PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Consent and recruitment: the reporting of pediatric trials published in 2012
AUTHORS	Gates, Allison; Caldwell, Patrina; Curtis, Sarah; Dans, Leonila; Fernandes, Ricardo; Hartling, Lisa; Kelly, Lauren; Williams, Katrina; Woolfall, Kerry; Dyson, Michele

VERSION 1 – REVIEW

REVIEWER	Reviewer name: M.L. Luchtenberg, A.A.E. Verhagen Institution and Country: Department of Pediatrics, Beatrix Children's Hospital, University of Groningen, University Medical Center Groningen. Competing interests: No competing interests.
REVIEW RETURNED	02-Oct-2018

GENERAL COMMENTS	I have read your manuscript with great interest and I think that some small adjustments will improve the quality of your manuscript. Please consider the following: - Objectives (abstract and introduction)): please clarify what you mean by "how trial information was presented" (abstract). In the introduction, you present this objective as follows: "the formats used to present trial information to families". However, in the results and conclusions (abstract) you only present the information about who the information was targeted/directed to, while in our opinion your objective suggests a broader view. (p2, 4.) - Methods – Trial selection: could you explain why you chose the age of 21 as cutoff age? (p5.18) - Methods: to improve the readability, please consider to rephrase some of the sentences of this part (by not beginning every sentence with 'we') (p5. 38 – p6. 22) - Results: it would be helpful for your readers to include a short description of Zelen's design. (p6. 32) - Results: what is meant by 'mature minor'. Since there is much debate on maturity of children, it would be useful to provide your readers with your definition. (p6. 49 + table 1) - Results: consider defining 'school-aged participants'. Do you refer to primary school/high school/other? There might be differences across different countries. (p6. 54 + abstract p2. 23) - Results: How old were children to whom information was targeted only (without information for parents)? Do you have other characteristics of those children? (If aged over 18 you might want to use other naming than 'child') (p9. 18) - Table 2 and table 5: the authors could improve readability by being more consistent in the order of characteristics in the table and description of characteristics in text. - Discussion: the description 'typical presentation' is unclear; please consider rephrasing to improve clarity (p12. 39) - Conclusion: Please specify what kind of knowledge you refer to? "…knowledge translation". (p13. 47)

	I hope my comments are helpful, and I would be very willing to re-review your manuscript after minor revisions were made if the editor appreciates this.

REVIEWER	Reviewer name: Peter Rohloff Institution and Country: Maya Health Alliance – Guatemala. Brigham and Women's Hospital - USA Competing interests: No competing interests
REVIEW RETURNED	03-Oct-2018

GENERAL COMMENTS	This is a very well written article, on an important topic, extending work already done by the authors. I agree with the authors' assessment that periodic evaluation of the quality in reporting and design of pediatric trials is important, and this work is a contribution. Because of the high quality of this work and the writing, I really only have a few minor points: 1. One slightly negative reaction to the article that I have is just that it feels dated - this data extraction was performed in 2013. I definitely appreciate the effort and time required to analyze and prep this kind of data for publication. But I do think in the introduction and discussion section of the manuscript that some additional contextualization is needed to help interpret the shortcomings identified for 2012 studies for 2018. For example, what else do we know from other published literature about trends post 2012 (and post StaR) in the reporting and design of pediatric trials that might be relevant? If we repeated this search on articles published in 2017 what might we hope to find? Some orientation to these observed or expected trends toward improved quality in report and design post 2012 (and relevant initiatives by professional and regulatory bodies) would help the readers better understand where the results reported here fit into the overall 10 or 15 year trend. 2. Can the authors be more explicit about why the report on exclusion of children with chronic/comorbid conditions? I believe this is because of the need for trials to do a better job of reporting on population reach (highly selected vs more generalizable) and not unfairly excluding children with chronic conditions from research. But this could be made explicit. 3. As the authors point out, some features of consent and assent procedures are strongly influenced by cultural norms (age and manner in which assent might be obtained) or local ethical standards - is there any information on variation in some of these reported indicators for LMIC studies, which are a decent proportion of the total number of studies discusssed here? 4. Similarly, there isn't any explicit discussion about why the reporting of incentives is disaggregated by geography but the other outcomes are not. Some discussion about these findings is needed 5. Table 1 disaggregates studies by country income level but Table 3-4 by continent - I'd suggest using income levels in all tables

	6. Missing from the analysis is a comparison of quality of reporting by studies that complied with the CONSORT checklist/were published in CONSORT-enforcing journals vs those that did not/were not. This seems to be an important omission, because consensus trial reporting standards are one of the main mechanisms the field is using to try to improve quality and so I think having a sense of there impact would be helpful.

REVIEWER	Reviewer name: Wim Pinxten Institution and Country: Hasselt University, Belgium Competing interests: NA
REVIEW RETURNED	18-Oct-2018

GENERAL COMMENTS	The paper is well written and addresses the important topic of what public reports reveal about consent procedures, recruitment strategies, incentives etc... The title could be more specific and refer to the 'reporting of pediatric trials', rather than to 'consent and recruitment in pediatric research'. The sample includes 300 studies that report outcomes for participants age 21 years or less. This age cut-off renders the sample very heterogeneous, as paediatric studies in neonates/infants and those in young adults may vary significantly on many of the studied aspects in function of the age of the participants (e.g. consent procedures will be different for a trial in young infants than in one with young adults between 17-21). These limitations could be better specified in the text. The sources for data extraction have been limited to protocols, trial registries and associated publications. Although it is transparently reported that authors were not contacted to obtain more details on recruitment and consent, this remains an important limitation of the study. More details, and more specific analysis (e.g. on what could explain for variations in the incentives) would be helpful. Notwithstanding these minors comments, the paper is interesting, timely and relevant for the readership of the journal.

VERSION 1 – AUTHOR RESPONSE

Response to the Comments from Reviewer 1

I have read your manuscript with great interest and I think that some small adjustments will improve the quality of your manuscript. Please consider the following:

Response: Thank you.

1. Objectives (abstract and introduction)): please clarify what you mean by “how trial information was presented” (abstract). In the introduction, you present this objective as follows: “the formats used to present trial information to families”. However, in the results and conclusions (abstract) you only present the information about who the information was targeted/directed to, while in our opinion your objective suggests a broader view. (p2, 4.)

Response: With regard to “how trial information was presented”, we are referring to how the family heard about the trial and who the trial information was targeted to. Thank you for identifying the inconsistency in our language. To improve consistency and clarity within the text, we have replaced “the formats used to present trial information to families” with “who trial information was targeted to.”

2. Methods – Trial selection: could you explain why you chose the age of 21 as cutoff age? (p5.18)

Response: We included studies that recruited participants aged 0 to 18 years, and trials including both children and adults if the upper age limit was 21 years. These criteria were selected as they are in line with Cochrane Child Health's selection criteria for inclusion of trials within their Trials Register (which originate from CENTRAL). We have added a statement to the Methods to clarify, as follows: "We ordered these randomly in Excel (v. 2016; Microsoft Corporation, Redmond, Washington) and selected the first 300 published trials that: (a) recruited participants aged 0 to 18 years, or (b) recruited both children and adults with an upper age limit of 21 years. The inclusion criteria were selected to match those used by Cochrane Child Health to select trials for their Trials Register (which originate from CENTRAL)."

3. Methods: to improve the readability, please consider to rephrase some of the sentences of this part (by not beginning every sentence with 'we') (p5. 38 – p6. 22)

Response: We appreciate that preferences for the active and passive voice differ from person to person. In the past, the passive voice was recommended in scientific writing due to its impersonal and objective nature. More recently, however, most medical and scientific style manuals support the use of the active over the passive voice. For example, the American Medical Association's AMA Manual of Style and Publication Manual of the American Psychological Association (APA) both recommend using the active instead of the passive voice as much as possible. For this reason, we chose to use the active voice within our manuscript.

Despite recommendations to use the active voice, we do not want it to detract from the readability of the manuscript. As such, we have edited the Methods to use the passive voice for most sentences. We hope that the Methods are now more readable.

4. Results: it would be helpful for your readers to include a short description of Zelen's design. (p6. 32)

Response: We have added a brief explanation of the Zelen's design, as follows: "Zelen's design, whereby participants are randomly allocated to treatment before seeking consent; participants can accept or decline the intervention offered."

5. Results: what is meant by 'mature minor'. Since there is much debate on maturity of children, it would be useful to provide your readers with your definition. (p6. 49 + table 1)

Response: We have added our definition of "mature minor" to the Methods, as follows: "Participants were considered "mature minors" if they were adolescents or young adults aged ≥12 years."

6. Results: consider defining 'school-aged participants'. Do you refer to primary school/high school/other? There might be differences across different countries. (p6. 54 + abstract p2. 23)

Response: We have added our definition of "school-aged participants" to the Methods, as follows: "Children were considered to be of "school age" if they were >5 years old."

7. Results: How old were children to whom information was targeted only (without information for parents)? Do you have other characteristics of those children? (If aged over 18 you might want to use other naming than 'child') (p9. 18)

Response: Thank you for raising this point. The participants in these studies ranged from 12 to 21 years of age, which fits our definition of a "mature minor". For consistency throughout the report, we have changed the text and table to term these participants "mature minors".

8. Table 2 and table 5: the authors could improve readability by being more consistent in the order of characteristics in the table and description of characteristics in text.

Response: You make a good point. We have reordered all tables such that they are now consistent with the text.

9. Discussion: the description ‘typical presentation’ is unclear; please consider rephrasing to improve clarity (p12. 39)

Response: you for informing us that this was not clear. We have elaborated a bit to improve the clarity of this concept, as follows: “Not understanding trial information discourages parents and children from enrolling in trials, and some presentations of the benefits and risks of trial participation (e.g., as dense text documents) can be more difficult for parents to understand.”

10. Conclusion: Please specify what kind of knowledge you refer to? “…knowledge translation”. (p13. 47)

Response: Thank you for informing us that this was not clear. We are referring to translation of evidence-based standards regarding the consent and recruitment procedures for research with children. Although these standards exist, it is possible that they are not presented in a format that is useful or appealing for trialists. Translating these into forms that appeal to trialists and are highly accessible may improve uptake. We have edited the sentence in the conclusion to read as follows: “Using this study as a baseline, continued monitoring of the state of the research will allow for the identification of changes over time and the need for the translation of evidence-based standards into forms that are more appealing and accessible to trialists.”

Response to the Comments from Reviewer 2

This is a very well written article, on an important topic, extending work already done by the authors. I agree with the authors’ assessment that periodic evaluation of the quality in reporting and design of pediatric trials is important, and this work is a contribution. Because of the high quality of this work and the writing, I really only have a few minor points:

Response:Thank you.

1. One slightly negative reaction to the article that I have is just that it feels dated - this data extraction was performed in 2013. I definitely appreciate the effort and time required to analyze and prep this kind of data for publication. But I do think in the introduction and discussion section of the manuscript that some additional contextualization is needed to help interpret the shortcomings identified for 2012 studies for 2018. For example, what else do we know from other published literature about trends post 2012 (and post StaR) in the reporting and design of pediatric trials that might be relevant? If we repeated this search on articles published in 2017 what might we hope to find? Some orientation to these observed or expected trends toward improved quality in report and design post 2012 (and relevant initiatives by professional and regulatory bodies) would help the readers better understand where the results reported here fit into the overall 10 or 15 year trend.

Response: Thank you for bringing up this pertinent point. We can only hypothesize (in the absence of equivalent data from a 2018 sample) that the quality of reporting of pediatric trials has improved over time, based on the previous comparison to 300 trials published in 2007 reported by our research team. We have added some elaboration to the opening Discussion paragraph to elaborate on these thoughts: “Our previous evaluation of risk of bias and trial registration among the same sample of trials and comparison to trials published in 2007 showed that some aspects of trial reporting had improved over time (e.g., reporting of allocation concealment improved and trial registration doubled).

Because the trials evaluated herein were undertaken before the publication of the StaR Child Health Standards (and prior to the development of a number of international pediatric trials initiatives to improve infrastructure and research capacity in child health),10 it is reasonable to speculate that research published today would be more completely reported compared to what we have presented. Nevertheless, reporting shortcomings likely remain and ongoing evaluation of the state of the research will be needed to inform areas in particular need for improvement."

2. Can the authors be more explicit about why the report on exclusion of children with chronic/comorbid conditions? I believe this is because of the need for trials to do a better job of reporting on population reach (highly selected vs more generalizable) and not unfairly excluding children with chronic conditions from research. But this could be made explicit.

Response: Thank you for pointing out that this was not clear. The StaR Child Health Standard on consent and recruitment stipulates that all eligible children should have an equal opportunity to participate in a trial (akin to your comment that children with chronic conditions should not be unfairly excluded from trials). As you mention, the exclusion of children with chronic or co-morbid conditions also renders the results of the research less generalizable to broad populations of children. To clarify in the manuscript, we added the following sentence to the Methods: "Whether children with chronic or co-morbid conditions were excluded was collected to estimate if children were fairly and equitably recruited into the trial." Moreover, in the Introduction we added "approaching all eligible children and not unfairly excluding any children" to our description of ethically-sound recruitment and consent procedures.

3. As the authors point out, some features of consent and assent procedures are strongly influenced by cultural norms (age and manner in which assent might be obtained) or local ethical standards - is there any information on variation in some of these reported indicators for LMIC studies, which are a decent proportion of the total number of studies discussed here?

Response: Thank you for your comment. As you have mentioned, assent and consent procedures will vary by setting depending on local ethical and cultural standards for research participation. Although it is possible that variation in the reported variables exists within our sample, our goal was to describe the quality of reporting of a heterogeneous sample of trials. In this respect, our findings may not be generalizable to research undertaken in specific settings. That said, it was beyond the scope of the present analysis to investigate reports by income level. Moreover, because reporting for many of the variables was so poor, the sample size would diminish substantially if stratified by income level, limiting the ability to identify differences between groups.

In acknowledgement of your comment, we have added a statement to the Limitations section of the manuscript, as follows: "Because the sample included studies that reported on participants aged 0 to 21 years and from countries that varied by income, the sample was highly heterogeneous (i.e., consent procedures are different for infants compared to adolescents and young adults, and are highly influenced by cultural norms and local ethical standards) limiting generalizability to specific age groups or regions by income level. Further investigation into trials examining participants in more discrete age groups (e.g., infants, young children, adolescents) and in regions of a specific income level (e.g., low income, middle income) would be of interest."

4. Similarly, there isn't any explicit discussion about why the reporting of incentives is disaggregated by geography but the other outcomes are not. Some discussion about these findings is needed.

Response: We have added a statement to the Methods to explain the presentation of incentives by country, as follows: "The data on the use of incentives were stratified by continent because allowable incentives for pediatric research vary by region (e.g., the European Union advocates banning all incentive payments for children, while incentive payment for children participating in trials is relatively common in the United States)."

We have also added further elaboration to the Discussion, as follows: “As mentioned previously, allowable payment incentives for children who participate in trials vary by region. As expected, just 4% of studies that recruited in Europe reported providing incentives, all of which were in the form of compensation. Conversely, 28% of studies that recruited in North America reported providing incentives, and 21% percent of these were in the form of payments. Given the poor reporting of incentive use, it was not possible to conclude whether offering incentives improved the chance of attaining the recruitment target. Nevertheless, from the few studies that reported whether or not incentives were used, it did not appear that this was the case.”

5. Table 1 disaggregates studies by country income level but Table 3-4 by continent - I’d suggest using income levels in all tables

Response: Thank you for the comment. As suggested by the Editor in Chief, we have maintained the presentation by continent.

6. Missing from the analysis is a comparison of quality of reporting by studies that complied with the CONSORT checklist/were published in CONSORT-enforcing journals vs those that did not/were not. This seems to be an important omission, because consensus trial reporting standards are one of the main mechanisms the field is using to try to improve quality and so I think having a sense of there impact would be helpful.

Response: We agree that CONSORT-endorsing journals may publish more complete research reports; however, as the focus of this manuscript was specifically the reporting of consent and recruitment, we have not included data regarding the completeness of reporting of other items (as required by CONSORT). We agree that this would be an interesting focus for future investigations.

Of note, our previously published report (based on the same sample of trials) describes the risk of bias, trial registration, and other indicators of trial quality within the sample:

Gates A, Hartling L, Vandermeer B, Caldwell P, Contopoulos-Ioannidis DG, Curtis S, Fernandes RM, Klassen MD, Williams K, Dyson MP. The conduct and reporting of child health research: an analysis of randomized controlled trials published in 2012 and evaluation of change over 5 years. J Pediatr. 2018;193:237-244.

As mentioned, the focus of the current report was the reporting of details related to consent and recruitment. As to not replicate data presented in our previous paper, we have not included additional data related to the reporting of other items.

Response to the Comments from Reviewer 3

The paper is well written and addresses the important topic of what public reports reveal about consent procedures, recruitment strategies, incentives etc... The title could be more specific and refer to the 'reporting of pediatric trials', rather than to 'consent and recruitment in pediatric research'.

Response: Thank you for the suggestion. We have edited the title, which now reads: “Consent and recruitment: the reporting of pediatric trials published in 2012”.

1. The sample includes 300 studies that report outcomes for participants age 21 years or less. This age cut-off renders the sample very heterogeneous, as paediatric studies in neonates/infants and those in young adults may vary significantly on many of the studied aspects in function of the age of the participants (e.g. consent procedures will be different for a trial in young infants than in one with young adults between 17-21). These limitations could be better specified in the text.

Response: Thank you for this comment. We have added this limitation to the Strengths and Limitations section, as follows: “Because the sample included studies that reported on participants aged 0 to 21 years and from countries that varied by income, the sample was highly heterogeneous (i.e., consent procedures are different for infants compared to adolescents and young adults, and are highly influenced by cultural norms and local ethical standards) limiting generalizability to specific age groups or regions by income level. Further investigation into trials examining participants in more discrete age groups (e.g., infants, young children, adolescents) and in regions of a specific income level (e.g., low income, middle income) would be of interest.”

2. The sources for data extraction have been limited to protocols, trial registries and associated publications. Although it is transparently reported that authors were not contacted to obtain more details on recruitment and consent, this remains an important limitation of the study. More details, and more specific analysis (e.g. on what could explain for variations in the incentives) would be helpful.

Response: Thank you for your comment. This is indeed a limitation, as we have mentioned in the Limitations section of the manuscript. Overall, incentive use was very poorly reported, limiting our ability to make any fruitful investigation of the cause of variation between studies. Nevertheless, based on your comment and the comments from Reviewer 2, we have added more detail within the Methods and Discussion with regard to the use of incentives in different regions and cultural groups, and the impact of the use of incentives on recruitment target attainment. Please see our responses to Comment 3 and Comment 4 from Reviewer 2 for further elaboration on the changes that we made within the manuscript.

3. Notwithstanding these minor comments, the paper is interesting, timely and relevant for the readership of the journal.

Response: Thank you.