PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Primary Outcomes Reporting in Trials of Pediatric Type 1 Diabetes Mellitus: A Systematic Review
AUTHORS	Khanpour Ardestani, Samaneh; Karkhaneh, Mohammad; Yu, Hai Chuan; Hydrie, Muhammad Zafar Iqbal; Vohra, Sunita

VERSION 1 - REVIEW

REVIEWER	Kieran Ayling Research Fellow, University of Nottingham, UK.
REVIEW RETURNED	01-Nov-2016

GENERAL COMMENTS	The paper presents a systematic review of RCTs in paediatric diabetes, conducted since 2001, examining the reporting of primary outcomes, measurements properties and adverse events. The primary conclusion of the manuscript is that reporting in these trials is poor and needs to be improved. In this sense, the manuscript is not particularly novel in that poor standards of reporting has widely been reported previously both generally for RCTs but also for paediatric diabetes specifically (e.g., Ayling, K., Brierley, S., Johnson, B., Heller, S., & Eiser, C. (2014). How standard is standard care? Exploring control group outcomes in behaviour change interventions for young people with type 1 diabetes. Psychology & Health, 30(1), 85–103). That being said, the issue of poor reporting remains prevalent – thus further bringing this to the attention of the research community through publishing manuscripts such like this may still be of benefit and interest to BMJ Open readers. I have a number of specific issues (listed below) with the current version of this manuscript that at present means I cannot recommend its publication without major revisions. 1. My most significant issue is that while I believe the aims of the manuscript is important, I consider the authors main finding that 55% of RCTs do not report their primary outcome is questionable and confused with the issue that RCTs may not identify what their primary outcome is. This semantic distinction is important because it is unclear to me as a reader whether the 55% includes trials in which it was unclear what the researchers considered to be the primary outcome (even if they might have reported outcomes for all variables measured – but just not said which is the 'primary outcome') or if these are trials where the primary outcome was clear but was not reported (which would be a very big issue – and one would question how such trials would get published). I suspect, the 55% refers to trials where what researchers considered to be the primary outcome was not identifiable – but this is very different to not reporting the primary outcome. In revising this manuscript, I would advise the authors to address this distinction and be clear in reporting findings relating to this.

	2. Abstract: In the results section of the abstract, 'used instruments to measure their primary outcome' is vague and uninformative. Please amend. 3. Searches: These were last updated in December 2014, so nearly 2 years ago. As a researcher who conducts systematic reviews I am loathed to ask you to update your searches, as I know the effort involved in doing this. However, at 2 years old the searches are past what should be reasonably acceptable for publication. The authors would strengthen their article by performing and including a search update, or even just a search of a single database such as MEDLINE, restricting to publications since December 2014 to see how many additional trials would have been identified and seeing if these would influence results. 4. Data Analysis: Saying 'statistical tests were performed' is inadequate. Please provide details of the actual tests performed so the appropriateness can be assessed. 5. Data analysis: The grouping by interquartile ranges seems confused. Do you mean fourth quartile for the last batch – as this would make more sense. 6. Adverse Events: Findings related to journal IF's and upwards trends in reporting outcomes seem to be under the subheading of adverse events inappropriately. These findings should be moved higher up or a new subheading provided. 7. Discussion: Authors would be advised to discuss the difference between non-reporting and not specifying primary outcomes, as per point 1. It seems likely that trials do report primary outcomes but do not necessarily explicitly identify them as such. 8. Please include completed PRISMA checklist as an appendix 9. PRISMA flow diagram has been adapted (e.g., no mention of duplicates), authors should either use original diagram or state that this is an adapted version of the diagram.

REVIEWER	Michael Haller University of Florida, USA
REVIEW RETURNED	31-Dec-2016

GENERAL COMMENTS	The authors of this manuscript have provided a systematic review of primary outcomes reporting in Pediatric diabetes trials. The paper is essentially a follow up piece to their previous manuscript demonstrating the poor reporting of primary outcomes in pediatric trials(J Clin Epidemiol. 2016 Sep 22. pii: S0895-4356(16)30425-5. doi: 10.1016/j.jclinepi.2016.09.003). Not surprisingly they report similar findings in this diabetes specific review noting that "clear reporting of primary outcomes of RCTS for pediatric DM is lacking". Overall the manuscript is well written and the methodology is clear, however, the paper does have some considerable weaknesses which could be further improved upon via revision and as it currently reads it fails to add considerable to what has already been published.

	Specific Critiques: 1. Because of the methodology used, the paper essentially focuses on type 1 diabetes studies (n=208). I would recommend that the authors omit the type 2 data (n=5) and focus on the type 1 data and refocus the paper to recognize the fact that the analysis really speaks only to type 1 diabetes 2. The study focuses only on "disease management" studies and not on prevention/intervention studies. This is not clear without reading the "fine print" of the search algorithm and makes the title somewhat misleading for those of us who focus on studies of immunomodulatory therapies to prevent or ameliorate the autoimmune process. I was expecting to read this paper and find some thorough discussion of the merits (or lack thereof) of the 2 hour vs 4 hour MMTT AUC C-peptide or other endpoints related to intervention trials. 3. While the paper states that many papers failed to report their primary outcome clearly the manuscript does not offer a clear recommendation as to what the primary outcomes should be or why they might differ from study to study depending on the studies primary purpose. While I certainly support the basic concept that core outcome sets are needed in all clinical trials reporting, one has to take into account the fact that many clinical trials are seeking to look at different outcomes (i.e. immunotherapies aimed at preserving C-peptide vs two new insulins looking to demonstrate non-inferiority related to hypogylcemia, or A1c). As such, my specific recommendation would be to focus on studies that are of similar intent/purpose and then within those suggest a specific set of core outcomes. Otherwise the paper serves to simply echo the findings of the original paper without adding anything particularly novel to the literature

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name: Kieran Ayling
Institution and Country: Research Fellow, University of Nottingham, UK.

The paper presents a systematic review of RCTs in paediatric diabetes, conducted since 2001, examining the reporting of primary outcomes, measurements properties, and adverse events. The primary conclusion of the manuscript is that reporting in these trials is poor and needs to be improved. In this sense, the manuscript is not particularly novel in that poor standards of reporting has widely been reported previously both generally for RCTs but also for paediatric diabetes specifically (e.g., Ayling, K., Brierley, S., Johnson, B., Heller, S., & Eiser, C. (2014). How standard is standard care? Exploring control group outcomes in behaviour change interventions for young people with type 1 diabetes. Psychology & Health, 30(1), 85–103). That being said, the issue of poor reporting remains prevalent – thus further bringing this to the attention of the research community through publishing manuscripts such like this may still be of benefit and interest to BMJ Open readers.
Answer: Thank you for your valuable feedback. We agree that our work builds on prior publications regarding RCT reporting. Unlike Ayling et al 2014, we highlight the issue of poor reporting of primary outcomes in the pediatric population with type 1 pediatric diabetes mellitus. Development of a core outcome set in this population may help reduce heterogeneity; enhanced primary outcomes reporting will help future efforts at knowledge synthesis.

Comment 1: My most significant issue is that while I believe the aims of the manuscript is important, I consider the authors main finding that 55% of RCTs do not report their primary outcome is questionable and confused with the issue that RCTs may not identify what their primary outcome is. This semantic distinction is important because it is unclear to me as a reader whether the 55% includes trials in which it was unclear what the researchers considered to be the primary outcome (even if they might have reported outcomes for all variables measured – but just not said which is the 'primary outcome') or if these are trials where the primary outcome was clear but was not reported (which would be a very big issue – and one would question how such trials would get published). I suspect, the 55% refers to trials where what researchers considered to be the primary outcome was not identifiable – but this is very different to not reporting the primary outcome. In revising this manuscript, I would advise the authors to address this distinction and be clear in reporting findings relating to this.

Answer: The objective of this study was to identify whether the included RCTs clearly state their primary outcome(s). As emphasized by the CONSORT statement, the primary outcome must be clearly and transparently reported to prevent any confusion for the readers.
In this review, if the authors explicitly specified their primary outcome (we accepted a wide range of terminology and their synonymous terms), that publication was considered as "reported primary outcome". On the other hand, if authors offered a list of outcomes without clearly identifying their primary, we considered this issue as a lack of reporting of the primary outcome(s). We have clarified this in the methods and discussion parts of the paper.

Comment 2: Abstract: In the results section of the abstract, 'used instruments to measure their primary outcome' is vague and uninformative. Please amend.
Answer: We changed that sentence to the following: "used instruments (e.g. questionnaires, scales, etc.) to measure their primary outcome."

Comment 3: Searches: These were last updated in December 2014, so nearly 2 years ago. As a researcher who conducts systematic reviews I am loathed to ask you to update your searches, as I know the effort involved in doing this. However, at 2 years old the searches are past what should be reasonably acceptable for publication. The authors would strengthen their article by performing and including a search update, or even just a search of a single database such as MEDLINE, restricting to publications since December 2014 to see how many additional trials would have been identified and seeing if these would influence results.

Answer: We have updated the search up until January 2017.

Comment 4: Data Analysis: Saying 'statistical tests were performed' is inadequate. Please provide details of the actual tests performed so the appropriateness can be assessed.

Answer: We have clarified that the Chi square test was used.

Comment 5: Data analysis: The grouping by interquartile ranges seems confused. Do you mean fourth quartile for the last batch – as this would make more sense.

Answer: Yes, the fourth quartile is the last batch. It is corrected in the manuscript.

Comment 6: Adverse Events: Findings related to journal IF's and upwards trends in reporting outcomes seem to be under the subheading of adverse events inappropriately. These findings should be moved higher up or a new subheading provided.

Answer: Thank you, a new subheading was added.

Comment 7: Discussion: Authors would be advised to discuss the difference between non-reporting and not specifying primary outcomes, as per point 1. It seems likely that trials do report primary outcomes but do not necessarily explicitly identify them as such.

Answer: This distinction has been amended in the manuscript (as per point 1). If the authors provided a list of several outcomes without clearly stating which one was their main/primary outcome(s), we considered this as a lack of reporting of the primary outcome. Therefore, not specifying the primary outcome was equivalent to not reporting according to CONSORT's reporting guidelines. We clarified this in the method and discussion sections of the manuscript.

Comment 8: Please include completed PRISMA checklist as an appendix
Answer: Completed PRISMA checklist has been included.

Comment 9: PRISMA flow diagram has been adapted (e.g., no mention of duplicates), authors should either use original diagram or state that this is an adapted version of the diagram.
Answer: Thank you, "Adapted version" was added to the legend of the figure 1.

Reviewer: 2
Reviewer Name: Michael Haller
Institution and Country: University of Florida, USA

Comment 1: Because of the methodology used, the paper essentially focuses on type 1 diabetes studies (n=208). I would recommend that the authors omit the type 2 data (n=5) and focus on the type 1 data and refocus the paper to recognize the fact that the analysis really speaks only to type 1 diabetes
Answer: We removed all type 2 diabetes mellitus articles from our review.

Comment 2: The study focuses only on "disease management" studies and not on prevention/intervention studies. This is not clear without reading the "fine print" of the search algorithm and makes the title somewhat misleading for those of us who focus on studies of immunomodulatory therapies to prevent or ameliorate the autoimmune process. I was expecting to read this paper and find some thorough discussion of the merits (or lack thereof) of the 2 hour vs 4 hour MMTT AUC C-peptide or other endpoints related to intervention trials.
Answer: This review focused on studies in children who had already type 1 diabetes mellitus (DM). As a result, preventive studies in participants at risk but not yet diagnosed with type 1 DM were not included, but intervention studies were. For example, if immunomodulatory therapies or studies with MMTT AUC C-peptide as their endpoint met our eligibility criteria including conducted in children less than 21 years old (not mixed with adults) with type 1 DM in a randomized controlled trial; they were included in this review. Our search strategy was comprehensive as we did not focus on specific interventions in this reviews; the main goal of the study was to assess the clarity of reporting of the primary/main outcome.

Comment 3: While the paper states that many papers failed to report their primary outcome clearly the manuscript does not offer a clear recommendation as to what the primary outcomes should be or why they might differ from study to study depending on the studies primary purpose. While I certainly support the basic concept that core outcome sets are needed in all clinical trials reporting, one has to take into account the fact that many clinical trials are seeking to look at different outcomes (i.e. immunotherapies aimed at preserving C-peptide vs two new insulins looking to demonstrate non-inferiority related to hypogylcemia, or A1c). As such, my specific recommendation would be to focus on studies that are of similar intent/purpose and then within those suggest a specific set of core

outcomes. Otherwise the paper serves to simply echo the findings of the original paper without adding anything particularly novel to the literature
Answer: The heterogeneity we identified in intervention trials of pediatric type 1 diabetes mellitus suggest that development of a core outcome set would benefit this field. As different researchers may have different research questions, they may have specific additional outcomes of interest (and some of these may represent the primary outcome(s) of the study), but these would not replace assessment/reporting of the core outcome set. This is the approach suggested by COMET (Core Outcome Measurement in Trials).

The main objective of this systematic review complements the work of COMET. Core outcome sets determine “what” to measure; PORTal assesses how such outcomes are measured.

In our paper, we document both poor reporting (where primary outcomes are not identified) and heterogeneity (where a diverse array of primary outcomes are reported); addressing both would improve published research in this field so that it can be more informative for decision-makers and knowledge synthesis efforts.

VERSION 2 – REVIEW

REVIEWER	Kieran Ayling University of Nottingham, UK
REVIEW RETURNED	26-May-2017

GENERAL COMMENTS	The authors have made appropriate amendments to the manuscript following the first round of peer review and I would suggest this is nearly ready for publication. A couple of minor points below should be addressed prior to this however. 1. The authors have done a good job at clarifying in the revised manuscript that they are assessing the 'clear statement of' or 'identification of' of what each included RCTs primary outcome is/are. This was my primary concern with the original manuscript - as it confuses the issue of poor reporting of what the primary outcome is versus not reporting the primary outcome at all (e.g., as can happen in drug trials where a primary outcome has unfavourable results so they are just never reported). However, there are a few places - most notably the abstract - where some minor wording changes would clarify it further. For example in the abstract results section they write "117 (50.65%) trials failed to report their primary outcome" - this could be 'failed to report what their primary outcome was' or similar to avoid any confusion. 2. Numbers in the abstract to not add up - please check and amend (Third sentence of results bit - 88 + 12 don't equal 114!)

REVIEWER	Michael Haller University of Florida, USA
REVIEW RETURNED	23-May-2017

GENERAL COMMENTS	The authors have reasonably responded to my previous critiques. .

VERSION 2 – AUTHOR RESPONSE

Reviewer 1:
The authors have reasonably responded to my previous critiques.
Answer: Thank you for your valuable comments and suggestions.

Reviewer 2:

The authors have made appropriate amendments to the manuscript following the first round of peer review and I would suggest this is nearly ready for publication. A couple of minor points below should be addressed prior to this however.
Answer: Thank you for your all great comments and suggestions.

1. The authors have done a good job at clarifying in the revised manuscript that they are assessing the 'clear statement of' or 'identification of' of what each included RCTs primary outcome is/are. This was my primary concern with the original manuscript - as it confuses the issue of poor reporting of what the primary outcome is versus not reporting the primary outcome at all (e.g., as can happen in drug trials where a primary outcome has unfavourable results so they are just never reported). However, there are a few places - most notably the abstract - where some minor wording changes would clarify it further. For example in the abstract results section they write "117 (50.65%) trials failed to report their primary outcome" - this could be 'failed to report what their primary outcome was' or similar to avoid any confusion.

Answer: We clarified the sentence in the abstract results section according to your suggestion.

2. Numbers in the abstract to not add up - please check and amend (Third sentence of results bit - 88 + 12 don't equal 114!)

Answer: Thank you. We corrected the mistake in the abstract section.