PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Phantom Motor Execution as a treatment for Phantom Limb Pain: Protocol of an international, double-blind, randomised, controlled clinical trial.
AUTHORS	Lendaro, Eva; Hermansson, Liselotte; Burger, Helena; Van der Sluis, Corry; McGuire, Brian; Pilch, Monika; Bunketorp-Käll, Lina; Kulbacka-Ortiz, Katarzyna; Rignér, Ingrid; Stockselius, Anita; Gudmundson, Lena; Widehammar, Cathrine; Hill, Wendy; Geers, Sybille; Ortiz-Catalan, Max

VERSION 1 – REVIEW

REVIEWER	Jacqueline Hebert University of Alberta, Canada
REVIEW RETURNED	20-Feb-2018

GENERAL COMMENTS	Very clear and well-designed study. It is not stated clearly if only the data from the initial treatment group enrolment is being analyzed, or if also the cross over data will be analyzed; if so will it be pooled with the initial cohort, and how will confounding be taken into account (same participant). Please clarify if the cross over design is being offered only for additional treatment, or also for the analysis.

REVIEWER	Jack Tsao, MD, DPhil University of Tennessee Health Science Center, Memphis, TN, USA
REVIEW RETURNED	23-Feb-2018

GENERAL COMMENTS	The authors describe a clinical protocol to examine muscle activation and its relationship to relief of phantom limb pain in the setting of visual feedback through a virtual reality system. The study is well-designed and will test the primary hypothesis. The study is under way at multiple sites and will provide additional information about whether muscle activity is correlated with phantom pain relief and the generalizability of findings across patient populations.

REVIEWER	Cormac Ryan Reader in Physiotherapy, School of Health and Social Care, Teesside University, UK.
REVIEW RETURNED	26-Feb-2018

GENERAL COMMENTS	This is an excellent protocol. The authors are to be commended for undertaking such an important study. It will be one of the highest quality pieces of research on a non-pharmacological intervention undertaken with this patient population. I have a couple of very

	minor points to raise - I hope the authors find them useful and I wish them every success with their study: Page 2: In the list of strengths, bullet point 1, I would consider rewording this point away from saying that it includes a large number of participants. The word large is relative. Instead I would suggest saying that it is appropriately powered to draw meaningful conclusions. Page 6 - you state that "controlled clinical trials on such treatments are scarce". I would recommend also stating that the work tends to be of poor quality and provide a reference e.g. "controlled clinical trials on such treatments are scarce and often of poor methodological quality (Batsford, S., Ryan, C.G. and Martin, D.J., 2017. Non-pharmacological conservative therapy for phantom limb pain: A systematic review of randomized controlled trials. Physiotherapy theory and practice, 33(3), pp.173-183." Page 6: Line 48 replace the word proven with shown or demonstrated. Page 7: Line 30 change the word expect to hyopthesise Page 7: Line 40 delete the words "and deemed superior" - one could argue that for an RCT to be ethical it must have equipoise. As such one group cannot be deemed superior to the other prior to undertaking the trial, though it may be hypothesised that one will be greater than the other. Page 11: Can it be clarified within the text that the Q-PLP is made up of the SF-MPQ and so both the Q-PLP and SF-MPQ will not be both used so that the same questions are not asked twice within the same session. Page 12: Line 42. I would delete the following "we predict with high confidence that the experimental treatment will outperform the control treatment". Sufficient reason is already given in that the 2:1 ratio randomization it will allow you to collect more data on the intervention group. See earlier point on Page 7. Table 2: the table legend should include an explanation for the following int the table (T/E), (T) and (E). Page 16: Line 14 - when discussing the exploration of baseline differences the authors seem to suggest they will statistically investigate if their are baseline differences "if significant differences exist". As I understand it the CONSORT guidelines do recommend exploring differences at baseline but do not recommend doing so statistically but rather making a reasoned judgment about differences that may be clinically relevant. Thus I would encourage the deletion of the word "significant".

REVIEWER	Alexander Boschmann Paderborn University, Germany
REVIEW RETURNED	06-Mar-2018

GENERAL COMMENTS	The study protocol presented here is well-described, reproducible and can potentially contribute to a better understanding of phantom limb pain treatment. The main research question (assessing the efficasy of PME to reduce PLP) is clearly defined, the methods are

	sound and presented adequately. The manuscript is generally very well-written and leaves no questions unanswered. Some minor mistakes: multicentre (p7 l35) -- multicenter (p7 l42) -- multi-centre (p6 l20) randomised (p2 l17) -- randomized (p7 l35) Ortiz-catalan (p9 l23) -- Ortiz-Catalan References: lower case (p17 l55) -- upper case (p18 l41)

VERSION 1 – AUTHOR RESPONSE

To all the Reviewers:
We (the authors) thank you for your remarkable support and positive comments. We did our best in trying to implement all suggestions you gave, helping us to improve the manuscript. In particular, you have helped us to correct and improve aspects that went unnoticed in the first version submitted: we are very thankful for this. Here attached you can find the new version.

To Reviewer 1:
It has been clarified under the statistical analysis section that the cross over data will be indeed analysed within the scope of the complementary analyses on the Per Protocol population. Possible confounding could be the carry-over effects of the first treatment and we minimize this by having an appropriate washout period and by letting the participant cross over on voluntary basis. In this way, it makes sense that only patients not benefiting from the first treatment will likely join the alternative therapy. Finally, we will not wait for the conclusion of the cross over treatment in order to perform the primary analysis on the ITT population.

To Reviewer 3:
All the comments have been acknowledged and implemented as suggested.

To Reviewer 4:
All the mistakes have been noted and corrected.

Dear BMJ Open Editor(s),
Our group has developed a novel technology for the treatment of Phantom Lim Pain (PLP) exploiting neuroplasticity via Machine Learning and Augmented Reality (AR). More specifically, this treatment promotes the execution of phantom limb movements decoded using myoelectric pattern recognition and visualized by a virtual limb in AR. We named our approach Phantom Motor Execution (PME). We introduced this concept in a case study (1) which received considerable attention from the scientific community and the media (media links: http://goo.gl/6SZGW7).
Motivated by this positive initial result, we established collaborations with four hospitals in order to conduct the first clinical trial on upper limb amputee patients suffering from intractable chronic PLP. This also represented the first clinical trial using virtual reality for the treatment of PLP. The work raised general interest to the medical field owing to its multidisciplinary nature, and the outcomes were published in The Lancet (2). A video demonstrating the treatment is available at: https://youtu.be/ek7JHGC-T4E
Finally, in a more recent work we have presented the methodology for the use of our system in lower limb amputees (video: https://youtu.be/In32hgScFAk) and treated the first lower limb PLP patient. Similar positive results were shown as in the case of upper limb patients (3), suggesting that this approach can help a considerable amount of patients and carries little to no risks.
We have now designed new clinical trial intended to extend and generalize our results on a more diverse population, where diversity is intended in the sense of the typology of amputation (upper and lower limb) but also in the geographical meaning of the term. In this manuscript, we submit the

protocol of our second clinical trial which has been designed following the SPIRIT guidelines as an international, multi-center, double-blind, randomized and most importantly, controlled investigation. The protocol has so far been approved by ethical committees in Sweden, Netherlands and Slovenia and has also been reviewed and registered with the Swedish Medical Device Agency (Läkemedelsverket).
We are submitting this manuscript to share the design of our clinical trial among healthcare professionals, the public, and other relevant groups Additionally we believe that the publication of the trial design at this stage will increase transparency and will strengthen the validity of our results when disseminated at the conclusion of the trial. Finally, with the publication of this protocol we the aim to obtain feedback from the editor(s) on its suitability for BMJ Open
The manuscript has been written in an exhaustive form in the attempt to cover every aspect, however it has been structured in a way that the extended methods section could be easily removed if deemed unnecessary.
We hope the editor(s) finds this concept worthy of communication as all the scientists, engineers, and clinicians, and more importantly, the patients involved in this study.
Eva Lendaro on behalf of all the authors

References
1. M. Ortiz-Catalan, N. Sander, M. B. Kristoffersen, B. Håkansson, R. Brånemark, Treatment of phantom limb pain (PLP) based on augmented reality and gaming controlled by myoelectric pattern recognition: A case study of a chronic PLP patient, Front. Neurosci. (2014), doi:10.3389/fnins.2014.00024.
2. M. Ortiz-Catalan, R. A. Guðmundsdóttir, M. B. Kristoffersen, A. Zepeda-Echavarria, K. Caine-Winterberger, K. Kulbacka-Ortiz, C. Widehammar, K. Eriksson, A. Stockselius, C. Ragnö, Z. Pihlar, H. Burger, L. Hermansson, M. Ortiz-Catalan, R. A. Guðmundsdóttir, M. B. Kristoffersen, A. Zepeda-Echavarria, K. Caine-Winterberger, K. Kulbacka-Ortiz, C. Widehammar, K. Eriksson, A. Stockselius, C. Ragnö, Z. Pihlar, H. Burger, L. Hermansson, Phantom motor execution facilitated by machine learning and augmented reality as treatment for Phantom Limb Pain, Lancet 388, 2885–2894 (2016).
3. E. Lendaro, E. Mastinu, B. Håkansson, M. Ortiz-Catalan, Real-time classification of non-weight bearing lower limb movements using EMG to facilitate phantom motor execution: engineering and case study application on phantom limb pain., Front. Neurol. 8, 1–12 (2017).

VERSION 2 – REVIEW

REVIEWER	Cormac Ryan Teesside University, UK
REVIEW RETURNED	28-Mar-2018

GENERAL COMMENTS	I would like to thank the authors for the opportunity to review their protocol. They have proposed a scientifically robust and clinically exciting study. I wish them well with it.

VERSION 2 – AUTHOR RESPONSE

Editor Comments to Author:
- We do not require the registry information to be included as part of the manuscript, we just ask that you include the registration number.
The registry information has been removed and the manuscript now just contain the registration number
- Do you have permission to use photographs in the patient information sheet? If not, please remove them.
Yes we have the permission to use the images