Author’s response to reviews

Title: Reporting Quality of Pilot Clinical Trials in Chronic Kidney Disease Patients on Hemodialysis: A Methodological Survey

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Author’s response to reviews:

RE: PAFS-D-18-00216
Feb 13, 2019

Dear Sameer Parpia,

Thank you for considering our manuscript entitled, “Reporting Quality of Pilot Clinical Trials in Chronic Kidney Disease Patients on Hemodialysis: A Methodological Survey” for publication in Pilot and Feasibility Studies.

We have revised the manuscript as per the reviewer’s suggestions and believe it is greatly improved.

Best Regards,
Yours Sincerely,

S. Daisy Kosa, BSc., MSc  
Vice-chair, Kidney Care Network International

Reviewer #1 Comment #1: Kosa et al. present a review investigating how well previously published reports of pilot trials, adhere to the relatively new CONSORT reporting checklist for pilot and feasibility studies. Clear and comprehensive reporting of research studies is important to ensure a transparent process which aids in critique and reproducibility of studies. Until 2016 there have been no specific guidelines from CONSORT for the reporting on pilot and feasibility studies.

The authors highlight in their manuscript that previous research has shown clinical trials involving haemodialysis patients have tended to have low reporting quality. However, the quality of pilot and feasibility trials in this patient population is not known. Furthermore, trials in haemodialysis patients are essential to improve outcomes for patients, who tend to have relatively low quality of life and high disease/treatment burden. This is reflected in the high economic burden for treatment, a trend seen globally.

Response: We thank the reviewer for their helpful comments.

Whilst highlighting issues surrounding reporting quality is important, I do have a few questions regarding the manuscript presented; these are listed below:

Reviewer #1 Comment #2: Introduction: Page 3 Line 11 contains a spelling error "priorized" -> prioritized

Response: This error has been corrected as per below:

There are many pressing clinical questions in chronic kidney disease patients on hemodialysis which require a definitive, well powered randomized clinical trial (RCT) [7]. Health care providers and patients alike have identified the need for further research across a range of priorities including how to best address vascular access problems; reduce fatigue, risk of mortality, and cardiovascular disease; and improve dialysis adequacy [6].
Reviewer #1 Comment #3: Page 3 Line 10-14: this sentence seems a little out of place in relation to the topics covered in this study. How do results from SONG-HD relate to reporting quality of studies?

Response: We agree that this was unclear and have revised the sentence as per below:

There are many pressing clinical questions in chronic kidney disease patients on hemodialysis which require a definitive, well powered randomized clinical trial (RCT) [7]. Health care providers and patients alike have identified the need for further research across a range of priorities including how to best address vascular access problems; reduce fatigue, risk of mortality, and cardiovascular disease; and improve dialysis adequacy [6].

Reviewer #1 Comment #4: Methods: Would it not have been more appropriate to exclude the CONSORT items with a "not applicable" option form calculating means, counts and percentages instead of including them as "yes"? Including them in the analysis as you have may inflate the results.

Response: As per the reviewer's suggestion we have removed these items from the calculation of means and total number of consort items reported as per below. Counts and percentages presented in the tables are already based on a valid N only.

Data Analysis

All statistical analyses were performed in SPSS version 25.

Descriptive Statistics

The completeness of reporting was summarized using descriptive statistics percentages for the general characteristics and number of articles reporting each CONSORT statement item (for items 6c, 7b, 11a, 11b, 18, and 19a, the percentage was calculated based on the total number of studies for which the item was applicable). The mean, standard deviation, and range for the total number of CONSORT statement items reported, sample size, and number of sites were also calculated. To calculate the mean number of CONSORT items reported, ‘not applicable’ responses to reporting items 6c, 7b, 11a, 11b, 18, and 19a were excluded.

Reviewer #1 Comment #5: The authors state they carried out a Poisson regression, however, do not present these results in the report. The description around calculating incidence rate ratios is lacking. How have the incidence rate ratios been estimated, by tabulating and calculating by hand, or from the Poisson regression? What/how have the adjusted IRR's been adjusted? More explanation of this would be beneficial and clearer.

Response: We have clarified the method to explain that the results of the poisson regression are presented as IRR, as well as clarifying that the adjusted IRR consider the other potential factors in the regression, as per below:
Inferential Statistics

We conducted a Poisson regression to explore factors, including year of publication, sample size, multisite study (yes or no), industry funding (yes or no), prelude to a definite trial (yes or no) and journal endorsement of CONSORT (yes or no), associated with completeness of reporting as measure by the number of reported CONSORT items (“not applicable” items were excluded). Based on previous research, we hypothesized that a later publication date [17], larger sample size [18], multisite study [16], industry funding [16,18,19] and journal endorsement of CONSORT [20] would be associated with better reporting. The results of the Poisson regression were reported as unadjusted and adjusted incidence rate ratios [IRR] including 95% confidence interval [CI] and p value (α = 0.05).

Journal of publication was also considered as a potential factor to include in the Poisson regression as some clustering has been observed in prior studies on reporting [16, 18], however, no clustering within journals was noted in exploratory analyses, likely due to the wide breadth of journals in which the included studies were published, with no more than 10 studies published in the same journals (see characteristics of included studies below).

Reviewer #1 Comment #6: Page 7 line 8 contains spelling errors: "measure" -> measured and the word "items" is repeated twice in the sentence.

Response: This spelling error has been corrected as per below.

Inferential Statistics

We conducted a Poisson regression to explore factors, including year of publication, sample size, multisite study (yes or no), industry funding (yes or no), prelude to a definite trial (yes or no) and journal endorsement of CONSORT (yes or no), associated with completeness of reporting as measure by the number of reported CONSORT items (“not applicable” items were excluded).

Reviewer #1 Comment #7: Results: Although results some IRR's have p-value <0.05, the actual values are still very small. For example, increasing sample size by 20 participants results in IRR =1.021 (1.004,1.037) this suggests a 2.1% increase in reporting completeness. Is this a significant increase or a statistical artefact (perhaps related to multiple hypothesis tests)?

Response: We agree with the reviewer that this is a small increase though statistically significant, and have added this to the discussion as per below:

Larger sample sizes were also associated with higher number of CONSORT pilot items reported, however the observed effect was relatively small (e.g., there is a 2.1% increase in reporting completeness for an increase in sample size of 20 participants).
Reviewer #1 Comment #8 General comments: It may aid readability to refer to the patient population as just haemodialysis (HD) patients rather than chronic kidney disease patients on haemodialysis.

Response: We have defined the population up front as per below and used a short form for the balance of the manuscript.

This methodological survey evaluates the completeness of reporting in pilot randomized controlled trials in chronic kidney disease patients on hemodialysis (HD patients), and explores factors associated with better completion of reporting.

Reviewer #1 Comment #9: Supplementary material

Some coding information appears to be missing.

Response: We have reexported and double checked the file to ensure all codes are available in the data dictionary.

Reviewer #2 Comment #1: Consider switching "chronic kidney disease" to CKD - it's a well known acronym and how it's usually referred to in literature

Response: We have defined the acronym as per below and used a short form for the balance of the manuscript.

Chronic kidney disease (CKD) is a significant and growing global health problem, with a prevalence estimated to be between 11 to 13% [1].

Reviewer #2 Comment #2: Page 3 Paragraph 1, line 6: "increases as kidney function declines"

Response: We have revised the manuscript as per below:

Risk of mortality, largely due to cardiovascular disease, is significantly increased in the CKD population and increases as kidney function declines [2].

Reviewer #2 Comment #3: Page 3 Paragraph 1, line 12: "best address vascular access problems, fatigue, risk of mortality, and cardiovascular disease, and to improve dialysis adequacy"

Response: We have revised the manuscript as per below:

Health care providers and patients alike have identified the need for further research across a range of priorities in HD including how to best address vascular access problems, reduce fatigue, risk of mortality, and cardiovascular disease; and to improve dialysis adequacy [6].

Reviewer #2 Comment #4: Page 4, paragraph 1, line 1: "screening, recruitment, coordination, acceptability, safety…"

Response: We have revised the manuscript as per below:
Response: We have revised the manuscript as per below:

Pilot studies can assess feasibility of screening, recruitment, coordination and acceptability, safety, and fidelity of the intervention and the study protocol, as well as inform power calculations for a large, multicenter study.

Reviewer #2 Comment #5: Page 4, paragraph 2: CONSORT published in 2010 with revision in 2016, please make explicit in this paragraph and refer to which one is being used in the study (becomes clearer later on but should be well understood up front)

Response: We have revised the manuscript as per below:

To address these issues, the Consolidated Standards of Reporting Trials (CONSORT) extension for reporting randomized pilot and feasibility trials was published in 2016, which builds on the statement published in 2010 [13]. The 2016 CONSORT extension, which will be utilized in this study, lays the groundwork for the reporting of pilot trials, as well as informs their design and implementation.

Reviewer #2 Comment #6: Page 4, paragraph 2 and 3: somewhat repetitive, consider combining paragraphs to be more concise

Response: We have revised the manuscript as per below:

There are many pressing clinical questions in HD which require a definitive, well powered randomized clinical trial (RCT) [7]. Health care providers and patients alike have identified the need for further research across a range of priorities in HD including how to best address vascular access problems, reduce fatigue, risk of mortality, and cardiovascular disease, and to improve dialysis adequacy [6]. However, the immense quantity of information and resources required for the conduct of adequately powered RCTs across these clinical areas in HD can act as a barrier to their conduct [7, 8]. Pilot studies can facilitate designing such definitive RCTs by assessing feasibility of screening, recruitment, coordination and acceptability, safety, and fidelity of the intervention and the study protocol, as well as informing power calculations [7, 9, 10].

Reviewer #2 Comment #7: Search strategy: nicely done and explained

Response: We thank the reviewer for their comment.

Reviewer #2 Comment #8: Page 6, paragraph 1, line 1: please clarify how completeness differs from number of items (primary vs secondary outcomes)

Response: We have revised the manuscript as per below:

The primary outcome of this survey was the completeness of reporting of each of the items on CONSORT statement extension for randomized pilot and feasibility trials checklist, measured as a number and proportion of studies reporting each of the 40 items. The secondary outcome was
the completeness of reporting of the CONSORT statement extension for randomized pilot and feasibility trials checklist, as measured by the total number of applicable items reported.

Reviewer #2 Comment #9: Page 6, paragraph 2, line 5: regarding the study being a prelude to a definitive study, this appears self-reported and not one of the CONSORT items. Unclear if this has ever been validated. Also, may not be self-reported in original articles as might be assumed by authors given that is the underlying purpose to pilot or feasibility studies

Response: The item has not been validated and is not one of the CONSORT items. We have revised the manuscript as per below to clarify this and acknowledge it’s limitations:

(Method) The Excel-based data extraction form was developed based on a previous methodological survey [16] and collected study characteristics including: year and country of publication, sample size, number of sites, type of funding (i.e., industry, non-industry), type of intervention (i.e., pharmaceutical, behavioral/educational, dialysis technology/technique, nutritional supplements, vascular access technology/technique, and other non-pharmaceutical interventions), whether the manuscript explicitly stated the pilot study to be prelude to definitive study (i.e., yes, no), journal endorsement of CONSORT statement if the article was published after 2010 (i.e., yes, no), and reporting of individual items on the CONSORT extension for pilot and feasibility studies (Additional File 1).

(Discussion) As this was a methodological survey and not a systematic review, this study’s search was restricted to PubMed. With respect to the study characteristics collected, the non-validated item (not a CONSORT item) of whether the manuscript explicitly stated the pilot study to be prelude to definitive study, may not have been reported as this as might be assumed by authors given that is the purpose of pilot studies.

Reviewer #2 Comment #10: Page 7, paragraph 1, line 4: setting all N/A to yes may make things appear better than they are (which is acceptable given the purpose of the paper is to see if reporting is worse than it should be so biased away from expected result). Another potential option could've been eliminating this question in analysis which would've changed denominator but would've made analysis more difficult, so not a definitive requirement, just an observation

Response: As per the reviewer's suggestion we have removed these items from the calculation of means and total number of consort items reported as per below. Counts and percentages presented in the tables are already based on a valid N only.

Data Analysis

All statistical analyses were performed in SPSS version 25.

Descriptive Statistics
The completeness of reporting was summarized using descriptive statistics percentages for the general characteristics and number of articles reporting each CONSORT statement item (for items 6c, 7b, 11a, 11b, 18, and 19a, the percentage was calculated based on the total number of studies for which the item was applicable). The mean, standard deviation, and range for the total number of CONSORT statement items reported, sample size, and number of sites were also calculated. To calculate the mean number of CONSORT items reported, ‘not applicable’ responses to reporting items 6c, 7b, 11a, 11b, 18, and 19a were excluded.

Reviewer #2 Comment #11: Page 8, paragraph 1, line 9: clarify number of significant digits used
Response: We have revised the manuscript as per below:

The mean sample size was 44.0 (standard deviation (SD) = 55.1, range = 4 - 448) and number of sites was 2.2 (SD = 2.7, range = 1 – 15).

Reviewer #2 Comment #12: Page 8, paragraph 2, line 4: Similar to previous, not clear this is a validated item and may not be explicit in manuscripts as assumed given nature of pilot studies
Response: We have revised the manuscript as per below:

Only 17.4% of studies explicitly indicated in the manuscript that the study was a prelude to a definitive trial.

Reviewer #2 Comment #14: Page 8, paragraph 3, line 1: state max score (can be found by going to actual questionnaire but will be easier to understand if in text
Response: We have revised the manuscript as per below:

The mean CONSORT reporting score across all included articles 18.4 (SD = 4.4, minimum = 8, maximum = 29) out of a possible 34 items (6c, 7b, 11a, 11b, 18, and 19a were excluded as they had a not applicable option).

Reviewer #2 Comment #15: Page 8, paragraph 3 , line 3: reword and shorten sentence
Response: We have revised the manuscript as per below:

The items reported by the largest proportion of articles (top 10%) were: “2b. Specific objectives or research questions for pilot trial” (97.7%), “4a. Eligibility criteria for participants” (93.0%), “12. Methods used to address each pilot trial objective whether qualitative or quantitative” (97.7%), and “22. Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence” (97.7%).

Reviewer #2 Comment #16: Page 9, paragraph 2, line 5: "7.9%" appears incorrect (not in table)
Response: We have revised the manuscript as per below:
The most poorly reported items (bottom 10%) were: “3b. Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons” (5.8%), “6b. Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons” (3.5%), “6c. When applicable, explanation of any interim analyses and stopping guidelines” (7.9%), and “24. Where the pilot trial protocol can be accessed, if available” (8.1%).

Reviewer #2 Comment #17: Page 9, paragraph 4, line 1: "one of the few" - either state that there are none that you have identified, or cite the ones that do exist. The following may be one you can quote.

Quantity and Reporting Quality of Kidney Research

Markos Kyriakos Tomidis Chatzimanouil, Louise Wilkens and Hans-Joachim Anders

JASN January 2019, 30 (1) 13-22; DOI: https://doi.org/10.1681/ASN.2018050515

Response: We have revised the manuscript as per below:

In this systematic survey, one of the few to examine the completeness of reporting in pilot and feasibility RCTs [14], we found that the mean number of CONSORT extension items for pilot and feasibility studies was 21.4.

...

Previously, reporting quality issues have been identified in clinical trials in nephrology [8, 21-23].

Reviewer #2 Comment #18: Page 10, paragraph 1, line "previously, reporting quality issues have been identified" - which issues?

Response: We have revised the manuscript as per below:

The number of reported items may continue to improve over time, particularly with the 2016 publication of the CONSORT extension for pilot and feasibility RCTs. Indeed, the completeness of reporting full RCTs in nephrology has improved over time, though reporting quality issues for certain CONSORT (2010) items such as clinical trial design, mode of randomization, and intention-to-treat analysis persists [8, 21-23].

Reviewer #2 Comment #19: Page 10, paragraph 2 is a bit repetitive and can likely be shortened

Response: We have revised the manuscript as per below:

Reviewer #2 Comment #20: Page 10, paragraph 2, line 12: 19.5% figure different than 17.4% listed on page 8

Response: We have revised the manuscript as per below:
The low levels of reporting for these items is consistent with our finding that only 17.4% of included studies indicated that they were a prelude to a larger trial, as well as the findings of a previous study on reporting completeness in pilot trials in behavioural interventions (13%) [14].

Reviewer #2 Comment #21: Page 10, paragraph 2, line 12: what percentage of overall trials in other fields indicate that they go on to larger studies (is this consistent with other literature?)

Response: We have revised the manuscript as per below:

The low levels of reporting for these items is consistent with our finding that only 17.4% of included studies indicated that they were a prelude to a larger trial, as well as the findings of a previous study on reporting completeness in pilot trials in behavioural interventions (13%) [14].

Reviewer #2 Comment #22: Page 11, paragraph 1: mentions that studies need to adhere to reporting but some questions (such as 22 which refers to the interpretation being consistent with pilot trial objectives and findings) are at 97% reporting which seems reassuring

Response: We have revised the manuscript as per below:

Though some items were well reported, going forward, it is critical that journals publishing pilot trials in HD patients ensure that these studies adhere to the pilot trial extension to the CONSORT reporting statement, as well as confirm that the primary objectives of these studies are related to feasibility—not efficacy—objectives.

Reviewer #2 Comment #23: Page 11, paragraph 1: states what you believe it's critical for journals to do going forward; please provide some suggestions on how this might be accomplished

Response: We have revised the manuscript as per below:

Though some items were well reported, going forward, it is critical that journals publishing pilot trials in HD patients ensure that these studies adhere to the pilot trial extension to the CONSORT reporting statement, as well as confirm that the primary objectives of these studies are related to feasibility—not efficacy—objectives. This may be accomplished as part of the peer review process or as a requirement of submission.

Reviewer #2 Comment #24: Page 11, paragraph 2, line 3: "though it should be noted that we included international studies" is not necessary

Response: We have revised the manuscript as per below:

We only included English-language studies due to feasibility purposes, which may limit the generalizability of these findings.