PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Design, implementation and reporting strategies to reduce the instance and impact of missing patient-reported outcome (PRO) data: A systematic review
AUTHORS	Mercieca-Bebber, Rebecca; Palmer, Michael; Brundage, Michael; Calvert, Melanie; Stockler, Martin; King, Madeleine

VERSION 1 - REVIEW

REVIEWER	Bárbara Antunes Centro de Estudos e Investigação em Saúde da Universidade de Coimbra Portugal
REVIEW RETURNED	26-Jan-2016

GENERAL COMMENTS	This systematic review addresses an important topic, relevant for collecting and measuring patient's outcomes in clinical research. However, there are some issues that could to be addressed in order to make this review more robust. I hope the authors find these comments useful. ABSTRACT Data sources: CINALH should be written in full (Cumulative Index to Nursing and Allied Health Literature) instead of using the acronym. Also, using one medical electronic database and one nursing database seems to be the absolute minimum for a systematic review. I think it would be important for the reader to understand why only two electronic databases were used and this should be added in the limitations section. I'm not sure if the text in page 4 - "The problem of missing PRO data: a summary of the issues" – and Box 1 really need to be in the manuscript. This would be more appropriate in a narrative review. For a systematic review perhaps the authors could make one paragraph in the introduction with all relevant references for readers who would like to pursue the topic further. Additionally, the authors make it clear that this paper "does not attempt to address statistical handling of missing PRO data" but have a section discussing it. METHODS I like this section. It is succinct and clear. However, authors only provide information for the Medline search in page 5, line 50 and make no reference to the other electronic databased used in this work, Cumulative Index to Nursing and Allied Health Literature. Authors should be consistent and provide search strategy information for both databases.

	The first sentence of the “Extraction and coding of recommendations” section informs the reader of the methodology used for analysing the data collected in this review. I don’t think it is appropriate to only reference one paper, particularly one which only provides 2 small paragraphs of the methodology used, namely, framework synthesis. I think authors should provide additional references which explore and provide a detailed description of the analysis methods used in this systematic review. DISCUSSION In the last paragraph of the “Strengths” section authors state that the majority of included papers were discussion or guidance pieces and that “…study quality criteria used in traditional systematic reviews did not apply.” I understand and agree with the authors, however, I also think that some form of appraisal including specific quality criteria is lacking. Furthermore, over 50% of included papers are discussions papers. This has an implication in terms of the quality of the data included in the review and the review itself. Therefore, if authors decide not to conduct any form of quality appraisal of the included studies and consider this as a strength, I would strongly suggest to add a phrase on why this is also a limitation in the “Limitations” section so that the reader has no doubts as to why a quality appraisal was not conducted, since this is a systematic review which follows the PRISMA guidelines and should include quality appraisal (See also Centre for Reviews and Dissemination. CRD’s guidance for undertaking reviews in health care. York: University of York, 2009, p. 292.) Titles for Tables 2, 3 and 4 could be a bit more coherent.

REVIEWER	Astrid Janssens University of Exeter Medical School
REVIEW RETURNED	10-Feb-2016

GENERAL COMMENTS	Help and support for academics and research teams to reduce missing data is very important and indeed understudied area. I was really pleased when I read the title, as with data collection comes missing data, and we all struggle with the issue. However, I was a bit disappointed when I reached the end of the paper. The paper contains a list of suggestions, some of which consist of one word only, without critically appraising them. The paper adds a new systematic overview of recommendations, briefly described in a table in appendix, to reduce the instance and impact of missing PRO data; yet, it is merely a list. I find the paper rather noncommittal. Some general comments: ABSTRACT: In your discussion it became clear to me what type of papers you selected: discussion or guidance pieces. I think it would be helpful for the reader to have this in the abstract – perhaps as part of the result section? ARTICLE SUMMARY Second bullet point: can you make this claim? Have you checked impact of these recommendations and what effect they have on missing PRO data? It remains to be tested whether when

	implementing all these recommendations will actually reduce missing data “in many cases”. MANUSCRIPT Statistical handling of PRO data: I find this section too long. I would prefer more details in the sections pg 7-8. The first part of the manuscript – you state you summarise the problems created by missing data – is too long compared to the second section of the paper. A short description of the different problems you will address later in the paper is helpful; I think it is out of balance with the attention given to the second part of the paper – which for me needs more details, more examples. METHODS Could the authors give an example of “general study/trial drop out”? – why is this not included? RESULTS General comment for this section Although the tables are available, I lack a good description for these strategies. I think readers will find this the most valuable bit of the manuscript. Yet, many of the strategies are unidentifiable as they are described in such limited wordings. Also, if limited by number of words; why repeat the ones the most frequently recommended implementation strategies for each section? Can we have some examples or perhaps even case-studies (similar to providing participant quotes in papers reporting qualitative work)? A second general comment is the – to me – arbitrary –or at least debatable - split between “design strategies” and “implementation strategies”. \ ->Providing guidance for site staff to standardise the administration of PRO questionnaires (could just as well be implementation) \ ->Using a PRO completion cover sheet – again, could be something you do in advance and is part of your design strategy or standard operating procedure (SOP) \ ->Appointing a site coordinator -> SOP? DISCUSSION My main issue with the discussion is that the authors are very “low-key” and add very little to the discussion. Funding and or finances have been mentioned several times: why not address commissioners / funding bodies? Many researchers acknowledge the importance of these strategies, yet can not get the funding. Also, are there success stories? Do these strategies deliver? How much can they reduce the missing data – I acknowledge the authors might not have the answer to all these questions, but I think they are worth raising in such a paper. Some sections from the discussion could be used in the result section – can I suggest that the authors give more examples, (similar to providing participant quotes in papers reporting qualitative work)? Even the tables do not provide this information. (eg. the case about patient engagement – as discussed in the discussion section – is this something for the result section?) OVERALL COMMENT: This is an important topic; a lot of work has gone in this review; my request is: can we have more (examples, case studies, elaborate

	description of the strategies, critical discussion)?

VERSION 1 – AUTHOR RESPONSE

Response to reviewer comments: We would like to thank both reviewers for their helpful suggestions to improve this manuscript. We have numbered and addressed each comment below. We have also annotated where each comment has been addressed in the manuscript using this numbering system.
RESPONSE TO COMMENTS FROM REVIEWER 1

ABSTRACT
Q1.1. Data sources: CINALH should be written in full (Cumulative Index to Nursing and Allied Health Literature) instead of using the acronym.
Response: we have spelled out CINAHL in full in the abstract and manuscript (Methods: search strategy section).

Q1.2. Also, using one medical electronic database and one nursing database seems to be the absolute minimum for a systematic review. I think it would be important for the reader to understand why only two electronic databases were used and this should be added in the limitations section.
Response: We developed our search strategy in consultation with three librarians and conducted several pilot searches to ensure our search was inclusive and robust. We also searched reference lists and citing articles. Although we cannot be sure we reviewed and captured all relevant papers in our review, we feel our findings would not be altered by the inclusion of additional databases. Medline and CINAHL databases were used in our search because they canvassed both medical and nursing literature - the disciplines of interest and relevance to our review, and because they indexed key papers already known to the authors. We have added a justification statement to our manuscript (METHODS: search strategy section & DISCUSSION: Limitations as we agree with Reviewer 1 this should be stated.

Q1.3. I'm not sure if the text in page 4 - "The problem of missing PRO data: a summary of the issues" – and Box 1 really need to be in the manuscript. This would be more appropriate in a narrative review. For a systematic review perhaps the authors could make one paragraph in the introduction with all relevant references for readers who would like to pursue the topic further. Additionally, the authors make it clear that this paper "does not attempt to address statistical handling of missing PRO data" but have a section discussing it.
Response: We feel it is important to include a lay summary of the problem of missing data, particularly for the benefit of researchers with limited knowledge of analysis of PRO data where missing data is present, as it adds value to paper and establishes the need for our review. We have provided a brief overview for interested readers which acknowledges that missing data can be handled statistically and have directed readers to specialised sources; note that we do not attempt to discuss the highly technical methods of how missing data can be addressed statistically, nor do we include any details about how missing data can be handled statistically in the systematic review component.
Based on this feedback we have clarified our aims to avoid reader confusion. We have revised the last sentence of the section on "The problem of missing PRO data: a summary of the issues" as follows: "Statistical handling of missing PRO data is not addressed in our systematic review below". We added line breaks to the Aims section to clearly show both aims of our manuscript. We have also shortened the section on the problem of missing data.

METHODS

Q1.4. I like this section. It is succinct and clear. However, authors only provide information for the Medline search in page 5, line 50 and make no reference to the other electronic databased used in this work, Cumulative Index to Nursing and Allied Health Literature. Authors should be consistent and

provide search strategy information for both databases.
Response: We would like to thank reviewer 1 for identifying this oversight in our paper. We have noted the databases used in the Methods: search strategy section. Note that search terms for both databases are included as Appendix A.

Q1.5. The first sentence of the "Extraction and coding of recommendations" section informs the reader of the methodology used for analysing the data collected in this review. I don't think it is appropriate to only reference one paper, particularly one which only provides 2 small paragraphs of the methodology used, namely, framework synthesis. I think authors should provide additional references which explore and provide a detailed description of the analysis methods used in this systematic review.
Response: We have added a dedicated reference that describes Framework Synthesis in detail for interested readers. Please note that we have described our process of coding and refinement of codes using the example of 'minimising patient burden' in this section.

DISCUSSION.
Q1.6. In the last paragraph of the "Strengths" section authors state that the majority of included papers were discussion or guidance pieces and that "…study quality criteria used in traditional systematic reviews did not apply." I understand and agree with the authors, however, I also think that some form of appraisal including specific quality criteria is lacking. Furthermore, over 50% of included papers are discussions papers. This has an implication in terms of the quality of the data included in the review and the review itself. Therefore, if authors decide not to conduct any form of quality appraisal of the included studies and consider this as a strength, I would strongly suggest to add a phrase on why this is also a limitation in the "Limitations" section so that the reader has no doubts as to why a quality appraisal was not conducted, since this is a systematic review which follows the PRISMA guidelines and should include quality appraisal (See also Centre for Reviews and Dissemination. CRD's guidance for undertaking reviews in health care. York: University of York, 2009, p. 292.)
Response: As noted by Reviewer 1, 55% of the sources included in this review were discussion pieces, many of which were written by highly regarded and experienced PRO experts based on strategies that their trials group or organisation has implemented with documented improvement in PRO completion rates. We do not feel that inclusion of the high proportion of discussion papers is a limitation of our study. However, the reviewer's other points are well made. So we have separated out the strengths and weaknesses of our inclusion of discussion and guidance pieces. We now include inability to apply study quality criteria as a weakness. We have also noted that although we could not use standard tools to assess the "quality" of the sources, we have critically appraised individual recommendations in the "potential drawbacks" column of results tables. Additionally, we have provided the number of times each strategy was recommended (although we acknowledge this is not necessarily a quality indicator, frequency of the recommendation does indicate that the strategy is found by people who have used it to be effective). Our revisions can be seen in the last paragraph of the Strengths section and the first paragraph of the Limitations section of the Discussion.

Q1.7. Titles for Tables 2, 3 and 4 could be a bit more coherent.
Response: Thank you for this feedback. We have revised the table headings as follows:
•Table 2. Study design and planning strategies to minimise the problem of missing PRO data;
•Table 3. Study conduct strategies to minimise the problem of missing PRO data;
•Table 4. Strategies for reporting studies with missing PRO data to minimise the potential for biased interpretation of findings.

RESPONSE TO COMMENTS FROM REVIEWER 2
Q2.1. Help and support for academics and research teams to reduce missing data is very important and indeed understudied area. I was really pleased when I read the title, as with data collection

comes missing data, and we all struggle with the issue. However, I was a bit disappointed when I reached the end of the paper. The paper contains a list of suggestions, some of which consist of one word only, without critically appraising them. The paper adds a new systematic overview of recommendations, briefly described in a table in appendix, to reduce the instance and impact of missing PRO data; yet,it is merely a list. I find the paper rather noncommittal.
Response:
Thank you for your helpful comments on how to improve our manuscript and for recognising the importance of this topic. Many of the sources included in this review were written by highly regarded and experienced PRO experts, based on strategies that their trials group or organisation has implemented with documented improvement in PRO completion rates. Our review therefore brings together the collective wisdom of experienced opinion leaders in the field (as stated in our response to 1.6 above). In so doing, we addressed our aim to identify and collate strategies to minimise the problem of missing data. We disagree that it is "merely a list"; rather, it is an experience-based summary of strategies that can be implemented by readers.
Although we included all recommendations for minimising the problem of missing data without assessing the "quality" of the sources, we have critically appraised individual recommendations in the "potential drawbacks" column of results tables. Additionally, we have provided the number of times each strategy was recommended (although we acknowledge this is not necessarily a quality indicator, frequency of the recommendation does indicate that the strategy is widely used, suggesting it may be effective). We have added a statement to this effect to the Discussion section.
"Further we have provided the number of times each strategy was recommended, which may indicate widespread use and effectiveness of highly cited strategies– although we acknowledge that some of the less frequently cited strategies may also be highly effective, and some strategies may only apply to specific disease or research contexts. Gathering empirical evidence as to the degree of effectiveness of the strategies identified in this review would be an interesting direction for future research".
Thank you for highlighting that further elaboration was needed in the results tables to clearly communicate the recommendations. We have added descriptions to many of the recommendations within the tables and further explained our findings in the Results section. Note that our Results tables are included in the main text body (not appendix).
Thank you also for the feedback that further comment on our findings was needed. Accordingly, we have added recommendations to the Discussion section.
Some general comments:

ABSTRACT:
Q2.2. In your discussion it became clear to me what type of papers you selected: discussion or guidance pieces. I think it would be helpful for the reader to have this in the abstract – perhaps as part of the result section?

Response: We have added details of the percentage of discussion papers compared to original research papers included in the review in the abstract. Complete details of the types of included papers are provided in the manuscript in Table 1. Please note that we did not exclusively include discussion papers in our systematic review; however most papers that met our eligibility criteria were discussion papers (54.7%). Other types of publications included: original research papers (26%), meta-analyses & systematic reviews (10%), text books (5%), guidelines (3%) & other types (5%).

ARTICLE SUMMARY
Q2.3. Second bullet point "Missing PRO data is preventable in many cases by implementing rigorous study design and methodological strategies described in this review.": can you make this claim? Have you checked impact of these recommendations and what effect they have on missing PRO data? It remains to be tested whether when implementing all these recommendations will actually reduce missing data "in many cases".

Response: Although we have not checked their impact (the extent to which the strategies actually reduce rates of missing data), the recommendations were extracted from papers which have made these recommendations based experience. To highlight that there is an element of uncertainty we have revised our bullet point as follows: “Missing PRO data may be preventable in many cases by implementing rigorous study design and methodological strategies described in this review.”

MANUSCRIPT
Q2.4. Statistical handling of PRO data: I find this section too long. I would prefer more details in the sections pg 7-8.The first part of the manuscript – you state you summarise the problems created by missing data – is too long compared to the second section of the paper. A short description of the different problems you will address later in the paper is helpful; I think it is out of balance with the attention given to the second part of the paper – which for me needs more details, more examples.
Response: Thank you for this feedback. As suggested, we have shortened this section, while retaining the overall message. We feel it is important to include a lay summary of the problem of missing data (Aim 1), particularly for the benefit of researchers with limited knowledge of analysis of PRO data where missing data is present, as it both motivates and adds value to our paper, and underlines the importance of the findings of our systematic review (Aim 2).

We have also added detail to the Results section and Tables as suggested, while keeping the word-count of our manuscript within the 4000 word limit of BMJ Open (excluding tables).

METHODS
Q2.5. Could the authors give an example of “general study/trial drop out”? – why is this not included?
Response: We thank the reviewer for highlighting the need for clarification of this exclusion criterion. We have revised as follows: “papers reporting general study/trial dropout rates.” Such papers did not report methods for preventing or minimising the problem of missing PRO data, they simply reported rates of participant dropout in trial reports and therefore did not address our aims.

RESULTS
Q2.6. General comment for this section: Although the tables are available, I lack a good description for these strategies. I think readers will find this the most valuable bit of the manuscript. Yet, many of the strategies are unidentifiable as they are described in such limited wordings. Also, if limited by number of words; why repeat the ones the most frequently recommended implementation strategies for each section? Can we have some examples or perhaps even case-studies (similar to providing participant quotes in papers reporting qualitative work)?
Response: We have added considerable descriptive detail to our Results Tables to clarify the meaning of the previously non-descript recommendations. We have also elaborated on the type of recommendations in the Results text.

Q2.7. A second general comment is the – to me – arbitrary –or at least debatable - split between “design strategies” and “implementation strategies”.
• Providing guidance for site staff to standardise the administration of PRO questionnaires (could just as well be implementation)
• Using a PRO completion cover sheet – again, could be something you do in advance and is part of your design strategy or standard operating procedure (SOP)
• Appointing a site coordinator -> SOP?
Response: We agree with Reviewer 2 that the distinction between design and implementation strategies is often blurred, as implementation strategies require thought and preparation at the design stage. However, there is practical rationale behind our presentation format: the trial protocol is written first (design and planning); the study is conducted subsequently, and the plans in the protocol are implemented, and finally the results are reported. Our categorisation also reflects the context in which the source papers have addressed the recommendation/s. We have noted throughout the paper that

implementation and reporting strategies require preparation from the design stage. We have also cross-referenced within the results tables on several occasions to acknowledge that certain recommendations may fit in more than one research stage: e.g. in Table 2 “Design Strategies” we have listed “Collect reasons for missing PRO data” and referred readers to Table 3 “Implementation Strategies” for details: “See ‘cover sheet’ section in Administration procedures in Table 3”. Ultimately, we feel we have addressed this issue as best we can and hope our approach is accessible to readers.

DISCUSSION

Q2.8. My main issue with the discussion is that the authors are very “low-key” and add very little to the discussion. Funding and or finances have been mentioned several times: why not address commissioners / funding bodies? Many researchers acknowledge the importance of these strategies, yet can not get the funding. Also, are there success stories? Do these strategies deliver? How much can they reduce the missing data – I acknowledge the authors might not have the answer to all these questions, but I think they are worth raising in such a paper.

Response: Thank you for this constructive feedback. We agree that given the need for adequate funding and resources for PRO studies features so heavily in our findings, we have added two statements:

“Trial investigators, sponsors and funding bodies have a responsibility to ensure research funds are allocated to quality assurance of PRO studies, and training regarding the importance and efficacy of specific quality assurance strategies may be the catalyst to securing such funding.”

And

“Funding organisations and sponsors should actively promote high quality PRO research by mandating PRO training for trial team members, and publication of PRO findings (adhering to CONSORT PRO extension where applicable) to optimise the value of PRO data and avoid wasting research funding and effort.

We have also commented on the role of journal editors in ensuring missing data issues are adequately reported …

“Journal editors should enforce reporting guidance such as CONSORT-PRO in order to promote and maintain a high standard of research evidence”

….and the importance of publishing trial protocols

“Trial registration and publication of research protocols is a motion towards avoiding such examples of publication bias, however further action towards improving the quality of PRO data is needed, beginning with more comprehensive training about PROs for all trial staff. “

Our discussion highlights several success stories as a result of implementing strategies to reduce missing data. For example two studies showed improvement in involving experienced data collection personnel in PRO study development, 4 studies reported success of centralised PRO completion monitoring systems & one study demonstrated that engaging patients by sending regular updates led to high PRO completion rates. We added some more examples: i.e. “Land and colleagues found that targeted communication with poorly performing sites led to reductions in rates of missing baseline PROs [25]”……AND… “The National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) has attributed high PRO completion rates to training the trial team about the importance of avoiding missing PRO data [43].”These examples are tagged with comments “2.8” in our discussion.

We do not know the extent to which other recommendations are successful in improving compliance, so have recommended this a future research question “Gathering empirical evidence as to the degree of effectiveness of the strategies identified in this review would be an interesting direction for future research”.

Q2.9. Some sections from the discussion could be used in the result section – can I suggest that the authors give more examples, (similar to providing participant quotes in papers reporting qualitative work)? Even the tables do not provide this information. (eg. the case about patient engagement – as

discussed in the discussion section – is this something for the result section?)
Response: Because our systematic review aimed to identify & collate strategies, we have listed and described recommendations in the Results section and discussed the success of these methods in previous studies in the Discussion. As noted above, further detail has been added to both sections.

OVERALL COMMENT:
Q2.10. This is an important topic; a lot of work has gone in this review; my request is: can we have more (examples, case studies, elaborate description of the strategies, critical discussion)?
Response: Thank you for your constructive feedback, which we have addressed, as described above. We feel our manuscript is much improved by these amendments.

VERSION 2 – REVIEW

REVIEWER	Bárbara Antunes Centro de Estudos e Investigação em Saúde da Universidade de Coimbra Portugal
REVIEW RETURNED	01-Apr-2016

GENERAL COMMENTS	The paper is much improved and will be very useful for readers.

REVIEWER	Astrid Janssens University of Exeter Medical School Institute of Health Research - Child Mental Health Research Group Exeter - UK
REVIEW RETURNED	25-Apr-2016

GENERAL COMMENTS	Thank you for addressing many of my comments. Particularly the extra information in the tables and result section add to the readability and impact of the reported findings. I am not convinced that the box adds any "new" information to the literature. Also, what is reported in the box is not the core of your message. The same goes for the summary of the statistical handling of missing data as you make it rather clear this paper is not going to address this issue. I (still) don't see the value of having this in your paper. I would like to ask a few more things from the research team/authors: I appreciate these comments come at a rather late stage, but I have to admit, this is a very long manuscript to review and I haven't been able to scrutinise the manuscript in all its details at each stage. 1) you suggest researchers to use a protocol and rigorous study design. Any chance we can find your protocol somewhere? Even if you add a protocol to your research gate profile (as data) or have it on your project webpage. 2) You mention you checked citations and references of papers found via Medline and CINAHL. Could you provide us with some more details regarding this backwards and forwards citation tracking? Did you set a PY range? Did you use any other inclusion and or exclusion criteria for this search, that are different from the main search? Did you check Title and ABstract as you did for the other searches or just title?

VERSION 2 – AUTHOR RESPONSE

AUTHORS' RESPONSE TO REVIRWER COMMENTS

We would like to thank both Reviewers and BMJ Open for considering our manuscript. We are very pleased that both Reviewers have recommended our manuscript for publication. We note that Reviewer 1 has not requested any further changes, however Reviewer 2 has requested two minor revisions. We have addressed these (and tracked changes) in our manuscript and provide a summary below.

1) We assume Reviewer 2 is referring to our PRO-specific checklist for protocol content. Our PRO Protocol Checklist is currently in development, as noted in our manuscript. References to the work completed so far are provided (see refs 60, 61 and 63). Previously these were included only in the Discussion. We have now added these references to appropriate sections of the Results tables (pgs 11, 24, 31.)

2) Titles of references lists and citing articles of the included papers were screened, using the same eligibility criteria applied to the database search. Titles that appeared potentially relevant were obtained in full text and assessed against eligibility. We have now clarified this in our Methods section on p5.

We also note that Reviewer 2 expressed concerns as to the relevance of Box 1 and the summary of missing data, but has not requested any changes in this regard. We would like to assure Reviewer 2 and the BMJ Open of the importance of this section in addressing the first aim of our paper; we have therefore made some minor clarifying changes to the paper.

Firstly we have amended the sub-heading of 'statistical handling of missing data' to 'difficulties in statistically handling missing PRO data'. This revised heading reflects the section's content, which states that statistical methods for handling missing PRO data are available (under certain circumstances), however they are not failsafe. This section does not explain how to implement such statistical strategies; rather it refers readers to specialised sources for further information.

Secondly we have amended two section headings to clarify that the structure of the paper corresponds to the two aims of our paper: "Part 1: The problem of missing PRO data: a summary of the issues" (p4, which corresponds to Aim 1) and "Part 2: A systematic review of strategies to maximise PRO compliance rates and reduce the potential for bias" (p5, corresponding to Aim 2).

Thirdly we have clarified that there are 2 aims in the Abstract (p1), Discussion (pp8-11) and Conclusion (p11) sections of the paper.

These amendments should clarify that Part 1 ("Aim 1") is an integral part of our paper as it provides a brief overview of statistical considerations for missing data. Box 1 and the 'Difficulties in statistically handling missing data' section are intended to provide an accessible summary of the literature. By its nature, this does not add new information – however this should not be viewed as a criticism as Reviewer 2 suggests. Rather, it is a cohesive and essential component of our paper, as it establishes the need for and importance of our systematic review (Aim 2) and will be a useful summary for readers, particularly those who are not aware of, or familiar with, these issues.

As we note in our introduction, there is a common misconception that missing data is a problem for trial statisticians to handle, but our systematic review findings (Aim 2) show that this is not the case. A key message from our paper is that it is essential that all researchers involved in design, conduct, analysis and reporting of PRO data appreciate why missing data is a problem, why in many circumstances statistical methods for handling missing data are not fail-safe (Aim 1), and how all members of the research team can assist in minimising the problem of missing data (Aim 2). We highlight this throughout our paper.

VERSION 3 - REVIEW

REVIEWER	Astrid Janssens University of Exeter Medical School, Institute of Health Research (UK)
REVIEW RETURNED	15-May-2016

GENERAL COMMENTS	I would like to congratulate the authors with this paper; it is a very important topic and I believe the revisions have drastically improved the quality and readability of the paper.