PEER REVIEW HISTORY

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)	"Give Us The Tools!" - Development of knowledge transfer tools to support the involvement of patient partners in the development of clinical trial protocols with patient-reported outcomes (PROs), in accordance with SPIRIT-PRO Extension.
AUTHORS	Cruz Rivera, Samantha; Stephens, Richard; Mercieca-Bebber, Rebecca; Retzer, Ameeta; Rutherford, Claudia; Price, Gary; Slade, Anita; Aiyegbusi, Olalekan; Edge, Philip; Roberts, Lesley; Gosden, Lesley; Verdi, Rav; Wilson, Roger; Calvert, Melanie

VERSION 1 - REVIEW

REVIEWER	Reviewer 1
REVIEW RETURNED	09-Aug-2020

GENERAL COMMENTS	I applaud the authors of the manuscript for involving patients in the development of resources that can help empower patients to participate in clinical research. Please note that the comments I give are my own and are not on behalf of the FDA. I think the manuscript could be a very useful resource for patients but I recommend the authors address the following edits and comments: 1. As currently worded, it appears that patients should only be included on the team if the trial includes a PRO and I don't think that is the intended message. I would recommend revising the language to mention this as one reason to include patients in the design and implementation of a clinical study protocol. 2. Do the authors mean to limit this involvement and the checklist only to clinical trials? While I understand that is the focus of SPIRIT, there may be the opportunity to mention in the discussion that this tool could potentially be used in other types of clinical studies. 3. Clinical trials for regulatory purposes are done for both diagnostic as well as therapeutic purposes. The text in the second paragraph of the introduction should be modified to reflect that. 4. The patient partners are very skewed towards oncology/cancer (not sure why one was used vs the other in Table 1). As such, the perspectives may not be reflective of a larger patient population. In addition, it is not clear the demographic composition of this group (race/ethnicity, SES, age) which could also impact the input they provide. Recommend revising the table to provide this information. In addition, this should be acknowledged as a limitation of the effort. 5. In table 2 page 6, I would recommend adding under the introduction section Key consideration column bullet 3, "on participants' symptoms, FUNCTION, and quality of life?" In addition,

	please consider that quality of life may be more distal to the intervention of interest in the clinical trial and less likely to be impacted over the course of a clinical trial for an investigational product. I would be less proscriptive about including it and instead say if likely to be impacted by the intervention in the course of the clinical investigation. 6. In Table 2 page 7, the authors mention proxy completion. Proxy completion can be problematic for regulatory-bound clinical trials. Regulators often dissuade the collection of proxy reports and instead encourage observer reports of behaviors. Would encourage the authors to replace proxy completion with observer-reported outcomes (see FDA PFDD# 3 discussion guide). 7. On page 8, the authors mention in bullet 2 that the time between assessments may miss important issues. It may be more accurate to say events instead of issues since that word implies that a concept may be missed which may require a different action. In addition, bullet 5 should ask not only when will it take place but also where. 8. The discussion is heavy-handed in its assertion that healthcare professionals do not effectively communicate. I would recommend the authors be more judicious since many do effectively communicate. The sentences from line 12-25 on page 10 do not seem to be connected in terms of the ideas or the logic. For example, regulators are listening to patients' perspectives because it can help with regulatory decision making since they do not make or develop medical products or design the studies to evaluate them. 9. There are a few places where the authors have not spelled out abbreviations (table 2 page 7 HRQL) as well as a number of spelling and grammatical errors throughout the document. For example, line 26 of introduction (inadequate is misspelled) or Table 2 page 6 column 2 should be corrected. In addition, the glossary is a nice opportunity to link the terms with the abbreviations.

REVIEWER	Harold Sox PCORI
REVIEW RETURNED	12-Aug-2020

GENERAL COMMENTS	This article describes the authors' set of instructions to assist patients who are partners in planning a clinical research study. The specific topic is incorporating patient-reported outcomes into the study protocol in a manner consistent with the guidance provided by an extension to the SPIRIT guidelines for writing a study protocol for a randomized clinical trial (I was a co-author of the original SPIRIT guidelines article). The authors have mis-referenced the SPIRIT-PRO extension (page 3, last paragraph). The sentence that begins "In 2018, The SPIRIT-PRO Extension…." ends with a reference to item 15 in the list of references. Item 15 is a 2013 JAMA article by M. Calvert which is about the consort PRO extension, not the SPIRIT-PRO extension. The manuscript does not contain a reference to the 2018 JAMA article that describes the SPIRIT-PRO extension (JAMA. 2018:319(5):483-94. While the instructions look reasonable, it was difficult for me to relate the specific items in the present manuscript to the content of the corresponding "explanation" items in the SPIRIT-PRO extension (which I was not involved with). Table 2 names each SPIRIT-PRO extension item but does not give its full title from the JAMA 2018 article. I think they should reproduce at least the title of each item, if not the full explanation. Comparing the title of some of the SPIRIT-

	PRO extension items with the corresponding content in the present manuscript, I have my doubts about how well the present manuscript is capturing the essence of each SPIRIT-PRO extension item. This problem relates to my second concern, listed below. A second concern is what appears to be little or no testing of their user-friendly version of the SPIRIT-PRO extension. If they had tested it, they might have learned better ways of conveying the content to patient partners. Perhaps it's not fair to hold them to the same scientific standards used by the original SPIRIT developers (several rounds of Delphi process to develop a consensus about the number of items and their specific wording), but there was no testing or even external review of the items and their wording. This is a significant process limitation. As a minor point, I noticed that Table 1 shows each PPI partner's healthcare condition and initials that seem to map to the list of co-authors. While I assume each person listed gave permission to disclose this information, I still think that including it is a poor idea, partly because it's hard to imagine how that information would help a reader to understand the article but mostly because it sets what I think is a bad example.

REVIEWER	Juan P Brito Mayo Clinic
REVIEW RETURNED	13-Aug-2020

GENERAL COMMENTS	Rivera et al. present a report that summarizes the development of two implementation tools for the SPIRIT-PRO extension recommendations. The goal of these tools is to support patient partners involved in the co-design of PRO clinical trials. This work is important for researchers developing clinical trials, particularly when they want to engage patients in the development phases of the trial. This work could also serve as an example for how guideline recommendations could be translated in a way makes sense for patients. Yet, one of my major concerns is that this work is mostly focused in shifting the language rather than the scope or type of recommendations already made by SPIRIT-PRO group. Suggestions to improve manuscript: What are the INVOLVE guidelines mentioned in the abstract? Please expand briefly what the GRIPP2 reporting checklist is? There is need to clarify the methods section to know exactly how partners contributed to the report and the method to reach agreement. Perhaps, a figure may help here Patient partners were already known by the study team, and also there were patients with experience in clinical trials. Was this report tested among patients with less trial experience or less experience with research? Likely testing these tools other users will help refine content. How were PPI partners selected? How was the involvement of patients at this stage different than the involvement of patients during the development of SPIRIT-PRO extension manuscript? Are these patients also part of the SPIRIT-PRO report? I find the effort to engage patients important and also one that has barriers and challenges. Is there any lessons learned during this process? For instance, did the patient partners find additional PRO related recommendations not listed in the SPIRIT-PRO document? Consider adding a limitations section to the discussion section

REVIEWER	Imke Schilling Institute of Public Health and Nursing Research, University of Bremen
REVIEW RETURNED	10-Sep-2020

GENERAL COMMENTS	GENERAL COMMENTS This an interesting manuscript on the development of tools to support the involvement of PPI partners in the development of clinical trial protocols with patient-reported outcomes. It was a very interesting read, thanks for the offer to review it. I especially liked, that the manuscript was developed in intense cooperation by patients and researchers. Please see below for some recommendations. ABSTRACT - in the abstracts' introduction there seems to be missing a word in the fourth sentence ("However, …"). - Aim vs. results: the authors stated two aims in the abstracts' introduction. If would be helpful to refer back to these aims when presenting the developed tools in the results section (especially making clear the connection between the second aim and the second tool). INTRODUCTION - I would be interested to learn more about the problems regarding the use of and reporting on PROs raised in the second paragraph of the introduction. Furthermore, I think these aspects could be a good starting point to extend the discussion section and add more depth to the reflection of the developed tools (see below). - The authors used an example from a review on cancer studies, stating that PRO data was left underreported for studies involving nearly 50,000 people. Could the authors please add information of the number of studies that involved those 50,000 people? - The authors used different terms for the "SPIRIT-PRO Extension guidance" (with and without "extension" and "guidance", "guideline" instead of "guidance", etc.). I would recommend standardizing the use of terms throughout the manuscript to aid clarity. Same applies for the term used for the developed user-friendly guidance (and I wondered, if the authors would like to use a more precise term than "user-friendly", that states who the user is, e.g. PPI partners). METHODS - The lay summary of the SPIRIT-PRO Extension guidance was drafted by a patient partner. I would be interested to learn more about how he was selected (or volunteered, or …?) for this task. Depending on the selection process of the PPI partners involved, their selection may be an aspect worth discussing in the discussion section, e.g. regarding "representation", experiences with involvement/clinical trials/PROs, patients' vs. carers' perspectives, etc. - Similar to the above-mentioned irritation regarding the aims and results in the abstract, the aims stated for the manuscript could be connected more strongly with the aims described for the conducted PPI session in the methods section. - In the last paragraph of the methods, the authors describe, that "PPI partners commented on the design and content of a previously published diagram […]". Both here in the methods section and later in the results section I had difficulties to imagine the diagram as well as the developed online tool. I would highly recommend to add

	further information in both sections to make the content more illustrative and practical. Regarding the above mentioned diagram, I would be interested to learn about its content and the discussions on it in the PPI session. RESULTS - Both the results and the discussion would profit from more detailed information/ discussions. - In the first sentence ("Seven PPI partners […]") the authors should be more explicit regarding their aim "to promote the uptake and dissemination of the SPIRIT-PRO extension guidance": uptake and dissemination by whom (patients, in general, …)? Furthermore, the achievement of this aim should be discussed in the discussion section. - I assume, the third sentence is missing a "partners" = PPI partners. - The description of tool a) would profit from some further explanations, e.g. to aid clarity regarding the difference between (2) and (3), and the purpose of each item. - I recommend to add a column with the original SPIRIT item descriptions in table 2, to enhance its understanding. - In general, I would recommend to ask a patient to review the manuscript as well (this is likely to be part of your review process, already). Especially, to get a patients' perspective on the tools developed with the aim of user-friendliness. - My main concern in a) relates to the question, why the user-friendly version (table 2) does not cover the items 18a, 18b, 20a, 20c, 22 from the SPIRIT-PRO Extension guidance? Would it not be user-friendly to give them a tool that addresses all items? The authors need at least to explain this decision, better though add a user-friendly version of the missing items. - In b) I had difficulties to get a clear idea of the web-based tool, that was developed: what is included in the flow diagram? How can it be utilized? In which context are the questions from Box 1 presented? etc. The authors need to extend and concretize their results for b). Perhaps some further figures (or screenshots?) might help. - I did not understand, where the questions 5 to 7 in Box 1 came from. DISCUSSION - Regarding the interesting background of the paper, I found the manuscript could profit from a longer and more clearly structured discussion section. In addition to the suggestions above (please see previous comments), I missed a more detailed reflexion on the potential use of the developed tools, on specific strengths and limitations, and a critical discussion of the methodical approach. Please be aware, that by now some contents from the background section are repeated in the discussion without further elaborations. REFERENCES - The list of references includes some abbreviations that need to be written out (e.g. 19. CPROR, 22. S.C.).

VERSION 1 – AUTHOR RESPONSE

Reviewer 1	Actions
It appears that patients should only be included on the team if the trial includes a PRO and I don't think that is the intended message. I would recommend revising the language to mention this as one reason to include patients in the design and implementation of a clinical study protocol. Do the authors mean to limit this involvement and the checklist only to clinical trials? While I understand that is the focus of SPIRIT, there may be the opportunity to mention in the discussion that this tool could potentially be used in other types of clinical studies.	This has been included in the discussion section, p. 18.
The patient partners are very skewed towards oncology/cancer (not sure why one was used vs the other in Table 1). As such, the perspectives may not be reflective of a larger patient population. In addition, it is not clear the demographic composition of this group (race/ethnicity, SES, age) which could also impact the input they provide. Recommend revising the table to provide this information. In addition, this should be acknowledged as a limitation of the effort.	Further detail around the PPI partners' characteristics has been added, p. 4. In addition, this limitation has been added to p.19.
Clinical trials for regulatory purposes are done for both diagnostic as well as therapeutic purposes. The text in the second paragraph of the introduction should be modified to reflect that.	This has been included, p.3.
In table 2 page 6, I would recommend adding under the introduction section Key consideration column bullet 3, "on participants' symptoms, FUNCTION, and quality of life?" In addition, please consider that quality of life may be more distal to the intervention of interest in the clinical trial and less likely to be impacted over the course of a clinical trial for an investigational product. I would be less proscriptive about including it and instead say if likely to be impacted by the intervention in the course of the clinical investigation.	These suggestions have been added, p.7.
On page 8, the authors mention in bullet 2 that the time between assessments may miss important issues. It may be more accurate to say events instead of issues since that word implies that a concept may be missed which may require a different action. In addition, bullet 5 should ask not only when will it take place but also where.	These suggestions have been added, p. 9.

The discussion is heavy-handed in its assertion that healthcare professionals do not effectively communicate. I would recommend the authors be more judicious since many do effectively communicate.	This sentence has been rephrased, p. 17.
The sentences from line 12-25 on page 10 do not seem to be connected in terms of the ideas or the logic. For example, regulators are listening to patients' perspectives because it can help with regulatory decision making since they do not make or develop medical products or design the studies to evaluate them.	This has been corrected, please see p. 18.
There are a few places where the authors have not spelled out abbreviations (table 2 page 7 HRQL) as well as a number of spelling and grammatical errors throughout the document. For example, line 26 of introduction (inadequate is misspelled) or Table 2 page 6 column 2 should be corrected. In addition, the glossary is a nice opportunity to link the terms with the abbreviations.	The document has been revised to spell out abbreviations and correct grammatical errors.
Reviewer 2	**Actions**
The authors have mis-referenced the SPIRIT-PRO extension (page 3, last paragraph). The sentence that begins “In 2018, The SPIRIT-PRO Extension….” ends with a reference to item 15 in the list of references. Item 15 is a 2013 JAMA article by M. Calvert which is about the consort PRO extension, not the SPIRIT-PRO extension. The manuscript does not contain a reference to the 2018 JAMA article that describes the SPIRIT-PRO extension (JAMA. 2018:319(5):483-94	The reference has been updated.
While the instructions look reasonable, it was difficult for me to relate the specific items in the present manuscript to the content of the corresponding “explanation” items in the SPIRIT-PRO extension (which I was not involved with). Table 2 names each SPIRIT-PRO extension item but does not give its full title from the JAMA 2018 article. I think they should reproduce at least the title of each item, if not the full explanation. Comparing the title of some of the SPIRIT-PRO extension items with the corresponding content in the present manuscript, I have my doubts about how well the present manuscript is capturing the essence of each SPIRIT-PRO extension item.	The table has been updated to include the SPIRIT-PRO extension titles. Please note this is now Table 1.
Little or no testing of their user-friendly version of the SPIRIT-PRO extension. If they had tested it, they might have learned better ways of conveying the	The manuscript already acknowledges that the tools were not tested among other patient partners. The following sentence was included:

content to patient partners. Perhaps it's not fair to hold them to the same scientific standards used by the original SPIRIT developers (several rounds of Delphi process to develop a consensus about the number of items and their specific wording), but there was no testing or even external review of the items and their wording. This is a significant process limitation. *Reviewer 3 also raised this issue.*	*However, the tools developed were not tested among patient partners with less trial experience or less experience with research, which could have helped in the refinement of the tools.* (p.18).
As a minor point, I noticed that Table 1 shows each PPI partner's healthcare condition and initials that seem to map to the list of co-authors. While I assume each person listed gave permission to disclose this information, I still think that including it is a poor idea, partly because it's hard to imagine how that information would help a reader to understand the article but mostly because it sets what I think is a bad example.	Thank you for highlighting this. Even though the PPI partners granted permission for their health conditions to be publicly available, we have removed this information. Please see methods section, p. 4.
Reviewer 3	**Actions**
This work is mostly focused in shifting the language rather than the scope or type of recommendations already made by SPIRIT-PRO group.	The aim of this research project was to facilitate the use of the SPIRIT-PRO Extension guidance by making the language and presentation of the guidance more accessible to facilitate the engagement of patient partners.
What are the INVOLVE guidelines mentioned in the abstract?	This has been explained in the methods section, p. 4.
Please expand briefly what the GRIPP2 reporting checklist is?	This has been explained in the methods section, p. 4.
There is need to clarify the methods section to know exactly how partners contributed to the report and the method to reach agreement. Perhaps, a figure may help here.	Figure 1 has been included in the methods section to aid clarification, p. 5.
How were PPI partners selected?	As previously discussed in the methods section, PPI partners were already known to the team. We selected different patients and carers with different health conditions and levels of involvement in the PRO trial research. This is included in the methods section, p. 4.
How was the involvement of patients at this stage different than the involvement of patients during the development of SPIRIT-PRO extension manuscript? Are these patients also part of the SPIRIT-PRO	Three patient partners were involved in the development of the SPIRIT-PRO Extension guidance, of which two participated in the co-development of tools for patients. To mitigate this, additional patient partners were invited to

report?	collaborate in the project. Patient partners were involved in the same way in both research projects. However, patient partners drove the agenda more of this project as the aim of this research was to develop a tool for them to use.
Is there any lessons learned during this process? For instance, did the patient partners find additional PRO related recommendations not listed in the SPIRIT-PRO document?	
Consider adding a limitations section to the discussion section	A limitations section has been included within the discussion section, p.18-19.
Reviewer 4	**Actions**
in the abstracts' introduction there seems to be missing a word in the fourth sentence ("However, …").	We have revised this section and we consider that there are not missing words.
Aim vs. results: the authors stated two aims in the abstracts' introduction. It would be helpful to refer back to these aims when presenting the developed tools in the results section (especially making clear the connection between the second aim and the second tool).	The aims have been stated in the results section as suggested.
The lay summary of the SPIRIT-PRO Extension guidance was drafted by a patient partner. I would be interested to learn more about how he was selected (or volunteered, or …?) for this task. Depending on the selection process of the PPI partners involved, their selection may be an aspect worth discussing in the discussion section, e.g. regarding "representation", experiences with involvement/clinical trials/PROs, patients' vs. carers' perspectives, etc.	The patient partner selected to produce the initial lay summary and glossary was originally involved in the development of the SPIRIT-PRO Extension guideline. In addition, the patient partner has experienced completing PRO questionnaires and has been involved in different PRO-specific projects to provide his perspective from a patient's perspective. This included in the methods section, p. 4.
In the last paragraph of the methods, the authors describe, that "PPI partners commented on the design and content of a previously published diagram […]". Both here in the methods section and later in the results section I had difficulties to imagine the diagram as well as the developed online tool. I would highly recommend to add further information in both sections to make the content more illustrative and practical. Regarding the above mentioned diagram, I would be interested to learn about its content and the discussions on it in the PPI session.	The previously published diagram has been added as Appendix 2. In addition, further detail regarding the development of the web-tool was added, p. 16.

Results section - Both the results and the discussion would profit from more detailed information/ discussions.	The results and discussion have been improved by adding further detail.
- In the first sentence ("Seven PPI partners […]") the authors should be more explicit regarding their aim "to promote the uptake and dissemination of the SPIRIT-PRO extension guidance": uptake and dissemination by whom (patients, in general, …)? Furthermore, the achievement of this aim should be discussed in the discussion section.	This has been updated to include the word patient partners. In addition, the achievement of this aim is included in the discussion section, p.
- I assume, the third sentence is missing a "partners" = PPI partners.	This has been updated to include the word patient partners.
- The description of tool a) would profit from some further explanations, e.g. to aid clarity regarding the difference between (2) and (3), and the purpose of each item.	Further details have been included in the results section.
- I recommend to add a column with the original SPIRIT item descriptions in table 2, to enhance its understanding.	The SPIRIT-PRO items have been added to Table 1 (previously Table 2) to aid the reader's understanding.
- In general, I would recommend to ask a patient to review the manuscript as well (this is likely to be part of your review process, already). Especially, to get a patients' perspective on the tools developed with the aim of user-friendliness.	Thank you for this suggestion. Two patient partners were included in the writing up process. In addition, the seven patient partners reviewed the manuscript and provided feedback.
My main concern in a) relates to the question, why the user-friendly version (table 2) does not cover the items 18a, 18b, 20a, 20c, 22 from the SPIRIT-PRO Extension guidance? Would it not be user-friendly to give them a tool that addresses all items? The authors need at least to explain this decision, better though add a user-friendly version of the missing items.	Thank you for noticing this. A mistake was made when uploading the file to the system. The complete SPIRIT-PRO Extension guidance co-developed with the patients has been incorporated to the manuscript.
In b) I had difficulties to get a clear idea of the web-based tool, that was developed: what is included in the flow diagram? How can it be utilized? In which context are the questions from Box 1 presented? etc. The authors need to extend and concretize their results for b). Perhaps some further figures (or screenshots?) might help. I did not understand, where the questions 5 to 7 in Box 1 came from.	Box 1 has been removed and further detail has been added to improve the results section.
DISCUSSION - Regarding the interesting background of the paper, I found the manuscript could profit from a longer and more clearly structured discussion section. In addition to the suggestions above (please see	The discussion section has been expanded to include these comments.

previous comments), I missed a more detailed reflexion on the potential use of the developed tools, on specific strengths and limitations, and a critical discussion of the methodical approach. Please be aware, that by now some contents from the background section are repeated in the discussion without further elaborations.	
REFERENCES - The list of references includes some abbreviations that need to be written out (e.g. 19. CPROR, 22. S.C.).	The references have been updated.