Author’s response to reviews

Title: EMPOWER-PD - A physical therapy intervention to empower the individuals with Parkinson’s disease: a study protocol for a feasibility randomized controlled trial

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Version: 1 Date: 10 Sep 2018

Author’s response to reviews:
August 13th, 2018.

Dear Editorial Board of Pilot and Feasibility Studies

Please find enclosure the reviewed version of the manuscript “PAFS-D-18-00025

EMPOWER-PD - A physical therapy intervention to empower the individuals with Parkinson's disease: a study protocol for a pilot randomized controlled trial” by Alessandra Swarowsky, Ph.D.; Helena de Oliveira Braga, PT, Master degree; Elaine Cristina Gregório, PT; Rafaela Simon Myra, PT; Ana Sofia Kauling de Sousa, PT; Talita Vitorina Kuhn, PT; Jéssica Klug, PT; Adriana Coutinho de Azevedo Guimarães, Ph.D.

The authors would like to thank you for the opportunity to review the manuscript. We addressed all the points suggested by the reviewers throughout the manuscript and carefully reviewed the
grammar and spelling to improve readability. All the changes done in this revising version were highlighted in yellow, therefore the reviewers can promptly find the corrections.

Sincerely yours,

Alessandra Swarowsky on behalf of the authors.

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Reviewer reports:

Reviewer #1: This protocol paper provides a detailed and well written description of a pilot RCT of a physical therapy aimed at empowering participants who have Parkinson's disease. The manuscript would benefit from some revision, both clarifications and additions, to improve readability.

In the abstract:

Line 29: Please state who is blinded, rather than stating 'single blind'. Please state pilot for a randomised controlled trial, rather than 'randomized clinical pilot'.

Authors: Thank you so much for your important contributions to the manuscript. Replaced by “A 12-week Pilot for a Randomized Clinical Trial will assess…”

The recruitment target (N=24) should be stated, as well as the allocation ratio 1:1.

Authors: We included this information as suggested “The target recruitment will be 24 PD individuals, between stages I - III of Hoehn & Yahr (HY), who will be recruited from Brazilian Parkinson’s disease Rehabilitation Initiative (BPaRkI) with allocation ratio 1:1”

Typos: line 31 'tough' should be 'through', line 32 'trough' should be 'through'. Remove 'the' from 'in a protocol that addresses the individual preferences.

Authors: All typing errors were corrected as suggested and can be found highlighted in yellow. Thank you so much.
In the Background:

Line 78: Replace 'EMPOWER-PD will presents with' with 'EMPOWER-PD will lead to' or similar

Authors: Replaced by: “We hypothesize that the EMPOWER-PD will lead to higher…”.

In the Methods:

I could not find the expected number of participants in the groups sessions. Would all 12 participants be expected at the same EMPOWER-PD session, or would the participants attend smaller groups?

Authors: I am sorry for the misunderstanding. Now, you can find this information on line 182 and 229, respectively as follow: “All the participants recruited and enrolled to EMPOWER-PD protocol will be training in a mixed circuit, at the same time…”; “All the participants recruited and enrolled to the CPh will be training at the same time as well as in the Empower-PD group”.

How will the authors judge the feasibility of conducting a definitive trial on the basis of the current protocol e.g. >80% of recruited participants retained to final follow-up?

Authors: Thank you for this observation. Yes, we will adopt >80% of participants recruited and retained to follow-up as feasibility to conduct a definitive RCT. We state this information as follow on line 244: “We will consider a recruitment and retained rate of >80% as feasible to conduct a future randomized control trial”.

Line 103 and elsewhere: the use of 'pillars' is slightly odd, unless this is what they are known was. Could 'goals' or 'levels' be more appropriate?

Authors: Thank you for your suggestion. We agree and changed the term to “goals”.

Line 136: the target sample size should be mentioned and the rationale for choosing this sample size should be explained, with reference to published work on sample sizes for pilot studies. For example, a sample size may be selected on the basis of obtaining reasonable precision of estimates of standard deviations of outcome measures.

Authors: We modified the session Sample Size as suggested and mentioned the rationale and the reference accordingly (line 140 to 1147). The primary outcome of this Pilot for a Randomized Clinical Trial will be the feasibility (adherence, recruitment rates and safety). As in feasibility studies a formal sample size calculation is not required [30], we estimated the number of
participants based on qualitative analysis. We will adopt the recruitment of 6-12 participants as a recommended for qualitative studies, being adopted the major value (n=12 per group) [31]. Accordingly, we will use the criteria of sampling saturation that means “collecting data until no new information is obtained” [32]. In relation to the quantitative variables, the present study it is not intended to be fully powered for detection of statistically significant effects, but it will enable a sample size calculation related to the quantitative variables for a future randomized trial. For that, we plan to select the sample size based on reasonable precision of estimates of standard deviation of quantitative measures which shown sensitivity in this feasibility study”.

Line 147: "closed and unsealed envelopes" is ambiguous. Why are the envelopes unsealed? This does not protect against selection bias.

Authors: Thank you, you are right. We changed to “closed envelopes” (line151).

Line 158: please replace 'illiterates' with 'illiterate participants'

Line 179: "during the 40 minutes of main part" would read better if written "from the main part of 40 minutes duration"

Line 190: Replace "several materials will be introduced to protocol" with "several materials will be introduced according to the protocol"

Line 192: replace 'pint' with 'paint'

Line 199: replace 'session' with 'sessions'

Line 201: insert 'at' between 'previously' and 'the'

Authors: All these spelling errors were corrected and were highlighted in yellow. Thank you.

Line 236: this does not describe the recruitment rate, which is the e.g. the number of participants recruited per month. Instead, it describes the proportion recruited who have been retained.

Authors: Thank you so much, the reviewer is right (line 243) “The recruitment rate will be expressed by percentage and analyzed by the number of eligible individuals recruited per month”.
Line 249: I am unsure what 'according to falls risk (<11 seconds)' means. Does it mean that participants who take fewer than 11 seconds to complete the task are expected to be at lower risk of falling?

Authors: Yes, the cut-off point of <11 seconds in the Timed Up and Go test was established for PD individuals to discriminate individuals who are at risk of falling or not [39,40]. It is established that if the patient performs the TUG in a fewer time than 11 seconds he is out of fall risk.

Line 267: suggest replace 'identificatory' with 'identification'

Line 268: 'on the "on" phase of the medication' may read better written as 'currently taking medication'

Line 269: 'randomized into two groups' would read better as 'randomized into one of two groups'

Line 270 and line 273: replace 'research' with 'researcher'

Line 276: delete 'may'

Line 284: rewrite 'inferences formulate' as 'formulate inferences'

Authors: All these spelling and typing errors were corrected and were highlighted in yellow. Thank you.

Line 286: please state version of SPSS used and provide a reference to the software.

Line 288: I would not recommend using tests for normality on such a small sample as these tend to have low power. Please state this as a limitation in the discussion.

Line 289: Fitting statistical models and conducting tests is not recommended for pilot studies as they are not usually powered to detect differences; analyses should be descriptive, and it should be planned that 95% confidence intervals will be reported for all estimates. Please remove reference to ANOVA or discuss limitations of low statistical power in the discussion. Rewrite "will be assessed by t Independent Test or Mann Whitney U" as "will be assessed by an independent samples t-test or Mann-Whitney U test. "A significance level of 95% was used for all analyses" should be rewritten as "A significance level of 5% will be used for all analyses". However, note previous comment about statistical testing in pilot studies. It would helpful to state what will be done with missing data.

Authors: The reviewer is right. We provide the reference for SPSS and we decided to withdraw the normality tests as well as the ANOVA test of the statistical analysis as follow: “To verify the
preliminary effectiveness regarding quantitative outcomes, the descriptive analysis will be performed with frequency, central tendency and variability (Mean and Standard Deviation or Median and Interquartile Interval) in the statistical program SPSS 20.0 for Windows (IBM-USA). All results of the preliminary efficacy of the feasibility trial will be described as estimates of 95% confident interval. An intention-to-treat analysis will be done with participants including who eventually will be missed in any part of the study. A significance level of 5% will be used for all analyses”.

In the Discussion:

Line 302: rewrite 'calculations to an adequate powered analysis' as 'calculations for an adequately powered analysis'.

Line 307: remove the apostrophe from it's

Line 309: 'but an act of love with itself' sounds colloquial. Please find another form of words.

Line 311: 'paradigm shift that opens in the health area' would also benefit from rewriting

Line 388: rewrite 'This study was no supported funding' as 'This study was not supported by any funding'

Authors: All spelling and typing errors were corrected according to the reviewer’s suggestion.

CONSORT flow chart: top box with MMSE<26 does not cover all of the exclusion senarios mentioned in the methods section. Further, one cannot assume that the target numbers will indeed be recruited, randomised, followed up and analysed. I suggest remove these numbers.

Authors: Thank you. We are right. We remove the numbers and correct the box of MMSE accordingly. Thank you so much for your valuable contributions to the manuscript.

Reviewer #2: Kieran Bromley completed this review under the supervision of Dr Ivonne Solis-Trapala as part of a peer review mentoring scheme endorsed in the journal.

Summary:
The paper outlines the EMPOWER-PD protocol for physical therapy in patients with Parkinson's disease. It aims to assess the feasibility of implementing the protocol in a trial and interpret preliminary results from pilot data.

Comments:

1. In both the abstract and the main paper, the sample size intended for the quantitative components of the study is not mentioned or justified. It is specified in the CONSORT diagram that n=24 across both groups with equal allocation, but this should be explicitly stated within both the abstract and the "Sample size" section of the manuscript, including justification for it, according to the CONSORT guidelines.

Authors: Thank you for your important and valuable contributions to the manuscript.

We include this information on abstract as follow: “The sample size will be based on the qualitative variables and will be adopted the recruitment of 6-12 participants per group as recommended”. We also modified the session Sample Size as suggested and mentioned the rationale and the reference accordingly (line 140 to 1147). The primary outcome of this Pilot for a Randomized Clinical Trial will be the feasibility (adherence, recruitment rates and safety). As in feasibility studies a formal sample size calculation is not required [30], we estimated the number of participants based on qualitative analysis. We will adopt the recruitment of 6-12 participants per group as a recommended for qualitative studies, being adopted the major value (n=12 per group) [31]. Accordingly, we will use the criteria of sampling saturation that means “collecting data until no new information is obtained” [32]. In relation to the quantitative variables, the present study it is not intended to be fully powered for detection of statistically significant effects, but it will enable a sample size calculation related to the quantitative variables for a future randomized trial. For that, we plan to select the sample size based on reasonable precision of estimates of standard deviation of quantitative measures which shown sensitivity in this feasibility study”.

2. There are no criteria specified which will determine whether succession to a main trial should be considered. Given that recruitment, retention and safety are all being monitored as feasibility outcomes, these outcomes should have some criteria around them which would then allow informed decisions to be made on the design of a future trial.

Authors: Thank you. We include this information on the subsection Primary Outcomes as follow: “We will consider a recruitment and retained rate of >80% as feasible to conduct a future randomized control trial. Safety will be reported by the number of adverse events. Adverse events were defined as exercise intolerance, injuries or falls during the intervention [38], being
consider < 5% of occurrence of adverse as acceptable to conduct a future randomized control trial. The acceptability of the protocol by the participants will be better elucidate by the qualitative analysis in a general way.”

3. The manuscript lacks focus making it unclear whether the main aim of the trial is feasibility or efficacy. If the main aim is to determine the feasibility of carrying out a main trial then assessment of feasibility outcomes should be the primary analysis alongside qualitative analysis to determine motivation and empowerment of health. Any subsequent analysis to determine preliminary findings should be listed as secondary analyses. It is perfectly reasonable to analyse some of the outcomes to help determine the necessary parameters for future power analyses, but a clear explanation is needed on what is going to be assessed and why.

Authors: Thank you so much. Rereading the manuscript, we agree with you. We modified the statistical analysis to make clear to the reader that our main aim is to access the feasibility data and the qualitative variables as follow: “To verify the preliminary effectiveness regarding quantitative outcomes, the descriptive analysis will be performed with frequency, central tendency and variability (Mean and Standard Deviation or Median and Interquartile Interval) in the statistical program SPSS 20.0 for Windows (IBM-USA). All results of the preliminary efficacy of the feasibility trial will be described as estimates of 95% confident interval. An intention-to-treat analysis will be done with participants including who eventually will be missed in any part of the study. A significance level of 5% will be used for all analyses.”

4. The inclusion and exclusion criteria seem quite brief, would they be consistent with the criteria to be used in the main trial? For example, as recruitment is being monitored in the feasibility study, estimates going forward will only apply to the same recruiting centres in a definitive trial, so this may not be a realistic representation of the main trial.

Authors: The inclusion and exclusion criteria will be the same for the main trial. We will recruiting the participants in the same center of this feasibility trial.

5. The rationale for carrying out a feasibility study and then also for carrying out a future definitive trial need explicitly stating.

Authors: Thank you. We include the rationale on the section Introduction as follow: “As a new intervention protocol, it is necessary to verify it feasibility when applied to the target population. This study presents the design of the feasibility randomized controlled trial that aims to…” In the section Discussion, we include this information as follow: “If feasible, this pilot randomized
controlled trial may help guide a larger, definitive, randomized controlled trial to determine the
effectiveness of EMPOWER-PD intervention in patients with Parkinson’s disease.

6. More information could be provided about the clinical setting in which the assessments are
carried out. For example, how exactly is HRmax monitored in the conventional therapy
group? Would this be through wearables, chest straps or other equipment? Should
availability, ease of use and patients' acceptability of such equipment be monitored as part of
the feasibility study?

Authors: We add some information about it in subsection Intervention groups as follow: “The
treatment sessions will be performed in group, twice a week, for 8 weeks, completing 16 sessions
followed by a 4-week follow-up period. Before and after each session, blood pressure will be
measured. The exercise intensity will be monitored every 5 minutes by an oximeter and the
Modified Borg Scale [36] will be applied to verify the perception of effort in both groups by two
physical educators for group. However, in the CPh group, the exercise intensity will be
controlled between 55% and 85% of maximum heart rate (HRmax) [2], according
to the Karvonen’s formula, that will be calculated previously the interventions and individually
verbally stimulated by the physical educator to keep up in to the recommended HR values,
increasing or slowing walking speed”. Regarding acceptability of equipment, we did not plan to
access it as part of feasibility study.

7. Is this an internal or external pilot? The nature of the trial leads to believing it is external but
needs clarifying.

Authors: We are not sure if we understand the question of the reviewer. If it is related to an
inpatient or outpatient setting, we added this information on subsection Intervention groups (line
174).

8. Please add to the title that this is a feasibility randomised trial.

Authors: As the CONSORT extension for the feasibility studies (Eldridge et al., 2016) does not
distinguish the term pilot or feasibility, we chose to leave pilot as suggested by reviewer 1.
Thank you.

9. The grammar and spelling throughout the manuscript could be improved, although it does
not affect the understanding of the paper. For example, in the abstract there are two cases of
misspelling 'through' as 'trough'. Also, 'One of the most barriers' could be changed to 'One of the greatest barriers'.

Authors: All spelling and typing errors were corrected according to the reviewer’s suggestion. Thank you so much for your contributions. We appreciate your suggestions.