PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	SPIRIT-PRO Extension explanation and elaboration: guidelines for inclusion of patient-reported outcomes in protocols of clinical trials
AUTHORS	Calvert , Melanie; King, Madeleine; Mercieca-Bebber, Rebecca; Aiyegbusi, Olalekan; Kyte, Derek; Slade, Anita; Chan, An-Wen; Basch, E; Bell, Jill; Bennett, Antonia; Bhatnagar, Vishal; Blazeby, Jane; Bottomley, Andrew; Brown, Julia; Brundage, Michael; Campbell, Lisa; Cappelleri, Joseph; Draper, Heather; Dueck, Amylou; Ells, Carolyn; Frank, Lori; Golub, Robert; Griebsch, Ingolf; Haywood, Kirstie; Hunn, Amanda; King-Kallimanis, Bellinda; Martin, Laura; Mitchell, Sandra; Morel, Thomas; Nelson, Linda; Norquist, Josephine; O'Connor, Daniel; Palmer, Michael; Patrick, Donald; Price, Gary; Regnault, Antoine; Retzer, Ameeta; Revicki, Dennis; Scott, Jane; Stephens, Richard; Turner, Grace; Valakas, Antonia; Velikova, Galina; von Hildebrand, Maria; Walker, Anita; Wenzel, Lari

VERSION 1 - REVIEW

REVIEWER	Brito, Juan Pablo Mayo Clinic
REVIEW RETURNED	13-Aug-2020

GENERAL COMMENTS	Calvert et al. report a document that supports the implementation of the SPIRIT-PRO recommendations. The authors provided examples from different trials for each of the checklist items, and a PRO protocol template. I find this document extremely useful as it gives tools for the design of clinical trials that include PROs as primary or secondary aims. Yet, given that the document is an extension of the SPIRIT-PRO, there is a significant amount of overlap with that document. Although the overlap is expected, it does reduce the originality of the publication. Furthermore, the document is focused on the implementation of specific guidance around the conduct of clinical trials and may not be of interest to the majority of the readership of the BMJ. The following are suggestions to improve the manuscript There are several limitations about the SPIRIT-PRO extension manuscript, including the date of the last search for the systematic review. It may be important to mention these limitations in this manuscript as well. The methods used to develop this manuscript are short and do not give a clear overview of how the examples were found, chosen, and how those decisions were made.

	Consider expanding in the introduction section the need for this manuscript. Why is SPIRIT-PRO not enough? Perhaps some examples of where SPIRIT-PRO has been used and been unclear may help clarify some of the subjectivity of the SPIRIT-PRO extension recommendations. A key aspect of the use of PRO is participant burden. The authors mentioned this potential burden and the importance of addressing it at the protocol stage. Yet, there is also the need to assess PRO related burden during the trial conduct. Could the authors recommend ways to achieve this?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Recommendation:

Comments:
Calvert et al. report a document that supports the implementation of the SPIRIT-PRO recommendations. The authors provided examples from different trials for each of the checklist items, and a PRO protocol template. I find this document extremely useful as it gives tools for the design of clinical trials that include PROs as primary or secondary aims. Yet, given that the document is an extension of the SPIRIT-PRO, there is a significant amount of overlap with that document. Although the overlap is expected, it does reduce the originality of the publication.

Response: As with other E&E papers it is only natural that there will be overlap with the original publication. We need to ensure consistency with the original checklist. The JAMA paper describes the rationale and methods for the SPIRIT-PRO checklist, and includes the 16 final SPIRIT-PRO checklist items. This E&E aims to support the implementation of the guidance. As such, we have added examples (not included in the original manuscript) and further evidence to support each of the items co-authored by leading international experts including: regulators, PRO methodologists, trialists, patient partners. In addition, the manuscript includes a brand new protocol template to support implementation.

Furthermore, the document is focused on the implementation of specific guidance around the conduct of clinical trials and may not be of interest to the majority of the readership of the BMJ.

Response: A recent review of the Australian New Zealand Clinical Trials Registry suggested that 455 clinical trials include a PRO endpoint as the primary or secondary outcome, and similarly 26,337 trials registered on ClinicalTrials.gov between 2007-2013 included a PRO endpoint . Both reviews found that the use of PRO endpoints is increasing over time. Therefore we believe this manuscript would be of relevance to a large proportion of BMJO readers. Although the main focus of our manuscript is on clinical trials, we note that the methods proposed should be considered for broader PRO research. The guidance applies to all clinical disciplines and as such we believe this will be of major interest to BMJ Open readers.

The following are suggestions to improve the manuscript

There are several limitations about the SPIRIT-PRO extension manuscript, including the date of the last search for the systematic review.

Response: The systematic review was undertaken as part of the original development of the SPIRIT-PRO guidance (published in 2018), to identify items to inform the Delphi and consensus exercise, and finalise the content of SPIRIT-PRO guidelines. As such, it does not make sense to update the review. The SPIRIT-PRO Extension is the latest international

consensus based guideline, and is endorsed by the EQUATOR network. We only mention the systematic search by way of background and to highlight the rigorous methodology use to develop the SPIRIT-PRO guidelines. The current manuscript does not address the development of SPIRIT-PRO, but rather provides support for its implementation.

It may be important to mention these limitations in this manuscript as well.

Response: As reasoned above we do not believe this is a limitation.

The methods used to develop this manuscript are short and do not give a clear overview of how the examples were found, chosen, and how those decisions were made.

Response: Thank you we have restructured the methods section. Protocol selection is described as follows (page 20):

Protocol excerpts for each checklist item were obtained from public websites, journals, trial investigators, and industry sponsors. In addition, protocols which adhered well to SPIRIT-PRO guidance were identified through a review of trial protocols (ref EPIC) and via international trials groups known to the coauthors. For those protocols unavailable in the public domain permission was sought to publish.

Real-world examples, quoted verbatim, were selected to reflect how key elements could be appropriately described in a trial protocol. Some examples illustrate a specific component of a checklist item, while others encompass all key recommendations for an item. Empirical data and references to support each SPIRIT-PRO item are provided. Reference numbers cited in the original quoted text are denoted by [Reference] to distinguish them from references cited in this E&E paper.

Consider expanding in the introduction section the need for this manuscript. Why is SPIRIT-PRO not enough? Perhaps some examples of where SPIRIT-PRO has been used and been unclear may help clarify some of the subjectivity of the SPIRIT-PRO extension recommendations.

Response: The introduction already includes justification for the E&E paper. We have noted that the protocol template is a new addition (page 5). The original SPIRIT-PRO manuscript describes the background, rationale and methodology for developing the SPIRIT-POR guidance, as well as the final 16 items. This E&E manuscript addresses how those items may be implemented in clinical trial protocols, and provides supportive resources to assist researchers and investigators to do this in a rigorous, complete and high-quality manner.

This E&E paper aims to promote understanding of the guidelines, provide examples from a range of different trials and facilitate uptake of the recommended checklist items. In addition, we describe the development of a new PRO protocol template for use in protocol development.

We have also added additional evidence and supporting reference (page 5)-

A recent review of cancer portfolio trials illustrates this point; PRO protocol content was frequently inadequate and PRO data from trials including 49 568 participants remaining unpublished.

A key aspect of the use of PRO is participant burden. The authors mentioned this potential burden and the importance of addressing it at the protocol stage. Yet, there is also the need to assess PRO related burden during the trial conduct. Could the authors recommend ways to achieve this?

Response: Thank you for noting this point. We believe that patient and public involvement is key here and we have included further text written by our patient partners on page 22. Qualitative work alongside the trial could help assess participant burden but is beyond the scope of the SPIRIT-PRO protocol guidance.

Patient and public involvement in all aspects of trial design, including but not limited to: selection of outcomes and measures, timepoints, mode of assessment, and reporting, can help minimise burden and ensure that data collected is patient-centred and relevant to participants and to the future patients who will benefit from the research.

VERSION 2 – REVIEW

REVIEWER	Peron, Julien Centre Hospitalier Lyon-Sud, Medical Oncology
REVIEW RETURNED	25-Nov-2020

GENERAL COMMENTS	The scientific topic is perfectly mastered by the consortium, and the manuscript has obviously already been extensively reviewed within the consortium of authors, as the messages are very clearly developed. I answer below the five questions corresponding to the specific point that need my opinion for this category of article. 1/ Are the issues raised by the article important to BMJ Open's broad and international readership that includes patients, researchers, policy makers, health professionals, and doctors of all disciplines? From my perspective, this is the only limitation of the manuscript. It will be of a clear and great interest for professionals of trial protocol development, and for researchers dedicated to quality-of-life measurements/analysis/interpretation. The interest for a broad health community is more dubious. I think this is an editorial decision. However the editor should consider that this article fulfills its purpose, as it will provide a concrete and clear guidance to researchers looking ofr clarifications on the SPIRIT-PRO extension. My opinion is that if this article can fit in the scope of any scientific journal, this journal should be BMJ Open (promotion of good science, not dedicated to any medical specialty). 2/ Is the article interesting and offering novel insights that have not been sufficiently considered in the existing published literature? Yes, this will be a useful work document for people specialized in clinical trial protocol development. 3/ Is the article well written and is the content clearly presented? Does it have a clear message? Yes and yes, without the need of any recommendation from my part. 4/ Will the article help medical researchers, patients or related groups of readers to make better decisions? Yes, as stated above 5/ Does the article demonstrate one or more of the following values: transparency, openness, collaboration, innovation, reproducibility, patient/ public involvement, improving peer review and journal best practice, and reducing research waste? The article is promoting the reduction of research waste, transparency, openness, and reproducibility. So yes.

REVIEWER	Van Hemelrijck, Mieke Kings College London, Translational Oncology & Urology Offices
REVIEW RETURNED	02-Dec-2020

GENERAL COMMENTS	The authors should be congratulated for this extensive piece of work. It is very timely. However, in order to truly ensure that the guidelines will be implemented and have an impact on patient care, the paper would benefit from some clearer structure in the headings (maybe use numbers) as well as an overview figure/table of what is required. Nobody will read the entire manuscript upfront, so it is important to make it as easy as possible to guarantee an uptake of the recommended methods.

VERSION 2 – AUTHOR RESPONSE

We thank reviewer 1 for their positive review and note that no further edits are required.

Reviewer 2 has noted that further signposting would be helpful to readers. We agree and thank the reviewer for raising this. In response, we have provided a new Table 2 - a table of contents, to facilitate rapid access to relevant sections by readers. The paper is formatted in a style consistent with other BMJ E&E papers. We believe that adding further numbering could be confusing but we believe that the addition of the new table of contents fully addresses the point raised.