PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Improved parental understanding by an enhanced informed consent form: a randomized controlled study nested in a pediatric drug trial
AUTHORS	Koonrungsesomboon, Nut; Traivaree, Chanchai; Tiyapsane, Charnunnut; Karbwang, Juntra

VERSION 1 - REVIEW

REVIEWER	David Blanco Universitat Politècnica de Catalunya
REVIEW RETURNED	11-Feb-2019

GENERAL COMMENTS	This report shows the results of an evaluation of the consistency between the CONSORT checklist you submitted and the information that was reported in the manuscript. Please, make the following revisions: • For CONSORT Item 8a ("Method used to generate the random allocation sequence"), please report in the section "Study procedure" how the random allocation sequence was generated. o Example extracted from CONSORT Explanation & Elaboration document: "For allocation of the participants, a computer-generated (R Statistical software) list of random numbers was used". • For CONSORT Item 11a ("If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how") please include in the "Methods" section a subsection called "Blinding" where you report the blinding status of the different parties involved in the study. o Example extracted from CONSORT Explanation & Elaboration document: "Whereas patients and physicians allocated to the intervention group were aware of the allocated arm, outcome assessors and data analysts were kept blinded to the allocation". • For CONSORT Item 13a ("For each group, the numbers of participants who were randomly assigned, received intended treatment and were analysed for the primary outcome"), please include the flow diagram of the study, specifying the numbers of participants who were randomly assigned, received intended treatment, and analysed for the primary outcome. o Example: Please see Fig. 3 in the CONSORT E&E document (http://www.consort-

	statement.org/Media/Default/Downloads/CONSORT%202010%20Explanation%20and%20Elaboration%20Document-BMJ.pdf) • For CONSORT Item 17a ("For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)"), please include for each secondary outcome in Table 2 a measure of the effect size and its precision.

REVIEWER	Ryan Spellecy Medical College of Wisconsin, United States
REVIEW RETURNED	22-Feb-2019

GENERAL COMMENTS	This manuscript provides further empirical evidence for an improved informed consent template, SIDCER, which intends to make the consent form easier to read and improve comprehension. While the SIDCER template has been studied previously, this is the first testing of SIDCER in a pediatric setting, specifically, to compare the understanding of parents who have been asked to give permission for their child to participate in a pediatric drug trial when consent is obtained with an informed consent document created following the SIDCER template, compared to a standard consent form. What creates even more value in this study is the fact that it was embedded within an actual clinical trial. Many enhanced informed consent studies have used a hypothetical setting, meaning they do not test the consent form on persons making a real decision regarding study participation. An important strength of this study is that it was conducted on actual parents deciding whether or not to allow their child to enroll in a clinical trial. Another strength of this paper is that they do an excellent job describing the challenges facing informed consent forms and the informed consent process as a whole, and they place this manuscript clearly among other enhanced consent form research and research on the SIDCER template in other patient populations. Unfortunately, there are two major problems with this study as it is currently written; the sample size justification and lack of detail on the instrument or quiz used to assess comprehension. Regarding sample size, the justification for enrolling 210 parents, with 105 in each arm, is justified based on an a priori estimate. This would be understandable were it not for the fact that there have been other studies using the SIDCER template. The authors need to address why they did not base their sample size calculations on the effect size in those studies. It is possible that those studies had not been published before this study began which would be sufficient explanation, but the authors should explain that. More troubling is that there is no evidence for the comparisons they make across subgroups. The authors provide a statistical justification for the overall sample size, but not the subgroup comparisons. Presumably, there exists a table from their regression analysis. Having a statistician look at that would be helpful. The other major concern is the questionnaire that was administered to test comprehension and compare comprehension between the two groups. The rough topics are described in table 3, and in the abstract they are described as "24 scenario-based questions," but there was no detail regarding how this was

	measured. For example, understanding of the right to refuse and the right to withdraw were evaluated in both the SIDCER and the standard consent groups. How that was evaluated is not explained, leaving the reader to wonder if the questions used to assess understanding were valid. This is another issue, that the validity of the questionnaire is never addressed. If this questionnaire was not validated, it severely limits the importance of these findings. As a reviewer, it was difficult to understand what exactly SIDCER does to improve the informed consent form. The authors do not describe it and they should in a few sentences. Eventually, I was able to track it down following multiple references, some of which are incorrect (Page 8, line 102, the authors state that the SIDCER ICF is comprehensively described elsewhere, reference 15, but reference 15 is a review article for consent improvements). A brief, 2-3 sentence description of SIDCER would help. Some minor points: Page 5, line 57 the authors state that inadequate understanding of a study could jeopardize subject safety. It is not clear how this is the case…via failure to follow study procedures designed to ensure safety? Failure to report adverse events? Page 5 line 60 do should be does. Additional positive features included their analysis of the least understood concepts (again, pending statistical justification) which would indicate promising areas for either modification of SIDCER, future research, or likely both. On page 15 line 228, the discussion of a remaining gap in understanding is very important. The authors note that it is important to look beyond the consent form to the conversation and visualization of complex information, which is essential. These methods have been proven to be effective (albeit visualization has mixed results) in Nishimura et al., cited by the authors. There is also some evidence though that potential research subjects decide whether or not to participate before they even receive the consent form(Kass, Sugarman, Faden, & Schoch-Spana, 1996), or don't read them(Spellecy et al., 2018), which may limit the real-world effectiveness of this study. By sitting with the patients while they read the consent and take the questionnaire, they may have limited the applicability of this study to real-world consent conversations.

REVIEWER	Rebecca Sheridan Department of Health Sciences, University of York, UK
REVIEW RETURNED	28-Feb-2019

GENERAL COMMENTS	General comments Many thanks for asking me to review this interesting paper which discusses an important topic, informed consent in paediatric research. The use of a Randomised Controlled Trial is a good choice of design for this question and the use of CONSORT to report the trial is beneficial. I do note that this appears to be a nested study (or Study Within A Trial, SWAT) so it would be useful to use this terminology in the paper. I think the manuscript would benefit from further proof reading with particular attention to the quality of written English, as there were some areas where this was not up to publication standard. My thanks also to Dr Peter Knapp, with whom I discussed my review.

	Specific comments Abstract As understanding is the primary end point, I think this should be reflected in the objective explicitly. Line 26: Age range of the children? Line 38: As you don't touch on the elements of the ICF in the rest of the abstract and just focus on total scores, I would either amend this to just state that it improved parental understanding or add further detail to the results. Line 38-39: remove unnecessary wording e.g. "Further improvement on the ICF is required as deficiencies in understanding were still prevalent." Introduction Line 54 – 56: this phrasing is awkward, consider revising e.g. "parents have consented to research without understanding the experimental nature of it, the risks involved or even that they are consenting on behalf of their child." Line 56 – 57: rephrase or remove this line, it's not clear how inadequate parental understanding would jeopardize the safety and interest – it's important to understand the risks, but the risks of the trial would be present irrelevant of whether the parent understood the risks were there or not. Line 58 - 62: I think this section could be clearer, simply highlighting that the purpose of the ICF is to provide trial relevant information to decision makers – "disclosure of research information" is ambiguous to me. It would be useful to highlight what is included in an ICF by your definition as, in the UK at least, it can be more conventional to refer to a Participant Information Sheet (PIS) which provides information about the trial, and an attached ICF which participants sign to accept or decline participation. You also note that the ICF can enhance of comprehension – I wonder what this is compared to as ICF are mandatory. Line 62: replace "in theoretical ideal" with "Ideally" Line 67: This is a strong assumption and as such I would expect further references or for it to be attenuated e.g. "It has been suggested that…" Methods The methods section would benefit from greater detail about the SIDCER methodology (e.g. how was the methodology used to develop the SIDCER ICF) and more specific examples of the changes that were made (e.g. was it just layout changes or was the wording changed etc.). Did both ICFs contain the same content? Perhaps the conventional ICF and the SIDCER ICF could be included as appendices. Greater detail about the questionnaire would also be welcome – is it the same as used in your other studies? What kind of responses were available? Perhaps you could include the questionnaire or an example of a scenario and possible responses. Is there any particular reason the thalassemia trial was chosen? A brief sentence on what thalassemia is and what the recruitment criteria are for the trial e.g. age of children etc. may be useful More detail needed about randomisation i.e. were participants blinded to their allocation? Did participants complete a consent form to take part in the ICF study? How were potential participants approached and who made the approach?

	I found the use of the terms “categorical aspect” and “elements” to be confusing throughout the paper. The elements appear to be the individual questions so they could be referred to as such. I would then perhaps just refer to the “categorical aspects” as categories. For example (line 106): “It consisted of 24 scenario-based questions which assessed parental understanding of relevant ICF content in the following categories: general (five questions), rights (four questions)...”. The category titles would also benefit from rephrasing e.g. “Right aspects” is ambiguous. Was there any Patient and Public Involvement in the study? This should be detailed in the methods if yes, if not then a statement to say patients were not involved should be included. I note the acknowledgements state that others provided assistance in reviewing the SIDCER ICF from a laypersons’ perspective – is this the SIDCER ICF used in the study? If yes, I would argue that this is part of the study method in terms of how the SIDCER ICF was developed. Results 210 parents were enrolled to take part, but how many people were approached to read the ICF in each group? Line 149 – 150: present the statistics next to the associated variables for ease of reading. Table 2: There are significant effects for the scientific and ethics aspects, but the total score is the same and the IQR similar – how was the p value calculated? Are these important effects? Participants took less time to read the SIDCER ICF but it was shorter than the conventional ICF so I am unsure how much this adds. The figure and tables need clearer headings. I appreciate this isn’t the main aim of the study, but I was interested in whether you had access to recruitment data for the drug trial to determine whether the ICF impacted on this? Discussion Line 164 – 166: Perhaps rephrase/add detail to the conclusion that the understanding level was significantly greater, as this was only true for some outcomes e.g. primary endpoint, but not the majority of individual questions. Line 166: “This indicates the applicability and effectiveness…” - I am unclear how the study defines and measures the former? Line 169: Independent how? They are conducted by at least some of the same authors. On this point, I note that the proportion of people scoring above 80% on the questionnaire is much higher in these other studies – I wonder if you had any thoughts on this? Line 170 – 175: This part could be reduced and perhaps rephrased to improve the clarity of argument, which I presume is that the SIDCER ICF resulted in greater understanding due to it being “simple, with increased processability”. Line 184: Do you have any empirical evidence of women being more information seeking etc.? Line 188: “Female parents might have had more concern about their child’s participation…” – I am unsure what this means, why would male parents have less concern? Line 191: This sentence needs rewording. Further, can you explain the relatively small number of male participants? For example, if women are more likely to take responsibility of the child’s health care, then perhaps this could also be why more women than men were recruited.

	Line 192 – 2016: This section could be significantly reduced by removing the commentary on why each point in the questionnaire is important as this level of detail doesn't appear relevant here. I would expect instead to see commentary on why improvements might have only been seen for so few of the individual questions. Line 228: Less than perfect understanding is reported generally which raises questions relating to whether the level of informed consent which can be provided by the parents is acceptable. I wondered whether your suggestions for improving understanding were linked to your SIDCER forms, or whether you were suggesting the use of alternative methods instead of the forms? Line 231: The relevance of this line is not clear to me – do children in this study have a relatively poor prognosis and how does this link to the results? Lines 241 – 243: This could be clarified – would understanding not be important for all research irrelevant of risk? Allocation – are groups similar in terms of demographics i.e. most of participants in the ICF group had high school or below and vice versa for the conventional one. Could differences in the sample between the groups have influenced the results? Ethical approval This part is missing.

REVIEWER	Lauren Samuels Vanderbilt University School of Medicine USA
REVIEW RETURNED	08-Jul-2019

GENERAL COMMENTS	This manuscript describes an evaluation of an enhanced informed consent form (ICF) compared to a standard ICF among parents whose children are eligible for participation in research requiring parent consent. The study has the potential to provide valuable insights about parents' comprehension of ICFs, but I have major concerns about the analytical approach, as follows: 1. My main concern is with the choice of primary endpoint. The manuscript gives no justification for the choice of >80% (>= 20/24) correct as a cutoff for "success." By choosing to dichotomize their primary outcome in this way, the authors are effectively asserting that a score of 19 is equivalent to a score of 0, and I doubt seriously that they would want to make such a claim. I recommend dropping the dichotomous endpoint altogether, and instead using the total score as the primary endpoint. For more information on the issue of dichotomizing continuous variables, see, for example, Altman Douglas G, Royston Patrick. The cost of dichotomising continuous variables. BMJ 2006; 332 :1080 https://www.bmj.com/content/332/7549/1080.1. 2. Like the main analysis, any subgroup analyses, if conducted, should use the total score as the outcome of interest. The manuscript currently states, however, that "Subgroup analysis was done to determine the impact of gender, age, and education on the primary endpoint" (lines 131--132), and this is not an appropriate rationale for a subgroup analysis. That is, conducting one analysis in a subgroup of men and another analysis in a subgroup of women does not provide information on the impact of gender on the primary endpoint. If, instead, the authors are interested in

	exploring the possibility that the intervention effect differs by gender, age, and/or education, exploratory analyses using interaction terms would be more appropriate than subgroup analyses. 3. Lines 132--133 say, "Multivariable logistic regression analysis was performed to obtain odds ratio (OR), a measure of association between demographic variables and the primary outcome." After switching the primary outcome to the total score, binary logistic regression will no longer be appropriate here; but regardless of the outcome variable, this is an odd justification for the use of multivariable regression in the context of a randomized trial. I would have expected a rationale along the lines of "to obtain a more precise estimate of the effect of the intervention." See, for example, Covariate adjustment increases statistical power in randomized controlled trials Lingsma, Hester, Roozenbeek, BobS, teyerberg, Ewout et al., Journal of Clinical Epidemiology, Volume 63, Issue 12, 1391 https://www.jclinepi.com/article/S0895-4356(10)00188-5/fulltext. The model itself, or at the very least a clear description of the covariates and their functional forms, should be included in the Data Analysis section, and the full model results should also be included in the paper or an appendix. Based on the limited information presented, the interpretation of the model results in lines 147--150 strikes me as almost certainly incorrect--- multivariable regression cannot tell us whether two things are "independently associated." The interpretation on line 151 is almost certainly incorrect as well, as a high p-value is not evidence of a lack of association. Other concerns: - Lines 90--91 say that "any refusal to read an ICF given was respected," but the manuscript provides no flowchart of sample size/refusals. - Rather than dichotomizing age, Table 1 should give the medians and interquartile ranges of age in the two groups. - The footnote to Table 2 should include the type of significance test used. - Table 3 should have a footnote giving the method used to calculate p-values and confidence intervals. - The caption on Fig 1 is incorrect--- the plot does not show proportions. With the switch to using the total score as the primary endpoint, however, this figure will need to be replaced by a different presentation of results altogether.

VERSION 1 – AUTHOR RESPONSE

Response to Reviewers

Reviewer: 1

Reviewer Name: David Blanco

Institution and Country: Universitat Politècnica de Catalunya

Please state any competing interests or state ‘None declared’: None declared

Comment:

This report shows the results of an evaluation of the consistency between the CONSORT checklist you submitted and the information that was reported in the manuscript. Please, make the following revisions:

• For CONSORT Item 8a (“Method used to generate the random allocation sequence”), please report in the section “Study procedure” how the random allocation sequence was generated.

o Example extracted from CONSORT Explanation & Elaboration document: “For allocation of the participants, a computer-generated (R Statistical software) list of random numbers was used”.

Answer:

We have revised the manuscript according to the reviewer’s comment, and it now reads “For allocation of the parents, a computer-generated list of random numbers was applied, and a randomization code was packed in an opaque sealed envelope before subject enrollment to this ICF study.” [Page 10, Line 133-135]

Comment:

• For CONSORT Item 11a (“If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how") please include in the “Methods” section a subsection called “Blinding” where you report the blinding status of the different parties involved in the study.

o Example extracted from CONSORT Explanation & Elaboration document: “Whereas patients and physicians allocated to the intervention group were aware of the allocated arm, outcome assessors and data analysts were kept blinded to the allocation”.

Answer:

This study was an open-label, randomized-controlled study; there was no blinding. In the revised manuscript, it reads “This open-label, randomized-controlled study determined the effectiveness of two different ICFs – the SIDCER ICF and the conventional ICF (1:1) – on parental understanding of research-related information.” [Page 8, Line 88-90]

Comment:

• For CONSORT Item 13a (“For each group, the numbers of participants who were randomly assigned, received intended treatment and were analysed for the primary outcome”), please include the flow diagram of the study, specifying the numbers of participants who were randomly assigned, received intended treatment, and analysed for the primary outcome.

o Example: Please see Fig. 3 in the CONSORT E&E document (http://www.consort-statement.org/Media/Default/Downloads/CONSORT%202010%20Explanation%20and%20Elaboration%20Document-BMJ.pdf)

Answer:

In the revised manuscript, we have added Fig. 1 to display the flow diagram of the study according to the reviewer’s suggestion.

Comment:

• For CONSORT Item 17a (“For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)”), please include for each secondary outcome in Table 2 a measure of the effect size and its precision.

Answer:

In the revised manuscript, we have included the estimated effect size and its precision in Table 2 according to the reviewer’s suggestion.

Reviewer: 2

Reviewer Name: Ryan Spellecy

Institution and Country: Medical College of Wisconsin, United States

Please state any competing interests or state ‘None declared’: None declared

Comment:

This manuscript provides further empirical evidence for an improved informed consent template, SIDCER, which intends to make the consent form easier to read and improve comprehension. While the SIDCER template has been studied previously, this is the first testing of SIDCER in a pediatric setting, specifically, to compare the understanding of parents who have been asked to give permission for their child to participate in a pediatric drug trial when consent is obtained with an informed consent document created following the SIDCER template, compared to a standard consent form. What creates even more value in this study is the fact that it was embedded within an actual clinical trial. Many enhanced informed consent studies have used a hypothetical setting, meaning they do not test the consent form on persons making a real decision regarding study participation. An

important strength of this study is that it was conducted on actual parents deciding whether or not to allow their child to enroll in a clinical trial.

Answer:

Thank you for your comments.

Comment:

Another strength of this paper is that they do an excellent job describing the challenges facing informed consent forms and the informed consent process as a whole, and they place this manuscript clearly among other enhanced consent form research and research on the SIDCER template in other patient populations.

Answer:

Thank you for your comments.

Comment:

Unfortunately, there are two major problems with this study as it is currently written; the sample size justification and lack of detail on the instrument or quiz used to assess comprehension. Regarding sample size, the justification for enrolling 210 parents, with 105 in each arm, is justified based on an a priori estimate. This would be understandable were it not for the fact that there have been other studies using the SIDCER template. The authors need to address why they did not base their sample size calculations on the effect size in those studies. It is possible that those studies had not been published before this study began which would be sufficient explanation, but the authors should explain that.

Answer:

Thank you for pointing this out. Indeed, the sample size in this study was based on the findings in our first ICF study [1]. We have added this information in the revised manuscript, and it now reads “This ICF study planned to enroll 210 parents (with 105 parents in each arm), based on an a priori estimate to detect the hypothesized effect size of 20% difference between two independent proportions of the primary endpoint (p1 = 0.8 and p2 = 0.6), with the precision and confidence level of 95%, 80% power and allocation ratio of 1, with a continuity correction. This hypothesized effect size was based on the findings in our previous study.” [Page 8-9, Line 102-106]

Reference:

[1] Koonrungsesomboon N, Teekachunhatean S, Hanprasertpong N, Laothavorn J, Na-Bangchang K, Karbwang J. Improved participants' understanding in a healthy volunteer study using the SIDCER informed consent form: a randomized-controlled study. Eur J Clin Pharmacol. 2016;72(4):413-21.

Regarding details about the questionnaire, we have added more details with one more reference [1] to address another concern raised by the reviewer. In the revised manuscript, it now reads “Parental understanding of essential research-related information was measured using the questionnaire (in Thai), which was modified from our previous studies.” [Page 9, Line 121-122] “Each question with three possible answers was structured in a way that the parents would have had to apply their understanding of information given in an ICF to the scenario.” [Page 10, Line 125-127]

Reference:

[1] Koonrungsesomboon N, Laothavorn J, Karbwang J. Understanding of essential elements required in informed consent form among researchers and institutional review board members. Trop Med Health. 2015;43(2):117-22.

Comment:

More troubling is that there is no evidence for the comparisons they make across subgroups. The authors provide a statistical justification for the overall sample size, but not the subgroup comparisons. Presumably, there exists a table from their regression analysis. Having a statistician look at that would be helpful.

Answer:

Another reviewer also mentioned on this issue, so we have reconsidered our statistical analysis. We have removed ‘subgroup analysis’ but added ‘multivariable regression analysis’ in the revised manuscript. Please refer to Page 11, Line 149-160, in the revised manuscript.

Comment:

The other major concern is the questionnaire that was administered to test comprehension and compare comprehension between the two groups. The rough topics are described in table 3, and in the abstract they are described as “24 scenario-based questions,” but there was no detail regarding how this was measured. For example, understanding of the right to refuse and the right to withdraw were evaluated in both the SIDCER and the standard consent groups. How that was evaluated is not explained, leaving the reader to wonder if the questions used to assess understanding were valid. This is another issue, that the validity of the questionnaire is never addressed. If this questionnaire was not validated, it severely limits the importance of these findings.

Answer:

We have added more details regarding how the comprehension was measured [1]. In the revised manuscript, it now reads “Each question with three possible answers was structured in a way that the parents would have had to apply their understanding of information given in an ICF to the scenario.” [Page 10, Line 125-127] Moreover, the validity of the questionnaire was tested in our previous study [2]. In the revised manuscript, we have put additional references to address the issue of the validity of the questionnaire. It now reads “Parental understanding of essential research-related information was measured using the questionnaire (in Thai), which was modified from our previous study.” [Page 9, Line 121-122]

Reference:

[1] Koonrungsesomboon N, Laothavorn J, Karbwang J. Understanding of essential elements required in informed consent form among researchers and institutional review board members. Trop Med Health. 2015;43(2):117-22.

[2] Koonrungsesomboon N, Teekachunhatean S, Hanprasertpong N, Laothavorn J, Na-Bangchang K, Karbwang J. Improved participants' understanding in a healthy volunteer study using the SIDCER informed consent form: a randomized-controlled study. Eur J Clin Pharmacol. 2016;72(4):413-21.

Comment:

As a reviewer, it was difficult to understand what exactly SIDCER does to improve the informed consent form. The authors do not describe it and they should in a few sentences. Eventually, I was able to track it down following multiple references, some of which are incorrect (Page 8, line 102, the authors state that the SIDCER ICF is comprehensively described elsewhere, reference 15, but reference 15 is a review article for consent improvements). A brief, 2-3 sentence description of SIDCER would help.

Answer:

A brief description of the SIDCER ICF has been added in the revised manuscript. It now reads “In brief, essential information as is relevant to the parents’ decision making was summarized in the SIDCER ICF template (available from http://ijme.in/pdf/appendix-1.pdf?v=1) in a narrative and illustrative manner, according to the SIDCER ICF principles. The drafted SIDCER ICF was, then, reviewed by laypersons to enhance the readability and understandability of written information.” [Page 9, Line 114-118] Moreover, what the SIDCER ICF methodology does to improve the ICF has been discussed in the revised manuscript. It now reads “In line with a recent integrative review on informed consent, it is reasonable to assume that the evidence of improved participants’ understanding by the SIDCER ICF is largely attributable to its simplicity and concise format with increased processability (using summary boxes, highlights, and illustrations, when appropriate).” [Page 14, Line 188-192]

Comment:

Some minor points: Page 5, line 57 the authors state that inadequate understanding of a study could jeopardize subject safety. It is not clear how this is the case … via failure to follow study procedures designed to ensure safety? Failure to report adverse events? Page 5 line 60 do should be does.

Answer:

Considering your comment and another reviewer’s comment on this point, we have removed that sentence in the revised manuscript.

Comment:

Additional positive features included their analysis of the least understood concepts (again, pending statistical justification) which would indicate promising areas for either modification of SIDCER, future

research, or likely both. On page 15 line 228, the discussion of a remaining gap in understanding is very important. The authors note that it is important to look beyond the consent form to the conversation and visualization of complex information, which is essential. These methods have been proven to be effective (albeit visualization has mixed results) in Nishimura et al., cited by the authors. There is also some evidence though that potential research subjects decide whether or not to participate before they even receive the consent form (Kass, Sugarman, Faden, & Schoch-Spana, 1996), or don't read them (Spellecy et al., 2018), which may limit the real-world effectiveness of this study. By sitting with the patients while they read the consent and take the questionnaire, they may have limited the applicability of this study to real world consent conversations.

Answer:

Thank you for your comment. While informed consent is a process that should involve interactive dialogue, an ICF also matters a great deal. A well-written ICF could guarantee that sufficient information is provided, while informed consent discussion with research staff may vary from one participant to another and may be soon forgotten. An ICF is also a written document that an independent ethics committee (IEC) can review, edit, and approve, whereas an IEC usually has little control over informal conversations that take place between research staff and research participants [1]. In the introduction of the manuscript, we stated that "Although the form alone may not be sufficient to achieve a proper, valid consent, it can and do serve multiple purposes in clinical trials, including the assurance of complete disclosure of information and enhancement of participants' comprehension." [Page 6, Line 64-67] Despite the importance of ICFs, the literature indicates that the quality of ICFs used in clinical studies is problematic due mainly to the extensive length and complexity [2, 3]. As such, improving the quality of ICFs is one of the pending issues in research ethics with the intention of strengthening the application of the basic principle of respect for persons in clinical research. Therefore, real-world consent conversations do not limit the applicability of this study. To be clearer on this point, we have added the term "In addition to" [Page 16, Line 221] in the revised manuscript in order to emphasize that both ICFs and conversation are important.

Reference:

[1] Resnik DB. Do informed consent documents matter? Contemp Clin Trials. 2009;30(2):114-5.

[2] Berger O, Gronberg BH, Sand K, Kaasa S, Loge JH. The length of consent documents in oncological trials is doubled in twenty years. Ann Oncol. 2009;20(2):379-85.

[3] Kass NE, Chaisson L, Taylor HA, Lohse J. Length and complexity of US and international HIV consent forms from federal HIV network trials. J Gen Intern Med. 2011;26(11):1324-8.

Reviewer: 3

Reviewer Name: Rebecca Sheridan

Institution and Country: Department of Health Sciences, University of York, UK

Please state any competing interests or state 'None declared': None declared.

Comment:

General comments

Many thanks for asking me to review this interesting paper which discusses an important topic, informed consent in paediatric research. The use of a Randomised Controlled Trial is a good choice of design for this question and the use of CONSORT to report the trial is beneficial. I do note that this appears to be a nested study (or Study Within A Trial, SWAT) so it would be useful to use this terminology in the paper. I think the manuscript would benefit from further proof reading with particular attention to the quality of written English, as there were some areas where this was not up to publication standard. My thanks also to Dr Peter Knapp, with whom I discussed my review.

Answer:

We have revised the title of this paper to add the term “nested”, and it now reads “Improved parental understanding by an enhanced informed consent form: a randomized controlled study nested in a pediatric drug trial.” [Page 1, Line 2-3] We do proof reading with particular attention to the quality of written English, as suggested.

Comment:

Specific comments

Abstract

As understanding is the primary end point, I think this should be reflected in the objective explicitly.

Line 26: Age range of the children?

Line 38: As you don’t touch on the elements of the ICF in the rest of the abstract and just focus on total scores, I would either amend this to just state that it improved parental understanding or add further detail to the results.

Line 38-39: remove unnecessary wording e.g. “Further improvement on the ICF is required as deficiencies in understanding were still prevalent.”

Answer:

We have revised the manuscript according to the reviewer’s suggestion. In the revised manuscript, it now reads “The objective of this study was to compare the parental understanding of information between the parents who read the SIDCER ICF and those who read the conventional ICF.” [Page 3, Line 26-27]

Note that the study population in this paper was parents of children, so age range of the children is not applicable. In the revised manuscript, it now reads “210 parents of children with thalassemia (age = 35.6 ± 13.1 years).” [Page 3, Line 30]

In the revised manuscript, the statement “Further improvement on the ICF is required as deficiencies in understanding were still prevalent” has been removed. The conclusion of the abstract section now reads “The SIDCER ICF was found to be superior to the conventional ICF in improving parental understanding of trial information.” [Page 4, Line 41-42]

Comment:

Introduction

Line 54 – 56: this phrasing is awkward, consider revising e.g. “parents have consented to research without understanding the experimental nature of it, the risks involved or even that they are consenting on behalf of their child.”

Answer:

We have revised the manuscript according to the reviewer’s suggestion, and it now reads “some parents have consented to research without understanding the experimental nature of it and the risks involved, or even that they are consenting on behalf of their child.” [Page 6, Line 59-61]

Comment:

Line 56 – 57: rephrase or remove this line, it’s not clear how inadequate parental understanding would jeopardize the safety and interest – it’s important to understand the risks, but the risks of the trial would be present irrelevant of whether the parent understood the risks were there or not.

Answer:

After reconsidering, we have removed this phrase from the introduction section.

Comment:

Line 58 - 62: I think this section could be clearer, simply highlighting that the purpose of the ICF is to provide trial relevant information to decision makers – “disclosure of research information” is ambiguous to me. It would be useful to highlight what is included in an ICF by your definition as, in the UK at least, it can be more conventional to refer to a Participant Information Sheet (PIS) which provides information about the trial, and an attached ICF which participants sign to accept or decline participation. You also note that the ICF can enhance of comprehension – I wonder what this is compared to as ICF are mandatory.

Answer:

The collective term ‘Informed consent form’ consists of two parts: the participant information sheet and the consent certificate (Reference from https://www.who.int/rpc/research_ethics/informed_consent/en/). To be more specific, we have revised the manuscript, and it now reads “An informed consent form (ICF) serves as a mandatory document to provide trial relevant information to the participants/surrogate decision makers and document their consent; it consists of the information sheet and the consent certificate.” [Page 6, Line 62-64]

Comment:

Line 62: replace “in theoretical ideal” with “Ideally”

Answer:

We have revised the manuscript according to the reviewer’s suggestion. [Page 6, Line 67]

Comment:

Line 67: This is a strong assumption and as such I would expect further references or for it to be attenuated e.g. “It has been suggested that…”

Answer:

We have revised the manuscript according to the reviewer’s suggestion, and it now reads “It has been suggested that the written language in quite a few ICFs stems from a desire to provide legal protection to investigators and sponsors rather than one designed to inform participants/surrogates for rational decision making.” [Page 7, Line 72-74]

Comment:

Methods

The methods section would benefit from greater detail about the SIDCER methodology (e.g. how was the methodology used to develop the SIDCER ICF) and more specific examples of the changes that were made (e.g. was it just layout changes or was the wording changed etc.). Did both ICFs contain the same content? Perhaps the conventional ICF and the SIDCER ICF could be included as appendices.

Greater detail about the questionnaire would also be welcome – is it the same as used in your other studies? What kind of responses were available? Perhaps you could include the questionnaire or an example of a scenario and possible responses.

Answer:

We have added details about the SIDCER methodology in the revised manuscript, and it now reads “In brief, essential information as is relevant to the parents’ decision making was summarized in the SIDCER ICF template (available from http://ijme.in/pdf/appendix-1.pdf?v=1) in a narrative and illustrative manner, according to the SIDCER ICF principles. The drafted SIDCER ICF was, then, reviewed by laypersons to enhance the readability and understandability of written information. Both conventional and SIDCER ICFs contained the same content.” [Page 9, Line 114-119] The structure of the questions and responses in the questionnaire was similar to our previous studies [1-3]. In the revised manuscript, it now reads “Parental understanding of essential research-related information was measured using the questionnaire (in Thai), which was modified from our previous study. ... Each question with three possible answers was structured in a way that the parents would have had to apply their understanding of information given in an ICF to the scenario.” [Page 9, Line 121-127]

Reference:

[1] Koonrungsesomboon N, Teekachunhatean S, Hanprasertpong N, Laothavorn J, Na-Bangchang K, Karbwang J. Improved participants' understanding in a healthy volunteer study using the SIDCER informed consent form: a randomized-controlled study. Eur J Clin Pharmacol. 2016;72(4):413-21.

[2] Koonrungsesomboon N, Tharavanij T, Phiphatpatthamaamphan K, Vilaichone RK, Manuwong S, Curry P, et al. Improved participants' understanding of research information in real settings using the SIDCER informed consent form: a randomized-controlled informed consent study nested with eight clinical trials. Eur J Clin Pharmacol. 2017;73(2):141-9.

[3] Koonrungsesomboon N, Traivaree C, Chamnanvanakij S, Rungtragoolchai P, Thanapat Y, Karbwang J. Improved pregnant women's understanding of research information by an enhanced informed consent form: a randomised controlled study nested in neonatal research. Arch Dis Child Fetal Neonatal Ed. 2018;103(5):F403-F407.

Comment:

Is there any particular reason the thalassemia trial was chosen? A brief sentence on what thalassemia is and what the recruitment criteria are for the trial e.g. age of children etc. may be useful.

Answer:

We chose the thalassemia trial because it was a pediatric study requiring parental consent and it was being conducted during that time. We have revised the manuscript according to the reviewer's suggestion, and it now reads "They were invited to read either the SIDCER ICF or the conventional ICF (by random assignment) for possible enrollment of their child (aged 1-18 years) in a drug trial which investigated the effects of furosemide on markers of volume overload in children with transfusion-dependent thalassemia." [Page 8, Line 96-99]

Comment:

More detail needed about randomisation i.e. were participants blinded to their allocation?

Answer:

We have added more details about randomization and allocation. In the revised manuscript, it now reads "For allocation of the parents, a computer-generated list of random numbers was applied, and a randomization code was packed in an opaque sealed envelope before subject enrollment to this ICF study." [Page 10, Line 133-135]

Comment:

Did participants complete a consent form to take part in the ICF study? How were potential participants approached and who made the approach?

Answer:

Informed consent was obtained verbally and by action, provided that answering the questionnaire inferred the parents' consent to this ICF study. We have revised the manuscript to address the reviewer's comment, and it now reads "Parents of children with transfusion-dependent thalassemia were informed about this ICF study and were recruited by study nurse at the Pediatric Outpatients Department, Phramongkutklao Hospital, Bangkok, Thailand. ... Informed consent was obtained verbally and by action, provided that answering the questionnaire inferred their consent for participation in this ICF study." [Page 8, Line 94-101]

Comment:

I found the use of the terms "categorical aspect" and "elements" to be confusing throughout the paper. The elements appear to be the individual questions so they could be referred to as such. I would then perhaps just refer to the "categorical aspects" as categories. For example (line 106): "It consisted of 24 scenario-based questions which assessed parental understanding of relevant ICF content in the following categories: general (five questions), rights (four questions) ...". The category titles would also benefit from rephrasing e.g. "Right aspects" is ambiguous.

Answer:

We have revised the manuscript according to the reviewer's suggestion, and it now reads "It consisted of 24 scenario-based questions which assessed parental understanding of relevant ICF content in the following categories: general items (five questions), patient's rights (four questions), scientific aspects (eight questions), and ethics aspects (seven questions)." [Page 9-10, Line 122-125] Also, the category titles in Table 3 have been revised.

Comment:

Was there any Patient and Public Involvement in the study? This should be detailed in the methods if yes, if not then a statement to say patients were not involved should be included. I note the acknowledgements state that others provided assistance in reviewing the SIDCER ICF from a laypersons' perspective – is this the SIDCER ICF used in the study? If yes, I would argue that this is part of the study method in terms of how the SIDCER ICF was developed.

Answer:

We have added the participant and public involvement section in the revised manuscript, and it now reads "The present study did not involve participants or publics during the development of research question and outcome measures as well as in the study design and recruitment plan. Participant burden was not assessed formally, but assumed to be low. Results will be disseminated via this publication, with a lay summary of the results in Thai." [Page 11, Line 145-148] With regard to the development of the SIDCER ICF, we have added "The drafted SIDCER ICF was, then, reviewed by laypersons …" in the method section as suggested. [Page 9, Line 116-118]

Comment:

Results

210 parents were enrolled to take part, but how many people were approached to read the ICF in each group?

Answer:

A total of 210 parents were approached and 210 parents (100%) were enrolled. In the revised manuscript, we have added Fig. 1 to display a flow diagram of this ICF study.

Comment:

Line 149 – 150: present the statistics next to the associated variables for ease of reading.

Answer:

After considering the overall comments from four reviewers, we have decided to delete that statement in the revised manuscript.

Comment:

Table 2: There are significant effects for the scientific and ethics aspects, but the total score is the same and the IQR similar – how was the p value calculated? Are these important effects?

Answer:

We have revised statistical analysis according to another reviewer's comment. In the revised manuscript, we have added the statistical method used to calculate p value in Table 2.

Comment:

Participants took less time to read the SIDCER ICF but it was shorter than the conventional ICF so I am unsure how much this adds.

Answer:

This demonstrated that the SIDCER ICF methodology could make an ICF more concise while complying with all regulatory requirements. A more concise (and simple) ICF reflected in less time spent reading an ICF.

Comment:

The figure and tables need clearer headings.

Answer:

We have revised the headings of Table 2 and Table 3, and it now reads “Table 2 Comparisons of the total score, the score in each category of the ICF content, and time spent between the two groups” and “Table 3 Comparisons of the parental understanding of each element of the ICF content between the two groups.” [Page 25-26]

Comment:

I appreciate this isn’t the main aim of the study, but I was interested in whether you had access to recruitment data for the drug trial to determine whether the ICF impacted on this?

Answer:

We agree with you that this information would be interesting, but unfortunately we did not collect the data to enable analysis for this aim.

Comment:

Discussion

Line 164 – 166: Perhaps rephrase/add detail to the conclusion that the understanding level was significantly greater, as this was only true for some outcomes e.g. primary endpoint, but not the majority of individual questions.

Line 166: “This indicates the applicability and effectiveness…” - I am unclear how the study defines and measures the former?

Answer:

We have revised those two sentences according to the reviewer’s comment, and it now reads “This is the first randomized-controlled study which was designed to test the applicability and effectiveness of the SIDCER ICF methodology in a setting of pediatric drug trial. The SIDCER ICF was found to be superior to the conventional ICF in improving parental understanding of several elements of the ICF content.” [Page 14, Line 183-186]

Comment:

Line 169: Independent how? They are conducted by at least some of the same authors. On this point, I note that the proportion of people scoring above 80% on the questionnaire is much higher in these other studies – I wonder if you had any thoughts on this?

Answer:

We have removed the term ‘independent’ from that sentence, and it now reads “The overall results of this study are consistent with three previous informed consent studies that exhibited the improvement of participants’ understanding by the SIDCER ICF.” [Page 14, Line 186-188] Also, we noticed that the proportion of people scoring above 80% on the questionnaire is higher in other studies than in the present study. One hypothesis is that different groups of population may have different levels of attention and comprehension. This is why testing of the SIDCER ICF methodology in various settings (involving diverse groups of population) is required.

Comment:

Line 170 – 175: This part could be reduced and perhaps rephrased to improve the clarity of argument, which I presume is that the SIDCER ICF resulted in greater understanding due to it being “simple, with increased processability”.

Answer:

We have rephrased the statement according to the reviewer’s suggestion, and it now reads “In line with a recent integrative review on informed consent, it is reasonable to assume that the evidence of improved participants’ understanding by the SIDCER ICF is largely attributable to its simplicity and concise format with increased processability (using summary boxes, highlights, and illustrations, when appropriate).” [Page 14, Line 188-192]

Comment:

Line 184: Do you have any empirical evidence of women being more information seeking etc.?

Line 188: “Female parents might have had more concern about their child’s participation…” – I am unsure what this means, why would male parents have less concern?

Line 191: This sentence needs rewording. Further, can you explain the relatively small number of male participants? For example, if women are more likely to take responsibility of the child’s health care, then perhaps this could also be why more women than men were recruited.

Answer:

Because we have revised statistical analysis according to another reviewer’s suggestion, we have deleted this paragraph in the revised manuscript.

Comment:

Line 192 – 216: This section could be significantly reduced by removing the commentary on why each point in the questionnaire is important as this level of detail doesn’t appear relevant here. I would

expect instead to see commentary on why improvements might have only been seen for so few of the individual questions.

Answer:

We have revised this paragraph according to the reviewer's comment, and it now reads "Close examination of the data revealed that the SIDCER ICF was superior to the conventional ICF in improving the parental understanding of trial information in five elements: who can access the data, right to receive new information, identification of experimental procedures, alternative course of treatment, and number of subjects required. The first three elements were highlighted and made salient in the SIDCER ICF, whereas the same content was ordinarily described in the conventional ICF. It is reasonable to assume that a higher understanding of these three elements in the SIDCER ICF group was partly attributed to a complementary technique being used to convey key information. This might be the evidence to support that increased processability of key or complex information in an ICF could contribute to a significant improvement in parental understanding of such information." [Page 14-15, Line 193-202]

Comment:

Line 228: Less than perfect understanding is reported generally which raises questions relating to whether the level of informed consent which can be provided by the parents is acceptable. I wondered whether your suggestions for improving understanding were linked to your SIDCER forms, or whether you were suggesting the use of alternative methods instead of the forms?

Answer:

Some suggestions were linked to the SIDCER ICF, while some were related to additional methods that can be concomitantly used to improve (or ensure) parental understanding in pediatric research. We have revised the manuscript to improve the clarity according to the reviewer's comment, and it now reads "It may be worthwhile to consider using more graphics or pictographs to enhance visualization of complex information in the SIDCER ICF, and further research may be required to determine the effectiveness of such additional means, especially in this group of population. In addition to the enhanced ICF, a dialogue between the investigator (or a person designated by the investigator) and the parents are still indispensable, while complimentary methods of delivering trial-related information (e.g., a multimedia video and website) may be warranted in some studies." [Page 15-16, Line 218-224]

Comment:

Line 231: The relevance of this line is not clear to me – do children in this study have a relatively poor prognosis and how does this link to the results?

Answer:

After reconsidering, we have removed that statement in the revised manuscript.

Comment:

Lines 241 – 243: This could be clarified – would understanding not be important for all research irrelevant of risk?

Answer:

Participants' understanding is important for all research irrespective of the level of risks. However, the process of informed consent should also be adapted to the level of research risks in order to provide adequate protection to research participants but avoid excessive burden to investigators and impeding socially valuable research [1]. It has been suggested that a formal evaluation of potential participants' (or surrogate decision makers') understanding prior to participation in high-risk research may be a reasonable, additional duty in the informed consent process, while informal testing may be sufficient in research involving low-to-moderate risks [1, 2].

Reference:

[1] Bromwich D, Rid A. Can informed consent to research be adapted to risk? J Med Ethics. 2015;41(7):521-8.

[2] Wendler D. How to enroll participants in research ethically. JAMA. 2011;305(15):1587-8.

Comment:

Allocation – are groups similar in terms of demographics i.e. most of participants in the ICF group had high school or below and vice versa for the conventional one. Could differences in the sample between the groups have influenced the results?

Answer:

According to the CONSORT 2010 statement, "significance testing of baseline differences in randomized controlled trials (RCTs) should not be performed, because it is superfluous and can mislead investigators and their readers" [1]. In fact, whether baseline differences are statistically significantly different does not have any implications for the validity of the results of a randomized-controlled study [2, 3]. Recently, de Boer and colleagues have clearly described evidence as to why testing for baseline differences between intervention groups serves no purpose and should not be done [4]. In brief, this 'unhealthy research practice' ignores the prognostic strength of covariates, which is more important characteristic when the interest is in adjustment for confounding. In other words, choosing covariates based on significant tests for baseline differences might lead to exclusions of some (important) covariates and, perhaps, to inclusion of only some (irrelevant) covariates in the analysis [4].

Reference:

[1] Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c869.

[2] Knol MJ, Groenwold RH, Grobbee DE. P-values in baseline tables of randomised controlled trials are inappropriate but still common in high impact journals. Eur J Prev Cardiol. 2012;19(2):231-2.

[3] Roberts C, Torgerson DJ. Understanding controlled trials: baseline imbalance in randomised controlled trials. BMJ. 1999;319(7203):185.

[4] de Boer MR, Waterlander WE, Kuijper LD, Steenhuis IH, Twisk JW. Testing for baseline differences in randomized controlled trials: an unhealthy research behavior that is hard to eradicate. Int J Behav Nutr Phys Act. 2015;12:4.

In the statistical analysis, we have applied multivariable regression analysis to evaluate the relationship between the variable of interest and the outcome after adjusting for covariates. The analysis showed that differences in the sample between the groups, if any, did not significantly influence the results. In the revised manuscript, it now reads “After adjustment for age, gender, and education, a significant difference in the total score between the two groups was still evident (B = 2.75, SE = 0.54, beta = 0.32, 95% CI = 1.69 to 3.81, p <0.001).” [Page 12, Line 171-173]

Comment:

Ethical approval

This part is missing.

Answer:

We have added this missing part, and it now reads “This study was approved by the Institutional Review Board of Royal Thai Army Medical Department. The informed consent was obtained by action.” [Page 17-18, Line 256-257].

Reviewer: 4

Reviewer Name: Lauren Samuels

Institution and Country: Vanderbilt University School of Medicine, USA

Comment:

This manuscript describes an evaluation of an enhanced informed consent form (ICF) compared to a standard ICF among parents whose children are eligible for participation in research requiring parent consent. The study has the potential to provide valuable insights about parents’ comprehension of ICFs, but I have major concerns about the analytical approach, as follows:

1. My main concern is with the choice of primary endpoint. The manuscript gives no justification for the choice of >80% (>= 20/24) correct as a cutoff for “success.” By choosing to dichotomize their primary outcome in this way, the authors are effectively asserting that a score of 19 is equivalent to a score of 0, and I doubt seriously that they would want to make such a claim. I recommend dropping the dichotomous endpoint altogether, and instead using the total score as the primary endpoint. For

more information on the issue of dichotomizing continuous variables, see, for example, Altman Douglas G, Royston Patrick. The cost of dichotomising continuous variables. BMJ 2006; 332: 1080.

Answer:

It is very important in the study design on whether which parameter should be the primary endpoint and we took this into consideration extensively during the protocol development phase. In this study, we decided to choose the proportion of the participants who had the score of more than 80% to be the primary endpoint, while the actual score was considered as a secondary endpoint. In addition to simple interpretation and implication, our decision was based on the rationale that in research the proportion (or number) of participants who achieves the satisfactory understanding level is deemed more important and meaningful than the actual score that each individual gets. Even if a new tool can significantly increase the actual score but the participants' understanding still does not reach the satisfactory level (e.g., a new tool increases the actual score from 30% to 50%), we cannot be confident that the new tool is good enough. The justification for the cut-off value at >80% (to be considered as a threshold of an optimal understanding level) is derived from most previous research on the subject of participants' understanding of information [1-5]. The level of this cut-off value was predefined in the study protocol and used in sample size determination of the present study.

Reference:

[1] Chaisson LH, et al. Repeated assessments of informed consent comprehension among HIV-infected participants of a three-year clinical trial in Botswana. PLoS ONE (2011).

[2] Fitzgerald DW, et al. Comprehension during informed consent in a less-developed country. Lancet (2002).

[3] Koonrungsesomboon N, Teekachunhatean S, Hanprasertpong N, Laothavorn J, Na-Bangchang K, Karbwang J. Improved participants' understanding in a healthy volunteer study using the SIDCER informed consent form: a randomized-controlled study. Eur J Clin Pharmacol. 2016;72(4):413-21.

[4] Koonrungsesomboon N, Tharavanij T, Phiphatpatthamaamphan K, Vilaichone RK, Manuwong S, Curry P, et al. Improved participants' understanding of research information in real settings using the SIDCER informed consent form: a randomized-controlled informed consent study nested with eight clinical trials. Eur J Clin Pharmacol. 2017;73(2):141-9.

[5] Koonrungsesomboon N, Traivaree C, Chamnanvanakij S, Rungtragoolchai P, Thanapat Y, Karbwang J. Improved pregnant women's understanding of research information by an enhanced informed consent form: a randomised controlled study nested in neonatal research. Arch Dis Child Fetal Neonatal Ed. 2018;103(5):F403-F407.

Comment:

2. Like the main analysis, any subgroup analyses, if conducted, should use the total score as the outcome of interest. The manuscript currently states, however, that "Subgroup analysis was done to determine the impact of gender, age, and education on the primary endpoint" (lines 131--132), and this is not an appropriate rationale for a subgroup analysis. That is, conducting one analysis in a subgroup of men and another analysis in a subgroup of women does not provide information on the impact of gender on the primary endpoint. If, instead, the authors are interested in exploring the possibility that the intervention effect differs by gender, age, and/or education, exploratory analyses using interaction terms would be more appropriate than subgroup analyses.

Answer:

We thank the reviewer for this valuable comment. After reconsidering, we have deleted ‘subgroup analysis’ in the revised manuscript.

Comment:

3. Lines 132--133 say, "Multivariable logistic regression analysis was performed to obtain odds ratio (OR), a measure of association between demographic variables and the primary outcome." After switching the primary outcome to the total score, binary logistic regression will no longer be appropriate here; but regardless of the outcome variable, this is an odd justification for the use of multivariable regression in the context of a randomized trial. I would have expected a rationale along the lines of "to obtain a more precise estimate of the effect of the intervention." See, for example, Covariate adjustment increases statistical power in randomized controlled trials Lingsma, Hester, Roozenbeek, BobS, teyerberg, Ewout et al.,

Journal of Clinical Epidemiology, Volume 63, Issue 12, 1391 https://www.jclinepi.com/article/S0895-4356(10)00188-5/fulltext. The model itself, or at the very least a clear description of the covariates and their functional forms, should be included in the Data Analysis section, and the full model results should also be included in the paper or an appendix. Based on the limited information presented, the interpretation of the model results in lines 147--150 strikes me as almost certainly incorrect---multivariable regression cannot tell us whether two things are "independently associated." The interpretation on line 151 is almost certainly incorrect as well, as a high p-value is not evidence of a lack of association.

Answer:

This is a common pitfall in research practice [1]. Thank you for pointing this out. We redesigned a regression model to study the effect of two different ICF interventions on the outcome of interest (i.e., participants’ understanding of information) after adjusting for demographic variables. A continuous variable (i.e., the total score) was kept continuous in the regression model [2]. In the revised manuscript, it now reads “Multivariable linear regression analysis was performed to evaluate the relationship between different ICF interventions and the total score after adjusting for age, gender, and education.” [Page 11, Line 156-158]. And, “After adjustment for age, gender, and education, a significant difference in the total score between the two groups was still evident (B = 2.75, SE = 0.54, beta = 0.32, 95% CI = 1.69 to 3.81, p <0.001).” [Page 12, Line 171-173]

Reference:

[1] Altman DG, Royston P. The cost of dichotomizing continuous variables. BMJ. 2006;332(7549):1080.

[2] Naggara O, Raymond J, Guilbert F, Roy D, Weill A, Altman DG. Analysis by categorizing or dichotomizing continuous variables is inadvisable: an example from the natural history of unruptured aneurysms. AJNR Am J Neuroradiol. 2011;32(3):437-40.

Comment:

Other concerns:

- Lines 90--91 say that "any refusal to read an ICF given was respected," but the manuscript provides no flowchart of sample size/refusals.

Answer:

We have added Fig. 1 to display the flow diagram of this study in the revised manuscript.

Comment:

- Rather than dichotomizing age, Table 1 should give the medians and interquartile ranges of age in the two groups.

Answer:

We have revised Table 1 according to the reviewer’s comment.

Comment:

- The footnote to Table 2 should include the type of significance test used.

- Table 3 should have a footnote giving the method used to calculate p-values and confidence intervals.

Answer:

We have revised Table 2 and Table 3 according to the reviewer’s comment.

Comment:

- The caption on Fig 1 is incorrect--- the plot does not show proportions. With the switch to using the total score as the primary endpoint, however, this figure will need to be replaced by a different presentation of results altogether.

Answer:

After reconsidering the overall comments on statistical analysis, we have deleted this plot in the revised manuscript.

VERSION 2 – REVIEW

REVIEWER	Ryan Spellecy Medical College of Wisconsin United States
REVIEW RETURNED	03-Sep-2019

GENERAL COMMENTS	The authors addressed all of my concerns. Phrasing the statistics in terms of descriptive statistics and providing additional information on SIDCER greatly improved the paper.

REVIEWER	Rebecca Sheridan Department of Health Sciences, University of York, UK
REVIEW RETURNED	12-Sep-2019

GENERAL COMMENTS	Many thanks to the authors for their careful consideration of the reviewers' comments and their revised manuscript. I do have a few minor suggestions/follow up comments. Informed consent "…by action, provided that answering the questionnaire inferred the parents' consent to this ICF study" – does this mean that they were aware of the nested ICF study but they didn't actually complete a consent form? If yes, is there a reason? Many thanks for the further detail about the questionnaire, though I feel it is still unclear and the references provided don't appear to give much more detail. I think an example question would be useful, or better yet for the questionnaire to be provided as an appendix. Re questionnaire validity - I don't think the reference the authors cite actually tests the validity of the questionnaire – it seems to be a study to "validate the applicability and effectiveness of the SIDCER ICF" not the questionnaire. Please correct if necessary. It would be useful for the authors to provide some commentary in the actual article about why they think comprehension scores are much higher in their other studies than the present study, or at least to acknowledge that they are higher. In their previous response they suggested this population have different levels of attention and comprehension to the other groups – how likely is this? Line 177 – Some context could be added e.g. '…improving parental understanding on five out of 24 elements…' – the discussion might also benefit from some consideration of why there may have been no improvement (statistically) for the other 19 elements, or for two of the four categories (general items, patients rights). Will still require some editing e.g. • Line 296: "especially in this group of population" • Line 73: "it can and do serve multiple purposes" • Line 145: "did not involve participants or publics" Also, the subheading 'Participant and Public Involvement' should be in line with journal guidelines and instead be 'Patient and Public Involvement'

REVIEWER	Lauren R Samuels Vanderbilt University School of Medicine USA
REVIEW RETURNED	07-Sep-2019

GENERAL COMMENTS	I found the revised manuscript to be much improved. I have the following minor concerns: - Lines 99--101: I don't understand this sentence. - Line 128: "total score" should be changed to something like "highest possible score" - Line 153: Where exactly was Fisher's exact test used? The footnote to Table 3 says that the chi-squared test was used for this table. - Line 213--214: I think that "demonstrated that the SIDCER ICF was proven superior to the conventional ICF" is too strong of an assertion. I would prefer "suggested that the SIDCER ICF was superior to the conventional ICF in this setting". After the authors address these concerns and the concerns of the other reviewers, I think the manuscript would benefit from editing by a professional English-language editor.

VERSION 2 – AUTHOR RESPONSE

Reviewer 2: Ryan Spellecy

Comment:

The authors addressed all of my concerns. Phrasing the statistics in terms of descriptive statistics and providing additional information on SIDCER greatly improved the paper.

Answer:

Thank you for your valuable comments that greatly improve our manuscript.

Reviewer 4: Lauren R Samuels

Comment:

I found the revised manuscript to be much improved. I have the following minor concerns:

- Lines 99--101: I don't understand this sentence.

Answer:

We have revised that sentence, and it now reads “Informed consent was obtained verbally and by action, that is, answering the questionnaire tacitly inferred their consent for participation in this ICF study.” [Page 8; Line 100-102]

Comment:

- Line 128: “total score” should be changed to something like “highest possible score”

Answer:

We have revised the manuscript according to the reviewer’s suggestion, and it now reads “In each question, there was only one correct answer, counting as a score of 1, making the highest possible score 24.” [Page 10; Line 128-129]

Comment:

- Line 153: Where exactly was Fisher’s exact test used? The footnote to Table 3 says that the chi-squared test was used for this table.

Answer:

We have removed ‘Fisher’s exact test’ from the manuscript, and it now reads “Dichotomous variables were compared using $\chi 2$ test.” [Page 11; Line 154]

Comment:

- Line 213--214: I think that “demonstrated that the SIDCER ICF was proven superior to the conventional ICF” is too strong of an assertion. I would prefer “suggested that the SIDCER ICF was superior to the conventional ICF in this setting”.

Answer:

We have revised the manuscript according to the reviewer’s suggestion, and it now reads “Although the overall results suggested that the SIDCER ICF was superior to the conventional ICF in this setting, the degree of parental understanding remained unsatisfactory.” [Page 15; Line 214-216]

Comment:

After the authors address these concerns and the concerns of the other reviewers, I think the manuscript would benefit from editing by a professional English-language editor.

Answer:

Thank you very much.

Reviewer 3: Rebecca Sheridan

Comment:

Many thanks to the authors for their careful consideration of the reviewers' comments and their revised manuscript. I do have a few minor suggestions/follow up comments.

Informed consent "…by action, provided that answering the questionnaire inferred the parents' consent to this ICF study" – does this mean that they were aware of the nested ICF study but they didn't actually complete a consent form? If yes, is there a reason?

Answer:

The potential individuals whose child was invited to take part in the drug trial were informed verbally about this nested ICF study. No signed consent was prerequisite for participation in this ICF study because we (and the local IRB) considered that informed consent for this nested ICF study involving no more than minimal risk could be done by action (i.e., answering the questionnaire could tacitly infer the parent's consent for participation in this ICF study) in order to avoid confusion between the two independent studies (the drug trial and the ICF study). In the process of obtaining informed consent, the parents were informed that 'Answering this questionnaire is entirely voluntary. You can refuse to participate or skip any questions if you don't want to answer. Answering the questionnaire means that you agree for the research team to use the data for analysis. Your answers will be used only for research purposes.' In the revised manuscript, it reads "Informed consent was obtained verbally and by action, that is, answering the questionnaire tacitly inferred their consent for participation in this ICF study." [Page 8; Line 100-102]

Comment:

Many thanks for the further detail about the questionnaire, though I feel it is still unclear and the references provided don't appear to give much more detail. I think an example question would be useful, or better yet for the questionnaire to be provided as an appendix. Re questionnaire validity - I don't think the reference the authors cite actually tests the validity of the questionnaire – it seems to be a study to "validate the applicability and effectiveness of the SIDCER ICF" not the questionnaire. Please correct if necessary.

Answer:

An example of questions in the questionnaire is provided in an appendix of the revised manuscript. The original questionnaire was validated by the experts in the Forum for Ethical Review Committees in Asia and the western Pacific region (FERCAP) before being used to validate the applicability and effectiveness of the SIDCER ICF.

Comment:

It would be useful for the authors to provide some commentary in the actual article about why they think comprehension scores are much higher in their other studies than the present study, or at least to acknowledge that they are higher. In their previous response they suggested this population have different levels of attention and comprehension to the other groups – how likely is this?

Answer:

We have revised the manuscript to acknowledge that the comprehension score in this study is much lower than the scores in the previous studies. In the revised manuscript, it now reads “Moreover, we have noticed that the level of parental understanding in this study is apparently lower than our observations in the previous ICF studies involving other groups of populations.” [Page 15; Line 217-219]

Comment:

Line 177 – Some context could be added e.g. ‘…improving parental understanding on five out of 24 elements…’ – the discussion might also benefit from some consideration of why there may have been no improvement (statistically) for the other 19 elements, or for two of the four categories (general items, patients rights).

Answer:

We discuss some plausible explanations as to why the parental understanding of some elements in the ICF was significantly improved. In the manuscript, it reads “The first three elements were highlighted and made salient in the SIDCER ICF, whereas the same content was ordinarily described in the conventional ICF. It is reasonable to assume that a higher understanding of these three elements in the SIDCER ICF group was partly attributed to a complementary technique being used to convey key information. This might be the evidence to support that increased processability of key or complex information in an ICF could contribute to a significant improvement in parental understanding of such information.” [Page 14-15; Line 197-203] However, with the data available at this moment, it is difficult to postulate credible explanations as to why there may have been no improvement (statistically) for the other 19 elements.

Comment:

Will still require some editing e.g.

• Line 296: “especially in this group of population”

• Line 73: “it can and do serve multiple purposes”

• Line 145: “did not involve participants or publics” Also, the subheading ‘Participant and Public Involvement’ should be in line with journal guidelines and instead be ‘Patient and Public Involvement’

Answer:

We have revised our manuscript according to the reviewer’s suggestion.

It now reads

- “especially in this group of populations” [Page 16; Line 224]

- “it does serve multiple purposes ....” [Page 6; Line 65]

- “Patient and public involvement” [Page 11; Line 145]

VERSION 3 - REVIEW

REVIEWER	Rebecca Sheridan Department of Health Sciences, University of York, UK
REVIEW RETURNED	09-Oct-2019

GENERAL COMMENTS	Many thanks to the authors for responding to my comments.