PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Protocol for a multi-center, single-blind randomized controlled trial comparing MyndMove neuromodulation therapy to conventional therapy in traumatic spinal cord injury
AUTHORS	Anderson, Kim ; Wilson, James; Korupolu, Radha; Pierce, Jacqueline; Bowen, James; O'Reilly, Daria; Kapadia, Naaz; Popovic, Milos; Thabane, Lehana; Musselman, Kristin

VERSION 1 – REVIEW

REVIEWER	Fabrizio Sergi University of Delaware, USA
REVIEW RETURNED	05-May-2020

GENERAL COMMENTS	Very interesting study, and a promising approach for improving upper extremity function in individuals with incomplete cervical spinal cord injury. I also appreciate that the authors are submitting a research protocol to allow for transparent execution and replication of clinical studies. I have a few comments that I believe would be important to increase transparency of this study: 1) Given the report, it is unclear if the study is in its planning stages, or has already started. The guidelines specify to define the timeline of the study at the time of report submission. 2) Either in the protocol or in the study - the authors should define clearly what is the intervention (i.e. which muscles are targeted, for which movements, how much stimulation is provided and what instructions are provided to the participants etc) 3) Which criteria will be followed for achieving "equivalent intensity" of the control group as opposed to the treatment group? Is it session duration, including wearing the electrodes, active therapy time, number of movement repetitions? 4) I appreciate that the study is powered to detect MCID change from baseline with 80% statistical power. The study seems to make a bit of confusion about the primary outcome measure. Page 12, line 3, seems to indicate three possible outcome measures (@ 6, 14, and 24 weeks), while the power analysis is based on a single outcome measure @ 24 weeks (line 17). Yet, the "outcome" section (Page 14, line 47) refers to the outcome measure being calculated at the end of the treatment (14 weeks). The authors should identify without ambiguity which one is the primary outcome measure. Also, the authors should clearly state if the selected analysis methods is a repeated-measure analysis of covariance to allow analysis of the repeated measurements collected on the same individuals over time.

	5) Adjustment for different sites may be useful if the breakdown of baseline correlates of outcomes is not balanced within site, for both groups (likely not the case given the small sample size) 6) Comment on the inclusion/exclusion criteria: First and second bullet of the exclusion criteria appear a bit vague. Examples for conditions affecting the 1st criterion? How far back do injuries occurred before SCI disqualify individuals from taking part to the study? Rationale for including in the study individuals who have used MyndMove more than 3 months ago is unclear. Exclusion based on botulinum toxin injections in the last 6 months may pose challenges with achieving target recruitment number, though this criterion definitely improves rigor of the study.

REVIEWER	Sarah Astill School of Biomedical Sciences University of Leeds Leeds Ls2 9JT UK
REVIEW RETURNED	12-May-2020

GENERAL COMMENTS	Given the rising number of people with a cervical level injury, and that most research concerns itself with ambulation, a properly powered RCT that addresses if FES, is significantly better than conventional therapy at restoring arm and hand function is warranted. This protocol is designed to examine this clear research question and should yield both scientific and patient benefit to the SCI community. Abstract Generally clear and well written, but it would be wise to include the AIS classification in the methods and analysis section. Introduction The introduction starts with a good justification of why this research is needed. While this section cover aspects of the neurophysiological underpinning of FES it is limited, an in fact simplistic in parts. The introduction does not outline other research that has examined FES, beyond one small pilot study, and does not really compare FES to other therapies despite listing them. There is no real justification as to why FES is better than Conventional theory. Both points need elaboration. In addition, in the methods section, it notes where possible that FES may be used bilaterally, again the introduction makes no case of uni or bilateral application of FES and the uni or bimanual therapy that may be used. This is also important given that the inclusion criteria notes there should be paresis in both limbs. Methods and Analysis I note in the allocation and blinding section the patients are randomized and stratified by site. However, I think it needs confirming if this is the only basis on which stratification occurs- what

	about AIS level, lesion level, time since injury? All of these will affect the response to therapy and the authors should take this into account. In the intervention can the authors confirm as to which type of practice each group will receive?? FES is usually used in conjunction with task specific practice. The selection of task outlined however this practice can vary. I wonder if the authors can elaborate if the practice will be massed or distributed, and if the task presented on p11, and then matched by the CT group will be blocked or randomized? On p12, the authors note adherence in that they will document any missed visits. This need clarification and I suggest the authors have a more objective outcome for this- e.g. number of sessions, or minutes of therapy. Page 16 documents the secondary outcomes, I think this section needs re-writing for clarity as it it is not clear exactly what the dependent variable for each measure used is- e.g. total score etc. They read more like a short description of each measure. The analyses of the data are comprehensive and appropriate statistical support in place. My one question is the covariate used in the ANCOVA. While baseline values are used which is appropriate, I cannot see how the analyses or methods in general deal with the variability in time since injury. Given the criteria is 4 months to some year after injury it spans quite a range from acute to sub-acute to chronic and I think this needs accounting for or explaining why there is no need to do this. In addition, the analyses plan does not clearly state how the data will be handled given there are data points at 6,14, and 24 weeks.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Fabrizio Sergi
Institution and Country: University of Delaware, USA
Please state any competing interests or state 'None declared': None declared

Very interesting study, and a promising approach for improving upper extremity function in individuals with incomplete cervical spinal cord injury. I also appreciate that the authors are submitting a research protocol to allow for transparent execution and replication of clinical studies. I have a few comments that I believe would be important to increase transparency of this study:

1) Given the report, it is unclear if the study is in its planning stages, or has already started. The guidelines specify to define the timeline of the study at the time of report submission.
This trial has already been started. We have added the timeline to the paragraph describing the trial design and setting.

2) Either in the protocol or in the study - the authors should define clearly what is the intervention (i.e. which muscles are targeted, for which movements, how much stimulation is provided and what instructions are provided to the participants etc)
We have created a table, which is now the new Table 1. Table 1 describes the MyndMove® intervention in greater detail, linking the movements practiced to the muscles stimulated. In the table legend, we have indicated the instructions that are provided to participants and provided a

reference. The amount of stimulation provided will be determined during the treatment sessions according to each participant's response to the stimulation. These details about the stimulation parameters will be reported in the manuscript that reports the study outcomes

3) Which criteria will be followed for achieving "equivalent intensity" of the control group as opposed to the treatment group? Is it session duration, including wearing the electrodes, active therapy time, number of movement repetitions?
Equivalent intensity of therapy for the control group is session duration and active therapy time. All sessions are 60 minutes in duration and active therapy time within that 60 minutes is maximized as much as possible.

4) I appreciate that the study is powered to detect MCID change from baseline with 80% statistical power. The study seems to make a bit of confusion about the primary outcome measure. Page 12, line 3, seems to indicate three possible outcome measures (@ 6, 14, and 24 weeks), while the power analysis is based on a single outcome measure @ 24 weeks (line 17). Yet, the "outcome" section (Page 14, line 47) refers to the outcome measure being calculated at the end of the treatment (14 weeks). The authors should identify without ambiguity which one is the primary outcome measure. Also, the authors should clearly state if the selected analysis methods is a repeated-measure analysis of covariance to allow analysis of the repeated measurements collected on the same individuals over time.
We apologize for this confusion. The primary outcome is SCIM self-care score at 14 weeks and the power analysis was based on 14 weeks. We have corrected this throughout the manuscript. The primary outcome will be a single time point, 14 weeks, so a repeated measure analysis of covariance will not be used. Secondary analyses will involve reapeated-measures

5) Adjustment for different sites may be useful if the breakdown of baseline correlates of outcomes is not balanced within site, for both groups (likely not the case given the small sample size)
Adjustments for age, time post-injury, baseline function, and baseline quality of life are included in the analysis plan. If needed, we will also adjust for site.

6) Comment on the inclusion/exclusion criteria:
First and second bullet of the exclusion criteria appear a bit vague. Examples for conditions affecting the 1st criterion?
Examples of conditions that fall under the first criterion could be muscular dystrophy, multiple sclerosis, or cerebral palsy. Examples of injuries or conditions that fall under the second criterion could be a brachial plexus injury or arthritis in joints of the upper extremity.

How far back do injuries occurred before SCI disqualify individuals from taking part to the study?
There is no time limit on those other injuries or conditions that fall under criteria 1 and 2.

Rationale for including in the study individuals who have used MyndMove more than 3 months ago is unclear.
From previous work in stroke and preliminary work in spinal cord injury, it appears that 3 months is the duration for any changes induced by MyndMove therapy that are not permanent to wash out.

Exclusion based on botulinum toxin injections in the last 6 months may pose challenges with achieving target recruitment number, though this criterion definitely improves rigor of the study.
We agree, but thus far have not experienced any recruitment barriers related to thus criterion.

Reviewer: 2
Reviewer Name: Sarah Astill
Institution and Country: School of Biomedical Sciences, University of Leeds, Leeds, Ls2 9JT, UK
Please state any competing interests or state 'None declared': None declared

Given the rising number of people with a cervical level injury, and that most research concerns itself with ambulation, a properly powered RCT that addresses if FES, is significantly better than conventional therapy at restoring arm and hand function is warranted. This protocol is designed to examine this clear research question and should yield both scientific and patient benefit to the SCI community.

Abstract
Generally clear and well written, but it would be wise to include the AIS classification in the methods and analysis section.
We have added AIS B-D to this section of the abstract.

Introduction
The introduction starts with a good justification of why this research is needed. While this section cover aspects of the neurophysiological underpinning of FES it is limited, an in fact simplistic in parts. The introduction does not outline other research that has examined FES, beyond one small pilot study, and does not really compare FES to other therapies despite listing them. There is no real justification as to why FES is better than Conventional theory. Both points need elaboration. In addition, in the methods section, it notes where possible that FES may be used bilaterally, again the introduction makes no case of uni or bilateral application of FES and the uni or bimanual therapy that may be used. This is also important given that the inclusion criteria notes there should be paresis in both limbs.
The limited word count does not allow for an extensive review of FES compared to other therapies. However, we have added a description of some literature suggesting that FES added to various therapies is more effective than conventional therapy alone. MyndMove therapy and conventional therapy are both being provided bilaterally in the current protocol, which is the reason for the inclusion criterion of paresis in both limbs. The intent is to determine if MyndMove therapy is more effective than conventional therapy, not to determine the effectiveness of unilateral versus bilateral therapy. For this reason, as well as limited space, a discussion of unilateral versus bilateral therapies has not been added to the introduction.

Methods and Analysis
I note in the allocation and blinding section the patients are randomized and stratified by site. However, I think it needs confirming if this is the only basis on which stratification occurs- what about AIS level, lesion level, time since injury? All of these will affect the response to therapy and the authors should take this into account.
The stratification is indeed only by site. This was put in place to address potential practice pattern differences in the comparison group between sites and to partially account for healthcare resource utilization (practice patterns) between Canada and the US. We acknowledge that further stratification would be ideal, but this would have significantly increased the sample size and thus limit the feasibility of completing the study in a reasonable timeframe.

In the intervention can the authors confirm as to which type of practice each group will receive?? FES is usually used in conjunction with task specific practice. The selection of task outlined however this practice can vary. I wonder if the authors can elaborate if the practice will be massed or distributed, and if the task presented on p11, and then matched by the CT group will be blocked or randomized?
The practice could be massed or distributed in either group, depending on the tolerance of the participant. For example, if the muscles being stimulated or activated fatigue quickly, the practice will be distributed. We have added the following information in the text to clarify this point:

1) When discussing the MyndMove® intervention (text added in revised version is in bold):
During each treatment session, therapists will select from a menu of pre-programmed stimulation protocols to facilitate various **task-specific** movements (Table 1). **Movement practice may be massed or distributed, depending on the tolerance of the participant (i.e. muscle fatigue).**

2) When discussing the control intervention (text added in revised version is in bold):
Conventional upper limb rehabilitation therapy, at the local institution, may include any or all of the following: a) facilitation of reaching or prehension movements; b) bilateral task**-specific movement practice (distributed or massed, depending on participant tolerance)**;

On p12, the authors note adherence in that they will document any missed visits. This need clarification and I suggest the authors have a more objective outcome for this- e.g. number of sessions, or minutes of therapy.
This has been clarified in the text. A minimum of 30 treatments (75% of allocated treatments) is required to be included in analyses.

Page 16 documents the secondary outcomes, I think this section needs re-writing for clarity as it it is not clear exactly what the dependent variable for each measure used is- e.g. total score etc. They read more like a short description of each measure.
The dependent variable for each secondary outcome has been identified in Table 2. The assessment time points to be analyzed for each secondary outcome has been described in the text.

The analyses of the data are comprehensive and appropriate statistical support in place. My one question is the covariate used in the ANCOVA. While baseline values are used which is appropriate, I cannot see how the analyses or methods in general deal with the variability in time since injury. Given the criteria is 4 months to some year after injury it spans quite a range from acute to sub-acute to chronic and I think this needs accounting for or explaining why there is no need to do this. In addition, the analyses plan does not clearly state how the data will be handled given there are data points at 6,14, and 24 weeks.
We included adjusting for time post-injury, this was mistakenly left out of the description of adjusted analysis. The primary outcome is at 14 weeks and all other time points are secondary analyses. This has been clarified throughout the text.

VERSION 2 – REVIEW

REVIEWER	Fabrizio Sergi University of Delaware, USA
REVIEW RETURNED	06-Aug-2020

GENERAL COMMENTS	The authors have addressed all my suggestions. Good luck with your clinical study!

REVIEWER	Sarah Astill School of Biomedical Sciences University of Leeds United Kingdom
REVIEW RETURNED	30-Jul-2020

GENERAL COMMENTS	The Authors have revised the manuscript in a thoughtful and purposeful manner. They provide additional detail and clarity where it was sought. I have only two further points for considration. 1.) Given the justification for whether massed or distributed practice may be used (due to patient fatigue), have the authors given consideration to how they will match the contorl group? The paper states they will be matched on duration and intensity of each session. I am assuming this will be done at the patient level in that when matched the 'control' individual will also undertake massed or distribute practice in line with the person with SCI they are matched with. 2.) Given the difference in practice types to be used, the absolute duration of practice will be matched e.g. there should be 60 minutes of active practice irrespective of whether the patient undertakes massed or distributed practice. Can the authors include a statement which clarifies this in the paper, and note how this will affect the therpay session as a whole.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Fabrizio Sergi
Institution and Country: University of Delaware, USA
Please state any competing interests or state 'None declared': None Declared

The authors have addressed all my suggestions. Good luck with your clinical study!
We thank the reviewer for the thoughtful revisions and support.

Reviewer: 2
Reviewer Name: Sarah Astill
Institution and Country: School of Biomedical Sciences, University of Leeds, United Kingdom
Please state any competing interests or state 'None declared': None declared

The Authors have revised the manuscript in a thoughtful and purposeful manner. They provide additional detail and clarity where it was sought. I have only two further points for consideration.

1.) Given the justification for whether massed or distributed practice may be used (due to patient fatigue), have the authors given consideration to how they will match the control group? The paper states they will be matched on duration and intensity of each session. I am assuming this will be done at the patient level in that when matched the 'control' individual will also undertake massed or distribute practice in line with the person with SCI they are matched with.
It is very difficult in any physical therapy RCT to match duration and intensity between experimental and control pairs. The prescription can be similar, but the execution will be specific to the participant (i.e. some days they are fatigued and participation is less, etc.). A situation where the authors think one could match number of reps exactly or duration of movement practice, would be if one were targeting therapy at a low level of challenge, such that one can be confident both paired participants will be able to achieve across days. This approach is rarely done in rehabilitation practice since practice of motor tasks that are challenging is known to facilitate experience-dependent neuroplasticity (Kleim and Jones 2008, https://www.jsmf.org/meetings/2008/may/Kleim%20&%20Jones%202008.pdf). To account for different practices between sites in the design, we havetratified the randomization by site, and the analysis will also be stratified by site.

2.) Given the difference in practice types to be used, the absolute duration of practice will be matched e.g. there should be 60 minutes of active practice irrespective of whether the patient undertakes massed or distributed practice. Can the authors include a statement which clarifies this in the paper, and note how this will affect the therapy session as a whole.
We will make every attempt to match absolute duration, but this can be very difficult as described above. We are taking detailed records of each therapy session already. In the publication of results, we will use the TiDieR reporting checklist for greater transparency. This statement has been added to page 13 of the manuscript.

VERSION 3 – REVIEW

REVIEWER	Sarah Astill School of Biomedical Sciences University of Leeds Leeds LS2 9JT United Kingdom
REVIEW RETURNED	27-Aug-2020

GENERAL COMMENTS	A pragmatic and thoughtful response. Good luck with the trial.