Author’s response to reviews

Title: Study Protocol for a Randomized Controlled Trial on the Effect of the Diabetic Foot Guidance System (SOPeD) for Prevention and Treatment of Foot Musculoskeletal Dysfunctions in People with Diabetic Neuropathy: FOotCAre (FOCA) Trial I

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Author’s response to reviews:

São Paulo, December 17th 2019.

Dear Professors Jeremy Grimshaw, Peter Jüni, Tianjing Li and Shaun Treweek

Editors-in-chief of Trials

We would like to resubmit the manuscript “Study Protocol for a Randomized Controlled Trial on the Effect of the Diabetic Foot Guidance System (SOPeD) for Prevention and Treatment of Foot Musculoskeletal Dysfunctions in People with Diabetic Neuropathy: FOotCAre (FOCA) Trial I” (TRLS-D-19-01081) for further analysis, together with a rebuttal letter answering all comments from the Editor. We expect that this revision fulfills the Editor’s expectations.

Bellow, we answered the Editor’s comments and suggestions.

Thanks in advance.
Responses to the editor’s and reviewers' comments on a point-by-point basis

TRLS-D-19-01081 - "Study Protocol for a Randomized Controlled Trial on the Effect of the Diabetic Foot Guidance System (SOPeD) for Prevention and Treatment of Foot Musculoskeletal Dysfunctions in People with Diabetic Neuropathy: FOotCAre (FOCA) Trial I"

We would like to thank the editor for the careful revision of the Spirit protocol. We provided answers to your comments and complemented in the revised manuscript the areas in need for improvement (underlined parts). Below we respond to your remarks on point-by-point basis. First, your comment is given in bold, subsequently we provide our answer.

REVIEWER #1:

Item 1: I had a few comments and have mainly used the SPIRIT checklist to structure my questions. It has, however, been difficult to check items in the SPIRIT checklist as the page numbers do not correspond to the manuscript, one item was page 1923. I believe you may have used the original protocol submitted to the funder for your SPIRIT checklist but please use the protocol submitted to Trials when completing. The protocol document you may be referring to is too large to submit as a supplementary document so please select the relevant information for your Trials protocol manuscript.

Answer: Thank you for this note and we apologize for the mistakes. We have checked all pages and lines.

Item 2: I am unclear why Trial 1? It suggests there is a Trial 2 etc. If that is the case I would suggest you insert a sentence saying this is part of a series of proposed trials OR one of two trials etc. Sorry if I have missed information regarding this.

Answer: This paper refers to a protocol from a series of two trials that are running in parallel with the same population, but different samples, involving health technologies: a software (Trial I) and a booklet (trial II). For better explanation, now we have added sentences in the paper, as follows:

“This study is part of a series of two clinical trials”, in the abstract.
“This study is part of a series of two clinical trials: FOCA trial I (SOPeD intervention) and FOCA trial II (booklet intervention)”, in the Trial design section.

Item 3: There seems to be duplication with page 15 "Intervention" and page 5 "Intervention Group".

Answer: In page 5, it is described the Treatments arms briefly. In page 15, there are more detailed description of all intervention and the control standard treatment. Thus, this is not duplication. We have changed the session title of page 5 to Treatment Arms to make it clearer.

Item 4. Figures 2, 3 and 4 are unclear - please check when zoom in details can be read by the reader.

Answer: Thank you for your suggestion. We have checked the figure quality and it was 300 dpi as resolution, which is high enough and follows the author’s guidelines. However, we tried to improve the quality and uploaded all figures again. Maybe, when the PDF is generated in the platform, the resolution of the higher resolution figures, drop down to allow building the document, thus, the quality of the figures, automatically and unintentionally drop down as well.

Item 2b: All items from the World Health Organization Trial Registration Data Set. Please state: Please refer to Item 2a and registration in the ClinicalTrials.gov Identifier: NCT04011267. Identifier cannot be N/A eg Version 2.0. Date.

Answer: Thanks for suggesting a solution. We have now added this info on page 21: “…ClinicalTrials.gov Identifier: NCT04011267 Version 1.0 07/08/2019.”

Item 5b: this item cannot be N/A. Please give the contact details for the sponsor.

Answer: We completed the information from the trial registry in page 1 as follows:

“Sponsor

University of Sao Paulo General Hospital. Rua Av. Dr. Enéas Carvalho de Aguiar, 255, Cerqueira Cesar, São Paulo, São Paulo, Brazil.

Principal Investigator: Isabel de Camargo Neves Sacco. Affiliation. Departamento de Fisioterapia, Fonoaudiologia e Terapia Ocupacional da Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil. Rua Cipotânea, 51 - Cidade Universitária, 05360-160 São Paulo, São Paulo, Brazil. Phone: + 55 11 3091 8426, Fax: +55 11 3091 7462

Collaborators: Conselho Nacional de Desenvolvimento Científico e Tecnológico.”
Item 5c: role of sponsors etc information needs to be inserted into the protocol. An example of what has been written is: "The sponsor played no part in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication"

Answer: Thank you for your suggestions. This information was detailed on page 24. We add this sentence: `The funders and sponsors will play no part in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication`.

Item 5d: This cannot be N/A. Perhaps you could give information on the composition, roles and responsibilities of the coordinating centre and trial steering committee and all groups providing day to day support for the trial. We also need information on who is responsible for all aspects of local organisation including identifying potential recruits and taking consent. Who is supervising the trial and how often they will meet, plus information on the Trial Steering Committee (TSC), and how often they will meet over the course of the trial to oversee conduct and progress. Plus, information and how often the Stakeholder and Public Involvement Group (SPIG) if there is one, and their specific role.

ANSWER: Thank you for your suggestion. We added this information on pages 18-19:

“Data Management: The study steering committee is comprised of two PhD student (blind evaluators), two master's students (responsible for data collection), two undergraduate students (responsible for data tabulation and codification), a coordinator (responsible for managing the project) and an assistant Research (responsible for the recruitment and scheduling of collections). All information collected during the protocol will be entered into an electronic form by those responsible for data collection. The integrity and validity of the data will be verified at the time of data entry (edit checks). Identification of potential recruits will be done by the project manager and the research assistant. The research assistant will be trained on how to approach the eligible subjects during the initial recruitment contact for the survey (made by phone calls) and how and when to contact them for follow-up and data collection”.

“Oversight and monitoring

The data monitoring committee (steering committee) and the Faculdade de Medicina da Universidade de Sao Paulo Board will regularly monitor (depending on the recruitment numbers and collections performed) the study datasets and make recommendations on necessary protocol modifications or termination of all or part of the study. A trimester meeting is held to facilitate the study development. All team members can request meetings as needed.

All adverse events occurring during the clinical trial period will be recorded. Minor adverse effects potentially expected are muscle sore and tiredness after performing the proposed exercises. The patients will be advised to report any discomfort and foot pre-ulcerative signs
(blisters, callus, or even foot ulcers) to the Researcher 3 who will ask for the blinded podiatrist nurse to assist the patient.”

Item 17b: N/A is not acceptable please answer the question and state why N/A for instance write in the SPIRIT checklist "the design is open label with only outcome assessors being blinded so unblinding will not occur”.

Answer: Thank you for your suggestion. This information was detailed on page 9. We added this sentence: “The trial design is an open label, where only the outcomes’ assessors are blind, so unblinding will not occur”.

Item 19: N/A is not acceptable. Please give details for data entry, coding, security, and storage, including any related processes to promote data quality (e.g. double data entry, range checks for data values). Reference to where data management procedures can be found, if not in the protocol. For instance, will paper based and electronic data entry will be used. Who will collect data? And who will enter the data into the database for screening and randomisation purposes? If paper forms used, will you ensure that the paper-based Case Report Form (CRF) data are delivered securely to the Trial Office for data entry?

Answer: Thank you for your suggestion. We added this information on pages 18-19:

“The study steering committee is comprised of two PhD student (blind evaluators), two master's students (responsible for data collection), two undergraduate students (responsible for data tabulation and codification), a coordinator (responsible for managing the project) and an assistant Research (responsible for the recruitment and scheduling of collections). All information collected during the protocol will be entered into an electronic form by those responsible for data collection. The integrity and validity of the data will be verified at the time of data entry (edit checks). Identification of potential recruits will be done by the project manager and the research assistant. The research assistant will be trained on how to approach the eligible subjects during the initial recruitment contact for the survey (made by phone calls) and how and when to contact them for follow-up and data collection”.

Item 20b: please complete methods for any subgroup analysis, if not please state this.

Answer: Thank you for your suggestion. This information is now added on page 19-20.

“The inferential statistical analysis will be based on an intention-to-treat analysis and per protocol analysis.”

“The per-protocol analysis will include only those patients who completed follow up in the allocated intervention group. If there is evidence that the difference in the treatment depends on certain patient characteristics identified in the baseline assessment, a subgroup analysis will be
performed. If there is evidence that the difference in treatment depends on certain patient characteristics identified in the baseline assessment, a subgroup analysis will be performed”.

Item 21-23 Monitoring cannot be N/A please insert this information and edit the SPIRIT checklist.

Item 21a requires information inserted into the SPIRIT checklist on Data Monitoring committee referring to page X stating that additional information is in the Appendix.

Item 21b please state why N/A re interim analyses and why there is not anticipated to be no formal stopping rules for the trial.

Item 22: Please insert information on reporting of Adverse events (AEs) or Serious Adverse Events (SAEs) and harms from the intervention. It may be that evidence suggests that SAEs are not anticipated so please state this and indicate what potential minor AEs may be anticipated. And that they will be reported to the DMEC and relevant regulatory bodies as required indicating expectedness, serious-ness, severity, and causality. For instance, page 16 Foot ulcer.

Item 23: Frequency and plans for auditing trial conduct - needs information, this cannot be N/A. For instance, how often Project Management Group meet to review trial conduct. The Trial Steering

Answer: Thank you for your advice. This information was added on page 19.

“Oversight and monitoring

The data monitoring committee (steering committee) and the Faculdade de Medicina da Universidade de Sao Paulo Board will regularly monitor (depending on the recruitment numbers and collections performed) the study datasets and make recommendations on necessary protocol modifications or termination of all or part of the study. A trimester meeting is held to facilitate the study development. All team members can request meetings as needed.

All adverse events occurring during the clinical trial period will be recorded. Minor adverse effects potentially expected are muscle sore and tiredness after performing the proposed exercises. The patients will be advised to report any discomfort and foot pre-ulcerative signs (blisters, callus, or even foot ulcers) to the Researcher 3 who will ask for the blinded podiatrist nurse to assist the patient.”

Item 25: protocol amendments - please details plans for notifying of any changes to the protocol i.e. notifying sponsor and funder first then the PI will notify the centres and that a copy of the revised protocol will be sent to the PI to add to the Investigator Site File. You may also want to state that any deviations from the Protocol will be fully documented using a breach report form. You can also include you will update the protocol in the clinical trial registry.
Answer: This information was now added on page 23. We added this sentence:

“Any changes made to the protocol will be amended and communicated via a report sent to the sponsor and funder. The ethics committee will also be communicated by submitting a form via the national website of the research ethics committee: http://plataformabrasil.saude.gov.br/. Changes will also be included in the clinical trial register (https://clinicaltrials.gov/)”.

Item 26b: Can suggest something like this "On the consent form, participants will be asked if they agree to use of their data should they choose to withdraw from the trial. Participants will also be asked for permission for the research team to share relevant data with people from the Universities taking part in the research or from regulatory authorities, where relevant. This trial does not involve collecting biological specimens for storage."

Answer: We reviewed as suggested and now is on page 23:

“On the consent form, participants will be asked if they agree to use their data in the study, if not agreed, they can choose to withdraw from the trial. Participants will also be asked for permission for the research team to share relevant data with people from the University taking part in the research or regulatory authorities, where relevant”. 

“This trial does not involve collecting biological specimens for storage.”

Item 30: Provisions for post-trial care - you could state "There is no anticipated harm and compensation for trial participation" and it would be helpful to know if there will be any provision for post-trial care.

Answer: Thank you for your suggestions. This information was added on page 24. We add this sentence: "There is no anticipated harm and compensation for trial participation. After the clinical trial, the same treatment given to the intervention group will be offered for the control group and all study participants will receive a kit containing materials needed to continue performing the exercises at home”.

Item 31a: This item is blank in the SPIRIT checklist and there does not appear to be information in the manuscript. Please document dissemination in the protocol and in the checklist. Perhaps you could state how results will be communicated to X and X and other relevant groups via publications, reporting results in databases, data sharing arrangements, twitter - social media or through the sponsor etc.

Answer: Thank you for your suggestion. This information was added on pages 23-24. We add this sentence: “Investigators and sponsors will communicate trial results to participants and healthcare professionals through scientific database and social medias. The results also will be

Item 31b: page x you state the author contributions please insert page number into checklist or you could also state "All named authors adhere to the authorship guidelines of Trials. All authors have agreed to publication." Or All authors have contributed to writing the manuscript as detailed pX, no professional writers have been involved.

Answer: Thank you for your suggestion. This information is on pages 25. We add this sentence: “No professional writers have been involved”.

Item 31 c: Access to data cannot be left blank - it is really important so complete information. Consider stating "The datasets analysed during the current study are available from the corresponding author on reasonable request."

Answer: Thank you for your suggestion. This information was added on page 23-24. We add this sentence: “The datasets analyzed during the current study are available from the corresponding author on reasonable request”.

Item 33: See above 26b there will be no biological specimens collected OR if applicable "For this SPIRIT item, please add information on plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trials and for future use in ancillary studies."

Answer: Thank you for your suggestion. This information was added on page 23. We add this sentence: “This trial does not involve collecting biological specimens for storage”.