limitations of previous treatments by ensuring that central and peripheral mechanisms in motor control are activated during therapy.

Study objective

This paper presents the study protocol for a RCT in which upper and lower limb amputees are treated. The investigation primarily aims at assessing the efficacy of PME aided by myoelectric pattern recognition, augmented and virtual reality, and serious gaming to reduce Phantom Limb Pain (PLP). In order to isolate the contribution of PME in alleviating PLP over potential placebo effects, Phantom Motor Imagery (PMI) is used in this study as an active control treatment.

The working hypothesis of PME is that execution of phantom limb movements would exploit competitive neuroplasticity and provide a more integral normalization of cortical, sub-cortical, and spinal circuits compared to interventions that do not enable integration of sensory and motor information. Therefore, in this superiority trial, we hypothesise that the participants receiving the experimental treatment (PME) to obtain a larger reduction in PLP levels than those randomized to the control treatment.

Trial design

This clinical study is an international, multicentre, double-blind, randomised controlled trial. The study takes place in seven counties and involves nine clinics, which are listed in Table 1. Participants are randomly assigned to receive either the experimental or the control treatment in a 2:1 allocation ratio. The choice of the allocation ration was made in order to collect more data on the intervention of interest. Each patient is followed up for a period of six months, at the end of which they are given the choice to undergo the alternative treatment. The total duration of the study is expected to be approximately three years.

Table 1: List of the investigational sites, divided by countries taking part to the international, multicenter randomized clinical trial.

Country	**Investigational site**
Sweden	Sahlgrenska University Hospital, Gothenburg
	Örebro University Hospital, Örebro
	Rehabcenter Sfären, Bräcke Diakoni, Stockholm
Slovenia	University Rehabilitation Institute, Ljubljana
Belgium	Fysische Geneeskunde en Revalidatie University Hospital Gent, Gent
Netherlands	Department of Rehabilitation Medicine, University Medical Centre Groningen, Groningen
Canada	Institute of Biomedical Engineering, University of New Brunswick, New Brunswick
Ireland	Centre for Pain Research, National University of Ireland, Galway
Germany	Department of Psychosomatic Medicine and Psychotherapy, LWL University

	Hospital, Ruhr-University Bochum, Bochum

Methods: Participants, interventions, and outcomes

A procedural overview of the trial is provided by the flow diagram of Figure 1. Recruitment of the participants is conducted via advertisements at local investigation clinics, on social media, and in local newspapers. People who are interested in taking part in the trial are invited to contact the principal investigator of the site, or a person appointed by the principal investigator, via phone or email.

Eligibility criteria

Interested people are invited to a pre-assessment visit (Visit 0). On this occasion, the therapist (clinical investigator) explains the study in detail and answers all the questions that might arise. Afterwards, the participants are asked to provide written informed consent (see Appendix A). If consent is granted, eligibility to the study is assessed according to the criteria presented below:

- The participants must be older than 18 years with chronic PLP
- Participants must have chronic PLP - at least six months should have passed since amputation. Participants with acute PLP are non-eligible.
- In case of pharmacological treatments, the dosage must have been stable for the previous month
- Any previous PLP treatments must have terminated at least 3 months prior to entering the study
- Any pain reduction potentially attributable to previous PLP treatments must have occurred at least 3 months prior to entering the study
- Voluntary control over at least a portion of biceps and triceps muscles in case of upper limb amputation, or quadriceps and hamstrings in case of lower limb amputation.
- Stable prosthetic situation (i.e. satisfaction with the fitting of the prosthesis) or being a non-user.
- The subject should not have a cognitive impairment that prevents them from following instructions.
- No abundant soft tissue on the stump that prevents sufficient myoelectric signals from being recorded.
- No presence of pain > 2 on NRS upon contact with the skin or muscle contraction in the stump
- The PLP must not be aggravated (NRS > 4) by the execution or imagination of phantom movements
- No condition associated with risk of poor protocol compliance
- No injury, disease or addiction that would render the individual unsuitable for the trial
- Pain Rating Index (PRI) > 0 as assessed in the Questionnaire for Phantom Limb Pain (Q-PLP) at Visit 0

Concomitant medications

Any co-intervention aiming to reduce PLP is prohibited during the trial. However, in the design of the trial it is acknowledged that there is a large possibility for patients with PLP to be high consumers of analgesic medicines. Therefore, the use of concomitant medications is allowed provided that at the time of inclusion, the patient has stable consumption for at least one month before entering the study and any pain reduction potentially attributable to the drug occurred at least three months before entering the study. Intake of pain medication in patients who show considerable improvement can be gradually reduced at the discretion of the responsible physician, given that the patient is followed up regularly.

Medication intake is thus monitored as an outcome variable called “need of concomitant medication”, which is used to describe and compare the amount of co-medication in the treatment groups.

Interventions

All of the therapists at the clinics are introduced to the technology with at least one practical demonstration by the first (EL) and/or last author (MO-C). The therapists conduct the interventions independently, and periodically the first author monitors the correct execution of the protocol. Participants in both intervention groups receive 15 treatment sessions of 2 hours’ duration, including system setup and a blinded outcome assessment. The frequency of the sessions is chosen by the participant and can be once, twice (advised frequency), or five times per week, yielding a total patient duration that ranges between 28 and 40 weeks. Both treatment groups use the same device and set up, which are sketched in Figure 2. The only difference between the two groups is the type of interaction with the virtual environments (active: motor execution; or passive: motor imagery). Allocated interventions for a given trial participant cannot be modified. Dates of the treatment sessions are recorded.

Experimental Treatment

In the PME intervention, motor volition is decoded by interpreting the signals from the stump muscles via myoelectric pattern recognition.(13,14) The decoded movement is visualized in the virtual environments (i.e. virtual limb or serious gaming). The end result is that the user, by training with the system, can achieve control over the virtual environments by performing phantom limb movements associated with kinetic sensations analogous to the ones pertaining to the limb prior to amputation.

A treatment session consists of the following steps:

1. Placement of the electrodes and fiducial marker;
2. Treatment cycles
    - Recording session
    - Practice of PME with VR/AR
    - Serious gaming using phantom movements
    - Practice of PME by matching random target postures of a virtual arm in VR (TAC Test,(15)).
3. Pain evaluation (Q-PLP, see Outcomes section)

Different treatment cycles (step 2) are repeated during a treatment session in order to execute various phantom limb movements or combinations of movements. The level of difficulty gradually increases during the treatment phase from 1 to 5 by adding degrees of freedom to be trained within the same treatment cycle. In this context, a degree of freedom is any pair of movements performing opposite actions such as opening and closing of the hand, or extension and flexion of the knee.

Clinicians are instructed to advance the level of difficulty once the previous level is accomplished successfully, and revert to the previous level if the patient shows considerable difficulty accomplishing the tasks. More details on the acquisition of myoelectric signals, prediction of motor volition, the various parts of the treatment session, and the different levels of difficulty are presented in Appendix B.

Control Treatment

In the control treatment (PMI), patients are not allowed to produce/execute phantom movements, but must imagine performing such movements while observing them executed autonomously by the VR/AR

environments. The device is identical to the one used in the experimental treatment, but here the myoelectric signals are used to monitor that the patient does not produce muscular contractions, rather than decoding motor volition.

The control treatment session is conducted using the same step-wise procedure as the experimental group with the addition of a calibration step at the beginning of the treatment cycle. Calibration is necessary to set the threshold for myoelectric signals above which the system alerts the user that a muscular contraction is performed. As in PME, the treatment cycle is repeated for different imaginary phantom limb movements or a set of imaginary movements following the same levels of difficulty. In the game format, the participants control the game using the keyboard with an able limb. Bilateral upper limb amputees use a joystick with any able limb. Details on the methods are presented in Appendix B.

Withdrawal or termination of individual participants

Participants are free to withdraw from participation in the study at any time upon request. An investigator may terminate participation in the study if:

- Any clinical adverse event, clinical abnormality, or other medical condition or situation occurs such that continued participation in the study would not be in the best interest of the participant.
- The participant no longer meets the eligibility criteria because of a condition newly developed or not previously recognized.

The main analysis will be conducted using the intention to treat (ITT) methodology. Missing data due to withdrawal or termination will be imputed using the 'last observation carried forward' method. From previous studies, the dropout rate is estimated at approximately 10% and this was taken into account for the calculation of the sample size.

Outcomes

Outcomes will be evaluated at every treatment session and three follow-up assessments at one, three, and six months' post-treatment. The outcomes are measured by the evaluators following the participant treatment schedule presented in Table 2.

Primary outcome measure

The primary outcome of the study is the change in PLP intensity measured by the difference in Pain Rating Index (PRI) between baseline (Visit 0) and at the post-treatment assessment (Visit 15). The PRI is computed as the sum of the scores for all descriptors of the Short Form of the McGill Pain Questionnaire (SF-MPQ).(16) Within this study, the SF-MPQ is included in one more extensive survey named Questionnaire for Phantom Limb Pain (Q-PLP), which is described below in the secondary outcome measures.

Secondary outcome measures

Secondary outcomes consider different aspects related to PLP such as pain frequency, pain duration, quality of pain, intrusion of pain in activities of daily living and sleep, disability associated with pain, pain self-efficacy, mood, presence of catastrophizing thinking, health-related quality of life and the patient's own impression about the effect of treatment. The secondary outcome measures are:

Pain Disability Index (PDI)

Pain Disability Index, a 7-item questionnaire designed to investigate the extent to which chronic pain interferes with a person's ability to engage in various life activities.(17) An over-all pain disability index score is obtained by summing the numerical ratings of the questionnaire's single items.

Questionnaire for Phantom Limb Pain (Q-PLP)

The Q-PLP is a 16-item questionnaire based on a combination of the SF-MPQ (Melzack 1987) and study-specific questions use in previous studies ((6,8,5)). The part containing the SF-MPQ is used for the calculation of the Pain Rating Index (primary outcome measure).

The Q-PLP assesses intensity, quality, duration, and frequency of phantom limb pain using the following metrics: the numeric rating scale (scale range 0 - 10) to assess the intensity of pain at present; the weighted pain distribution (scale range 0 - 5) to capture the time-varying nature of chronic pain by adding the contributions of weighted portions of time spent in six pain levels (present pain intensity scale,(18)); and a study-specific descriptive scale of seven steps: "never", "once per month", "once per week", "few times per week", "once per day", "few times per day", and "always" to measure the frequency of pain.

In addition, the Q-PLP is used to monitor the intensity of stump pain, phantom limb sensations, phantom motor ability, intrusion of phantom limb pain in activities of daily living and sleep, by one question each using a numeric rating scale. Changes in prosthetic hardware, medication, presence of telescoping (feeling that the phantom limb is gradually shortening over time), and location of pain are also monitored by the Q-PLP.

Euroqol-5D-5L (EQ-5D-5L)

The EQ-5D-5L is a standardised questionnaire used to investigate health-related quality of life which is constituted by two components: health status and health evaluation.(19) Health status is measured in terms of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) on a five-point scale (no problems, slight problems, moderate problems, severe problems and extreme problems). In the health evaluation part, the EQ Visual Analogue Scale (EQ VAS) records the respondent's health on a vertical VAS where the end points are labelled 'best imaginable health state' and 'worst imaginable health state'.

Pain Self-Efficacy Questionnaire (PSEQ-2)

The PSEQ-2 is a 2-item questionnaire that measures pain self-efficacy, which is the belief held by people with chronic pain that they can carry out certain activities and enjoy life, despite experiencing pain.(20,21) The items of the questionnaire are rated on a numeric rating scale from 0 to 6.

Pain Catastrophizing Scale – 6 (PCS-6)

The PCS-6 is a 6-item questionnaire that investigates catastrophizing thinking in a range from 0 to 4.(22,23) Pain catastrophizing denotes a negative cognitive-affective response to pain and is associated to increased pain severity, disability and depressive symptoms and is associated with poor adjustment to chronic pain.(24)

Patient Health Questionnaire-2 (PHQ-2)

The PHQ-2 is a screening instrument consisting of two items assessing the presence of a depressed mood and a loss of interest or pleasure in routine activities.(25,26) The items of the questionnaire are rated on a numerical scale from 0 to 3.

Patients' Global Impression of Change (PGIC)

The PGIC is a single question used to identify clinically significant change by rating the patient's belief about the efficacy of treatment on a 7-point scale, ranging from 'no change (or condition has got worse)' to 'a great deal better'.(27)

Additional measurements

Participants are asked to supply details regarding background information such as age, gender, height, weight, type and use of the prosthesis, level of embodiment of the prosthesis, onset of PLP, details about previous and ongoing intervention for PLP and side, level and date of amputation. Additionally, we also survey: patients' expectancy of benefit using the Expectations for Complementary and Alternative Medicine Treatments (EXPECT-SF);(28) patients' judgment about the credibility of the treatment using the Opinion About Treatment (OAT)(29) and patients' perception of therapists' supportive behaviour using the short form of the 6-item Health Care Climate Questionnaire (HCCQ).(30)

Sample size

The calculation of the sample size was based on our primary hypothesis and informed by our previous clinical trial with no control group.(6) In order to find a mean difference of 4 between the two randomised groups in the primary outcome measure (PRI), with power of 80% resulting from a two-sided Fisher's non-parametric permutation test at 5% significance level, is estimated that at least 60 participants are required. As a drop-out rate of 10% is expected, a total of 67 patients will be randomised.

Methods: Assignment of intervention

Randomization

Participants are assigned to the experimental or control group according to the optimal allocation scheme of minimization, aimed at reducing the imbalance between the number of patients allocated to each treatment group. The randomization proportion is 2:1, with twice as many subjects assigned to the experimental treatment. The allocation ratio was chosen to collect more information on important variables regarding the intervention of interest. The allocation aims to minimize the imbalance of the following factors:

- Level of amputation (upper and lower)
- Baseline PLP based on the NRS (low 1 to 4, and high 5 to 10)
- Investigation site (9 centres)

The minimisation process is conducted using the open source desktop application MinimPy,(31) operated by the monitor of the clinical trial. Every time a research team at a particular investigational site recruits a new participant, they assess the person's eligibility for the study (Visit 0). Afterwards, if the participant is deemed eligible, the research team sends the minimization factors relative to the enrolled participant to the monitor, who runs the randomisation, and informs the research team of the allocation.

Blinding

This investigation has been designed in such a way that participants of the two treatment groups use the same device under the same circumstances.

Even though the patients are necessarily aware of the treatment they are receiving, they do not have an expectation of superiority of the experimental over the control treatment (or vice versa), since the trial is framed as a comparison between two different interventions previously described in the literature. It is worth noting that the distinction between motor execution and motor imagery is often imperceptible, even for professionals in the field, who have often described voluntary movements of the missing limb as imaginary movements.(9,32–37) We take this fact as a corroborant of our assumption that there are no differences at baseline with respect to expectations and opinions about the assigned treatment among participants. Nevertheless, individuals' expectations regarding outcomes and credibility of the assigned treatment are assessed with the EXPECT-SF and the OAT questionnaires respectively.

The nature of the investigation does not allow the masking of the treatment for the therapists. However, it is still important to check for possible differences between the two groups concerning the therapists' supportive behaviour. For this reason, the HCCQ, is included as a measure of the extent to which a health care provider (or the staff) interacts with their patient in a supportive manner.

The outcome assessments are conducted by independent persons who are blinded to the group allocation, making the trial double blind. In order to keep group allocation confidential, participants are requested prior to each assessment not to reveal allocation or therapy content to the evaluators.

The raw data resulting from the outcome assessment has the same structure for both interventions, making it impossible to tell the group assignment without being in possession of the documents containing links between participant's identity and their code number.

Methods: Data collection, management and analysis

Data collection and management

The monitor of the study (EL) is in charge of overseeing the progress of the RCT and ensuring that it is conducted, recorded, and reported in accordance with the protocol, Good Clinical Practice (GCP), and regulatory requirements.

The monitor supplies Case Report Forms (CRFs), which are filled in by the evaluator at each site. The evaluator is responsible to document all data obtained during the study which is identified by participant code number. This also applies to data for patients who, after having consented to participate, undergo the baseline examinations required for inclusion in the study, but who are not included. No items in the CRF are to be left unattended: if data are missing or are impossible to obtain, these should be documented as "not available" (NA) and the reasons for missing data must be noted in the document.

All data are recorded and stored in digital form on encrypted electronic devices. Documents containing links between a participant's identity and their code number exist only in paper form and are kept in locked file cabinets with limited access at the investigation site where the participants have been

treated. In accordance with the regulations issued by The Swedish Data Protection Authority, a personal register will be established.

The clinical investigators are responsible to probe, via discussion with the participant, for the occurrence of adverse events during each visit and record the information in the patient CRF. Adverse events must be described by duration (start and stop dates and times), severity, outcome, treatment and relation to study device, or if unrelated, the cause. The investigator must report any reportable event to the monitor in acceptable timely conditions, but not later than three working days after the occurrence of the event.

Table 2: Summary of the different items (intervention, forms and questionnaires) to be completed at each evaluation appointment. Questionnaire for Phantom Limb Pain (Q-PLP), Pain Disability Index (PDI), 2-item Pain Self-Efficacy Questionnaire (PSEQ-2), Euroqol-5D-5L (EQ-5D-5L), Pain Catastrophizing Scale Short Form (PCS-SF), 2-item Patient Health Questionnaire (PHQ-2), Patients' Global Impression of Change (PGIC), Opinion About Treatment (OAT), Health Care Climate Questionnaire (HCCQ) and Expectations for Complementary and Alternative Medicine Treatments Short Form (EXPECT-SF). In brackets the indication of whether the therapist (T) or the evaluator (E) is responsible of conducting a particular item is

Session	**Summary of content**
Visit 0	• Patient Information (T) • Study Consent (T) • Pre-Assessment (T) • Background Information (T) • Q-PLP (T) • PDI (T) • EQ5D-5L (T) • PSEQ-2 (T) • PCS-SF (T) • PHQ-2 (T) • EXPECT-SF (T)
Randomization	
Visit 1	• Treatment session (T) • Q-PLP (E) • OAT (E) • EXPECT-SF (E) • HCCQ-SF (E)
Visit 2-14	• Treatment session (T) • Q-PLP (E)
Visit 15	• Treatment session (T) • Q-PLP (E) • PDI (E) • EQ5D-5L (E) • PSEQ-2 (E) • PCS-SF (E) • PHQ-2 (E) • PGIC (E)

	• HCCQ-SF (E)
1-month follow-up	• Q-PLP (E) • PDI (E) • EQ5D-5L (E) • PSEQ-2 (E) • PCS-SF (E) • PHQ-2 (E)
3-month follow-up	
6-month follow-up	

The sponsor must report to the Medical Products Agency (Läkemedelsverket) any serious adverse event which indicates an imminent risk of death, serious injury, or serious illness and that requires prompt remedial action for other patients, users or other persons immediately, but not later than two working days after becoming aware of a new reportable event or of new information in relation to an already reported event.

Once all the data are collected, checked, and corrected, the database is closed and analyses performed. All data transfer, processing and analyses are done using depersonalised data and all the data sets are protected by password. In order to promote data quality, the evaluators are trained on all the data collection and management procedures and are provided with written instructions by the first (EL) and last (MO-C) authors.

To incentivise the completion of the follow-up, the patients are given the choice to participate in these assessments at the clinic or via a phone interview with the evaluators. When possible, follow-up assessments are also conducted with participants that had discontinued the treatment or withdrew from the study.

Statistical methods

The main analysis will be performed in terms of change from baseline to the measurement at treatment completion using the ITT population. Complementary analyses will be performed on the Per Protocol (PP) population with respect to the change from baseline to the follow up assessments at 1,3 and 6 months after completion. These complementary analyses will include also the data coming from patients that after appropriate washout period to exclude carry-over, have crossed over to the alternative treatment. Both the ITT population and the PP population will be specified in detail at the Clean file meeting before the database lock and before breaking the code. The PP population will be restricted to the participants who successfully complete all 15 treatment sessions.

Suitable graphical and numerical summaries will be provided for all the variables measured and for corresponding changes in scores.

For the main unadjusted comparison between two groups, Fisher's non-parametric permutation test will be used for continuous variables, Mantel-Haenszel chi-square test for ordered categorical variables, Fisher's exact test for dichotomous variables and Pearson's chi-square test for non-ordered categorical variables. Confidence intervals at 95% for the mean differences between two groups will be given when appropriate. If differences exist between the two randomised groups between baseline variables that could influence the outcome variables, a complementary adjusted analysis will be performed for these baseline variables.

For adjusted comparison between two groups, analysis of covariance (ANCOVA) will be used for continuous outcome variables not obviously non-normally distributed with intervention/control as independent variable and all confounders as covariates.

For analysis of change within groups, Wilcoxon Signed rank test will be used for continuous variables and Sign test for ordered categorical and dichotomous variables. A complementary mixed model analysis between the two treatments regarding the primary efficacy variable with centre as random effect will be used to correct for the centre-effect in the statistical models.

All correlations will be performed with Spearman's correlation coefficient. The distribution of continuous variables will be given as mean, standard deviation, median, minimum and maximum, and distribution of categorical variables will be given as numbers and percentages. All statistical tests will be two-sided and conducted at the 5% significance level. The theory of sequential multiple test procedures will be applied for the primary analysis and for secondary analyses. If a test gives a significant result at the 5% significance level, the total test mass will be transferred to the following number in the test sequence until a non-significant result is achieved. All these significant tests will be considered confirmative. A Statistical Analysis Plan (SAP) will be written with all detailed statistical analyses specified.

Patient and Public Involvement

The design of the study was informed by the experience with our previous clinical investigation, (6) thanks to which patients' priorities, experience, and preferences were identified and used for the development of the research question and outcome measures of the current RCT. The burden of the control intervention was assessed with a pilot study on volunteers with past experience with the experimental intervention.

Ethics and dissemination

Research ethics approval

There are no known risks associated with the experimental or control treatments and clinically significant deterioration is rare. Possible individual benefits include reduced phantom limb pain, reduced disability associated with pain, and improvement in various aspects related to quality of life. This trial has been approved by the governing ethical committees of each participating country. Important protocol modifications will be reported in a timely manner to all the relevant parties.

Access to data

The principal investigator, MO-C, has full access to all of the data in the study except the documents containing the link between patient's identity and their code number, which will be accessible only after the completion of the data analyses. MO-C takes responsibility for the integrity of the data and the accuracy of the data analysis.

Dissemination Policy

Regardless of the significance, direction, or magnitude of effect, the consortium will publish the findings of this study in scientific, peer-reviewed journals and conferences following the CONSORT guidelines. All the clinical investigators will author the scientific article reporting the results of the trial. Results will be also disseminated to all the participants of the study with a report. No professional writers external to the study will be used aside from conventional English proof reading. Access to the detailed clinical

investigation plan, participant-level dataset, and statistical code will be granted based on reasonable requests after the publication of the study.

Trial status

This clinical trial is currently in the participant enrolment phase. Fourteen patients have been randomized and are under treatment at November 2017. It is anticipated that full analysis will be finalised in April 2020.

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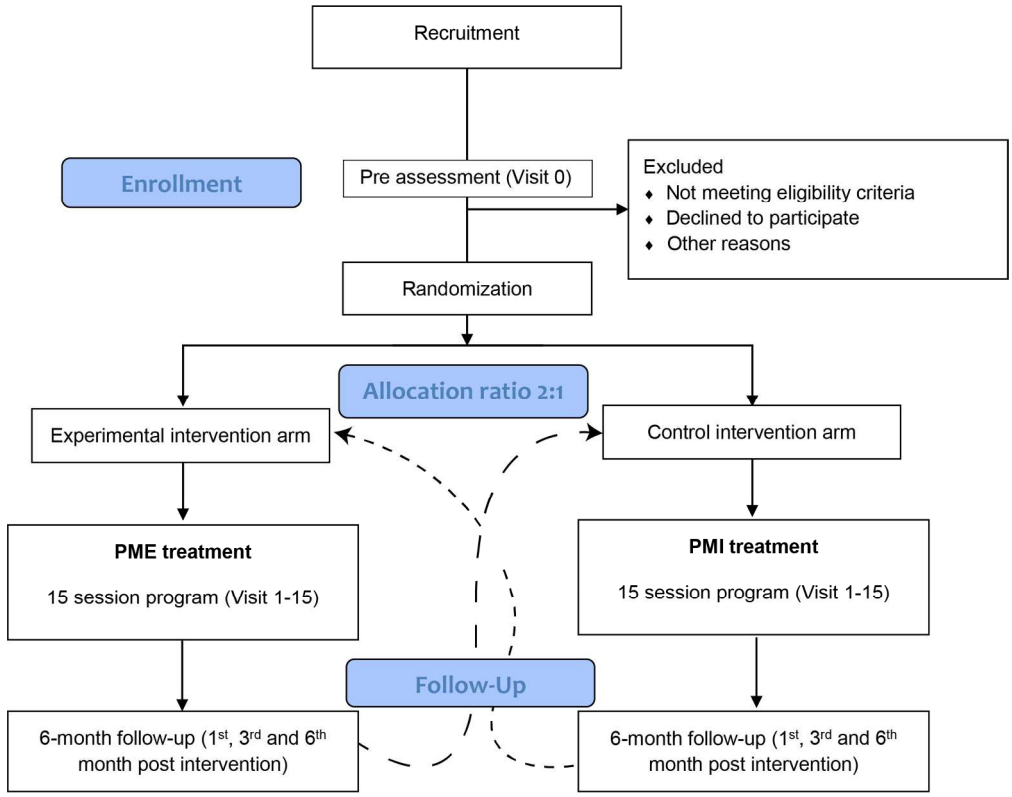
Figure legends

Figure 1: Flow diagram for the randomized controlled clinical trial. At least sixty-seven patients are recruited and randomly allocated to either Phantom Motor Execution (PME) or Phantom Motor Imagery (PMI) interventions in allocation ratio 2:1. Following the completion of the treatment protocol and

wash-out period of six months it is possible for the patient to cross over to the parallel interventional arm, according to their will.

Figure 2: Schematic illustration of the clinical investigation device with all its components. Myoelectric signals are acquired though surface electrodes (A) by a myoelectric amplifier (B), electrically isolated (C). The signals are then processed by the software installed on the computer (D). The camera (E) films the participant and the recorded image is displayed on the monitor (F) with a virtual limb superimposed where the marker (G) is detected. Figure courtesy of Jason Millenaar.



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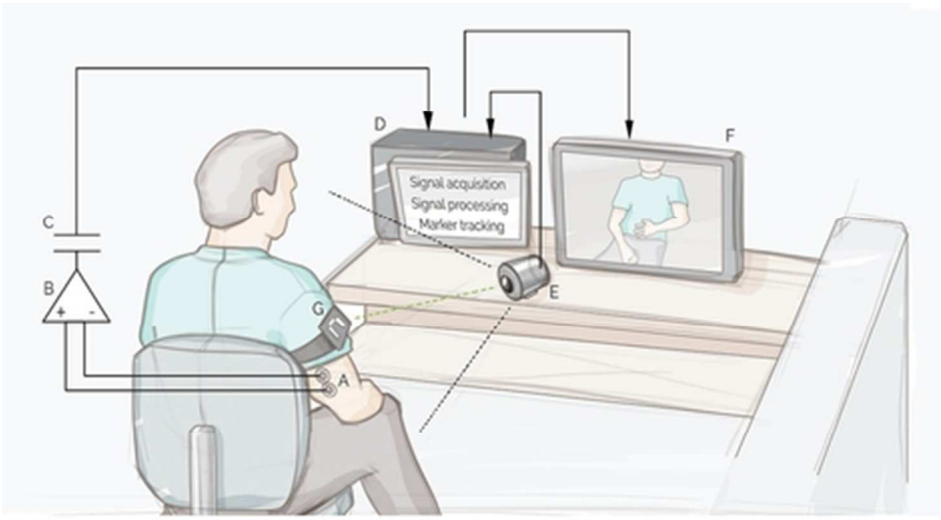

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39x22mm (300 x 300 DPI)

PARTICIPANT INFORMATION SHEET

1. Introduction

Title of Project: Virtual Reality as a Treatment for Phantom Limb Pain – A Randomised Controlled Trial

2 Invitation

You are being invited to take part in a research study investigating the effect of two different forms of virtual motor training as a treatment for phantom pain. Before you decide, it is important for you to understand why the research is being done and what it will involve. This *Participant Information Sheet* will tell you about the purpose, risks and benefits of this research study. If you agree to take part, we will ask you to sign a Consent Form. If there is anything that you are not clear about, we will be happy to explain it to you. Please take as much time as you need to read it. You should only consent to participate in this research study when you feel that you understand what is being asked of you, and you have had enough time to think about your decision. Thank you for reading this.

3 Purpose of the Study

Phantom pain occurs in about 70-80% of all amputees and many continue to feel the lost body part which is called phantom arm or phantom leg. Some individuals feel that they can move their phantom arms or legs while others feel that the phantom limb is immobile and very painful. Although there are many different ways to treat phantom limb pain, there is still no satisfactory treatment to help all patients. During the last decade, TENS and mirror therapy have started to be used to treat phantom limb pain. A further development has taken place with the help of modern computer technology which enables the training of the amputated body part in a virtual reality. The method involves performing virtual motor training exercises i.e. patients learn to move an image of their phantom arm or leg and this is believed to stimulate repair mechanisms in the brain. We aim to investigate whether two different variants of this new technology effectively reduce phantom pain in amputees.

4 Study Design

The study is a randomized, controlled clinical trial. This means that the you have been randomly assigned to one of two groups that will receive different treatments for phantom limb. Both treatment methods are believed to be effective but we will examine if there is something in one of the two methods more effective than the other. If the current treatment does not give you any improvement, you'll be able to undergo the second form of treatment, if you wish, after completion of the first programme.

5 Taking part – what it involves

What will happen to me if I take part?

In the treatment, adhesive electrodes will be used: these will be attached to the skin on your stump. With these electrodes, signals from the stump muscles can be recorded. When the virtual arm or leg on the screen moves, you should either imagine or perform the same movements with your own phantom arm or leg. Activity in the stump muscles is recorded via the adhesive pads. The training also includes various computer games that are controlled by the system.

There are several possible explanatory mechanisms for the analgesic effect that can be achieved with virtual motor training. It is believed that the areas of the brain required for movements in the amputated arm are partially reactivated. The patient receives visual feedback that tricks the brain into thinking that there is an arm that receives the brain's movement commands. After each treatment, you will be asked to answer questions about how you experience phantom pain. At the first and last treatment session, you will also answer questions about how you experience your health overall. Individual interviews will be conducted on a sample of the study participants after treatment. The objective of the qualitative part is to explore how individuals experienced the treatment, and if and how this is perceived to have affected their health in general. To investigate whether the treatment has a lasting effect, you will be called for examination 1, 3 and 6 months after treatment.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form, a copy of which you can also keep. If you decide to take part, you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect your rights in any way.

How long will my part in the study last?

There will be a total of 15 treatment sessions that last about 2 hours each. You can choose to receive the treatment one, two or five times a week.

What are the possible benefits in taking part?

If the treatment has the effect we expect, your phantom pain is likely to decrease. In the unlikely event that the treatment does not produce results, you will get the opportunity to try the other treatment option after the completion of the long-term follow-up.

What are the possible disadvantages and risks of taking part?

All elements of the study are done under safe conditions by trained and skilled staff and you will not be exposed to any risks associated with either treatment or evaluation. If you come into the treatment group that uses the stump muscles during exercise, you may experience tiredness in your muscles at the beginning of treatment. This, however, is transient.

What happens at the end of the study?

When the long-term follow-up is completed, you will have the opportunity to have a copy of your own results. On request, you can also get information about the overall results of the study. The study and its results will be announced by publication in international scientific journals.

What happens if I change my mind during the study?

You are entitled to change your mind about participating in this at any time without disadvantage or penalty. If you decide to withdraw, all your data will be destroyed and will not be used in the study.

6 Confidentiality

All information that is collected about you during the course of the research will be kept strictly confidential and will not be shared with anyone else. The information collected in this research study will be stored in a way that protects your identity.

Information obtained during this study will be compiled with the help of a computer to analyze the results. The information is treated as confidential and will be stored for 10 years. All data processing

will be done with coded identity (individuals cannot be recognized from their data) and the results will be presented in a way in which no individual can be identified. Your personal information is securely protected and cannot be accessed by unauthorized persons. The identity code concerning research participants will be kept securely at the project leader's site.

7 Responsible for the investigations

Coordinating Investigator:
Max Ortiz Catalan, Chalmers University of Technology, Institution for Electrical Engineering, 412 96 Gothenburg.
E-mail: maxo@chalmers.se
Tel: + 46 (0) 708 46 10 65

Thank you for taking the time to read this information sheet.

Appendix B – Extended Methods

Interventions

Possible phantom movement for upper limb amputees are hand open and close, pronation and supination, wrist flexion and extension, elbow flexion and extension, flexion and extension of the individual fingers. Possible movements for lower limb amputees are knee extension and flexion, femoral rotation outwards and inwards, ankle plantar flexion and dorsiflexion, tibial rotation outwards and inwards, ankle eversion and inversion, flexion and extension of the toes. Upper and lower limb movements can be performed individually and simultaneously (more than two movements at the same time). Depending on the level of amputation, some movements are omitted from the treatment because they involve the residual rather than the phantom limb: e.g. elbow movements in transradial amputees. According to whether the subjects are assigned to the control or experimental intervention, they are asked to either imagine or execute these phantom movements as naturally and intuitively as possible.

Experimental Treatment

A Phantom Motor Execution (PME) treatment session consists of the following components:

1. **Placement of electrodes and fiducial marker.** To place the electrode in an appropriate way, subjects are asked to execute different phantom movements while the stump is palpated to localize the muscles. Areas with excess of soft-tissue between muscles and skin are avoided. Four to eight bipolar superficial electrodes (pre-gelled, adhesive, Ag/AgCl, one cm diameter, and two cm inter-electrode distance) are then placed along the muscle fibres where possible, else one electrode is placed on the target muscle while the other is placed on a more electrically neutral area. In the case of transfemoral amputations, electrodes are placed according to the *targeted monopolar configuration* described in detail in reference: (Lendaro et al., 2017).
2. **PME training cycle** (see Figure B1)
    a. **Recording session.** The subjects are asked to perform three repetitions of the movements as shown by a virtual limb alternated by rest periods. The standard contraction time is set to three seconds followed by three seconds of relaxation. However, this time might be increased in case longer time is required to complete the phantom movement. This step is necessary to collect myoelectric data used to train the motor volition decoding algorithms. The movements performed are dictated by the current level of difficulty (see “Levels of difficulty”).
    b. **Phantom motor execution in augmented reality (AR).** The subjects are then asked to control the virtual limb by performing the movements previously trained.
    c. **Serious gaming.** Each phantom movement trained during the recording session is then paired to activate a specific key on the computer keyboard. Computer games that would normally be controlled by those keys can then be controlled by the phantom movements, enabling the control of the game through *phantom motor execution*.
    d. **Target achievement control (TAC) test.** In this part of the training cycle the subjects are asked to move a virtual limb aiming to match a target posture determined by the movements previously trained. The target posture is considered achieved when the subject is able to position the virtual limb within ±5 degrees range in less than 20 seconds, and hold it for a two-second dwell interval. The trained movements are randomly requested six times each. This test was originally designed to evaluate control strategies for multi-functional prosthetic devices represented in virtual reality (Simon et al., 2011) In this study, the TAC test is used only for rehabilitation purposes and it is used as implemented in our open source platform named BioPatRec (Ortiz-Catalan et al., 2013).

3. **Outcomes evaluation.** Depending on the specific visit different outcome measures are recorded by blind evaluators at the end of the treatment, as reported in Table 2.

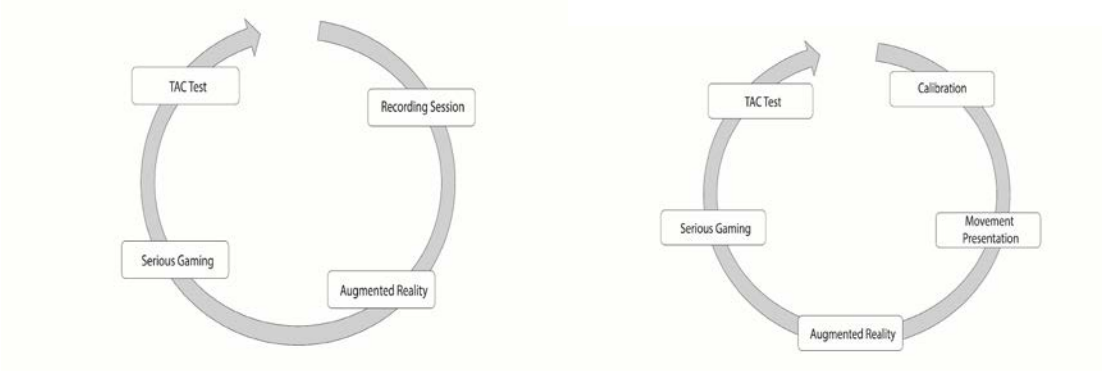

Figure B1: Training cycle for the Phantom Motor Execution (PME) intervention (left) and Phantom Motor Imagery (PMI) intervention(right)

Control Treatment

A Phantom Motor Imagery (PMI) treatment session consists of the same components as the experimental intervention, however there are some differences in the treatment cycle (see Figure B1), which are listed below:

- **Calibration.** The training cycle starts with the calibration. During this step, the patient is asked to relax the muscles completely and stay still. This phase is required in order to set the relaxation or "non-activity" level and enable the detection of contractions associated with unwanted motor execution.
- **Movement presentation.** This step is the analogue of the recording session in the experimental treatment and is meant to present a sequence of selected movements to the subject. The movements are chosen based on an increasing level of difficulty (see "Levels of difficulty"). Every movement is presented three times, for a period of three seconds in each repetition, and alternated by rest periods of equal length. During this phase the subject is asked to practice the imagination of the movements.
- **Serious gaming.** In the gaming step, the subjects will control the game using the keyboard with an able limb. No imagination is required for this step. However, the patient is expected to engage in an entertaining activity and divert cognitive resources that would be otherwise devoted to pain processing. Bilateral upper limb amputees will use a joystick with any able limb.
- **Phantom motor execution in augmented reality (AR) and TAC test.** The subjects are asked to imagine being in control of the movements autonomously performed by the virtual limb in both AR and VR environments.

Levels of difficulty

Interventions can be performed at five levels of difficulty. Subjects start at the easiest level and advance to the next level following different modalities depending on their intervention group. Subjects assigned to the PME group move to the next level when they achieve 85%-100% completion rate in the TAC test. If subjects are unable to achieve over 30% of completion rate in the new level, they are advised to move back to the previous level. On the other hand, subjects assigned to the PMI group are instructed on the specific amount of time to spend in each level, which increases with the number of degrees of freedom (DoF) exercised within the same treatment cycle.

- Level 1: Individual movements (1 DoF).

- Level 2: Individual movements (2 DoF). In the second level more than two movements are requested within the same training cycle while keeping each movement independent.
- Level 3: Simultaneous movements (2 DoF). Subjects are required to combine more than one DoF, i.e. pronation while opening or closing the hand, or supination while opening or closing the hand.
- Level 4: Individual movements (3 DoF).
- Level 5: Simultaneous movements (3 DoF).

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Page
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	3-5
Protocol version	3	Date and version identifier	5
Funding	4	Sources and types of financial, material, and other support	5
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	5
	5b	Name and contact information for the trial sponsor	5
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	5
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	5, 17
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	6,7
	6b	Explanation for choice of comparators	7

Objectives	7	Specific objectives or hypotheses	7
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8,9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8-9, Appendix B
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	12
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	8
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	9
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	12-14
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10,16

Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	14
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	8
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	14
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	14
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	14
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	15
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	17
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	17

	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	17
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	17,18
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	17,18
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	12, 17,18
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	NA
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	17
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	17
Ethics and dissemination			

Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	18
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	18
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	8
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	6
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17,18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	8
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	19
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	19
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Appendix A

Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated.