PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Cultural considerations for informed consent in pediatric research in low and middle income countries: A scoping review
AUTHORS	Colom, Marcela; Rohloff, Peter

VERSION 1 – REVIEW

REVIEWER	Reviewer name: Shalini Ojha Institution and Country: University of Nottingham Competing interests: None
REVIEW RETURNED	24-Aug-2018

GENERAL COMMENTS	Thank you for your work on this very important and often overlooked topic. Minor comments: 1.Page 4, line 77 words missing between with and as - suggest - with groups such as 2. Page 8 line 142 "to" missing between best and operationalize 3. Page 8 line 134: How many guidelines were found in the literature search and why were these 5 selected for inclusion? 4. Page 16 line 253 "due" instead of "do" 5. Page 51 line 195: The authors make an important point here. It might also be worth considering that the need to "first seek permission from the elder" may not only remove the autonomy for opting-out but also may take away the right to participate in research. This could, for example, be particularly important in research in culturally sensitive themes where the less empowered family member may wish to participate against the wishes of the patriarch. Major comments: 1. The literature search was limited to the English language. For a review exploring cultural considerations in LMICs, this, I believe, is a major limitation of the study. Although the authors have mentioned that they have excluded non-English language studies in the methods and results section, the effects of this limitation is not explored in the discussion. 2. Table 2. This is a comprehensive table and clearly, a lot of work has gone into putting it together. The author must be commended for this work. However, some reorganisation of the content would benefit the reader. Currently, it is a list of studies without any thematic order which makes it difficult to comprehend the overall picture. I would suggest, at least, separating review articles and opinion pieces from the original research papers. It may also be possible to explore grouping the studies thematically. 3. Some important issues such as consent for randomisation and participation in intervention studies are not explored in detail.

	4. In the recent years some countries such as India have introduced legislation mandating audio-visual documentation of consent for some types of studies. The authors have briefly talked of audio recording of consent but there is no discussion on possible challenges created by such rules both for the potential participants and for researchers. 5. Page 26 Row 4 Swain T 2014 Column 4 "Consent for neonatal studies should be done in an opt-out way". In this otherwise wide exploration of issues around informed consent in paediatric studies, I find a lack of mention of neonatal studies except for this one sentences. I am unable to understand why "opt-out consent should be done" in neonatal studies. This is not something that is currently acceptable in the high resource settings expect with specific ethical approval given only when an adequate case is made. I am unable to accept then, that it "should" be done in LMICs without further exploration of why Swain et al. have expressed this opinion and the authors' view on this.

REVIEWER	Reviewer name: Elaine M. Bennett Institution and Country: Saint Vincent College; Latrobe, Pennsylvania,United States Competing interests: Reviewer has collaborated with the second author on a grant proposal that is unrelated to this topic.
REVIEW RETURNED	29-Aug-2018

GENERAL COMMENTS	This scoping review pulls together and summarizes the literature discussing informed consent processes in pediatric research in low- and middle-income countries (LMICs). This is an important issue that researchers working in LMICs should carefully consider. This review, which draws out themes from a range of studies that acknowledge and address this challenge, is an important step in helping researchers who attempt this work to know which questions they should be asking, and which factors they should be considering. The paper left me with as many questions as it answered and points to a need for ongoing discussion and debate (both philosophically and practically) about the complex nature of informed consent in different cultures and contexts. (Note: some of the comments below reflect those questions and addressing them may expand the scope of the article beyond the author’s intent.) Comments on specific parts of the article: P6, Results section The inclusion criteria are clearly explained. The authors should add a little more detail about the articles that were excluded—what did they discuss, if not the process of informed consent? That is, explain why, if they showed up in the search results, what did they discuss that did not sufficiently address the criteria. Did they mention, but not discuss informed consent? Did they not involve pediatric participants? Summary of guidelines and commentaries—general comment It would be helpful to have some discussion of whether/how criteria such as “informed” and “voluntary” are supposed to be assessed according to these guidelines. This would help to ground the later discussion of more nuanced issues with these concepts from the literature.

	P7, Lines 137 and 141, and other parts of article as well. The use of “several” is not supported by the citation of two articles. I suggest either referring to additional reviewed articles, and/or adding “e.g.” to acknowledge others that were not cited, or avoiding use of “several” when only two examples are given. P8, Line 156 (paragraph) How is assent defined in these guidelines? Is the definition consistent across guidelines? Is it operationalized at all? Page 11, Line 32 (rightmost column)—Are there any guidelines regarding the characteristics of the witness (e.g., identity, relationship to child, relationship to research)? Based on the comment in the discussion on p34, I am guessing not, but maybe note that here. Page 13 Line 215—Again, are there any guidelines regarding the characteristics of the witness beyond literacy and training? Are there any details as to the content of training that could prepare a witness to secure real consent? While a trusted family member sounds like a good option, some consideration should be given to the burden on the family to provide their own advocate. Line 219—Remove “by” add “may”—This is an example where the authors added their own analysis and suggestions to the summary of articles—as noted in comments on the discussion, more of this kind of analysis and recommendation would increase the value of the article (but I also accept if that is not part of the intended scope). Page 14 Line 220—"but" to "by" Line 232—What were some of these difficulties? Line 238—How is successful informed consent assessed? Percentage of participants from whom consent was secured? Low dropout/high retention rates (which are affected by other factors)? Page 15 Line 241—Unclear…when soliciting consent from male or female caregivers? Also, does the study cited imply that the male’s authority is definitively overriding the woman’s inclination to consent? Gender dynamics should be discussed with greater nuance as there are more possibilities than the two noted here, for example, a woman may not want to have her child participate, but not feel empowered to refuse of her own volition, so she cites her husband’s refusal, or signals to him to refuse. Does this lack of nuance may simply reflect the narrow ideas of autonomy and gender dynamics projected on families by Western academia. Line 257—This is a significant challenge, especially in situations where resources and access are limited. Did the reference that recommends “explicit attention to this dynamic while designing consent procedures” report any success in mitigating misconceptions? Do any of the articles reviewed discuss the role of incentives as a source of benefit? Page 16 Line 281—What constitute “appropriate early, equitable 282 benefit-sharing measures”?

	Page 33/34—Discussion The discussion nicely summarizes the major themes, offering some synthesis of the literature; however, more detailed analysis of the themes outlined would greatly improve its potential impact. This review could be very helpful to researchers if it were to more clearly extract the lessons or discuss details in the issues and challenges faced by researchers, from the reviewed literature. Basically, more detailed discussion would be valuable. That being said, that may broaden the scope of the paper beyond the authors' original intent, and not adding detail would not diminish the importance of the review as contributing to a structured discussion of the issue. P34 Line 340—"when authorities are approached first" would be more precise. Table 2: The summaries of articles included in Table 2 are invaluable as a briefly annotated bibliography, but there are some key themes in them that I think should be added to the main body of the article. One theme that could be addressed is the issue of recall and retention of information, which was noted in a few of the summaries, with Sarkar (54) also pointing out the need for continuous reinforcement of consent. Another (related to recall and retention) is "comprehension" of the purposes, methods, sampling, risks, benefits, etc. The authors referred to methods for probing comprehension and consent with adolescents, but the theme was represented in several of the articles in Table 2, and could be worth separate discussion. Part of this is noted in the discussion of therapeutic misconception on p33, L334, in theme (4), but I think that a discussion of comprehension of factors such as methods, required commitment, and right to withdraw could be separated. General comment: The manuscript needs a detailed line editing. I commented on a few typos but did not line edit.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1

1.Page 4, line 77 words missing between with and as - suggest - with groups such as

Response: We have made the correction.

2. Page 8 line 142 "to" missing between best and operationalize

Response: We have made the correction.

3. Page 8 line 134: How many guidelines were found in the literature search and why were these 5 selected for

inclusion?

Response: We have clarified this point in the manuscript, which now reads:

“We identified seven guidelines that addressed issues of informed consent in international settings and in research involving children in our scoping review. Of these, we selected for detailed review five that were most comprehensive, summarizing key recommendations in Table 1.”

4. Page 16 line 253 "due" instead of "do"

Response: We have made the correction.

5. Page 51 line 195: The authors make an important point here. It might also be worth considering that the need to "first seek permission from the elder" may not only remove the autonomy for opting-out but also may take away the right to participate in research. This could, for example, be particularly important in research in culturally sensitive themes where the less empowered family member may wish to participate against the wishes of the patriarch.

Response: We agree! We have added this consideration to the sentence in question.

Major comments:

1. The literature search was limited to the English language. For a review exploring cultural considerations in LMICs, this, I believe, is a major limitation of the study. Although the authors have mentioned that they have excluded non-English language studies in the methods and results section, the effects of this limitation is not explored in the discussion.

Response: We agree! We have added a paragraph to our discussion discussing the limitations of our review and review strategy, and we have included this point.

2. Table 2. This is a comprehensive table and clearly, a lot of work has gone into putting it together. The author must be commended for this work. However, some reorganisation of the content would benefit the reader. Currently, it is a list of studies without any thematic order which makes it difficult to comprehend the overall picture. I would suggest, at least, separating review articles and opinion pieces from the original research papers. It may also be possible to explore grouping the studies thematically.

Response: The original table organization was simply chronological, by date of publication, and we agree that this is not very helpful to the reader. We’ve restructured the table. We’ve separated out review articles and opinion pieces, as the reviewer suggested, and we’ve also provided a few high-level thematic groupings which correspond roughly to the thematic analysis in the text. Of note, changes to the table are not tracked in the tracked changes copy of the manuscript, as they are for other parts, because Microsoft Word doesn’t handle tracked changes well in such a large embedded table.

3. Some important issues such as consent for randomization and participation in intervention studies are not explored in detail.

Response: We agree with the reviewer that we do not provide great detail on these points. However, the summary section on “Disclosing potential benefits and risks of participation in research” is meant to address these issues and most of the articles cited in this section that explore disclosure, therapeutic misconception, etc. are doing so in the context of randomized, controlled trial designs. We’ve modified some of the wording in the first paragraph of this section to make this clearer. We also think that the restructured Table 2, with grouping by themes, will help the interested reader locate the articles that discuss these themes in more detail.

4. In the recent years some countries such as India have introduced legislation mandating audio-visual documentation of consent for some types of studies.

The authors have briefly talked of audio recording of consent but there is no discussion on possible challenges created by such rules both for the potential participants and for researchers.

Response: This is a really important point, and one which we had neglected to include in the review. We've added a new paragraph to the section on "Adapting consent procedures to low-literate settings" based on a reference from a review article from India.

5. Page 26 Row 4 Swain T 2014 Column 4 "Consent for neonatal studies should be done in an opt-out way". In this otherwise wide exploration of issues around informed consent in paediatric studies, I find a lack of mention of neonatal studies except for this one sentences. I am unable to understand why "opt-out consent should be done" in neonatal studies. This is not something that is currently acceptable in the high resource settings expect with specific ethical approval given only when an adequate case is made. I am unable to accept then, that it "should" be done in LMICs without further exploration of why Swain et al. have expressed this opinion and the authors' view on this.

Response: We think that we created unnecessary confusion here through poor word choice, and we apologize. The author is talking about deferred consent models for high-acuity settings. We have edited this entry in the Table to make this clear, and we hope that this answers the Reviewer's concern.

Reviewer 2

Comment: This scoping review pulls together and summarizes the literature discussing informed consent processes in pediatric research in low- and middle-income countries (LMICs). This is an important issue that researchers working in LMICs should carefully consider. This review, which draws out themes from a range of studies that acknowledge and address this challenge, is an important step in helping researchers who attempt this work to know which questions they should be asking, and which factors they should be considering. The paper left me with as many questions as it answered and points to a need for ongoing discussion and debate (both philosophically and practically) about the complex nature of informed consent in different cultures and contexts.

Response: We agree with the Reviewer's sentiment here. When we started this review, we anticipated finding very little published work in the literature and that the article would take the form of a small set of detailed case studies exploring a couple of issues in depth. However, we found a great deal more published work, and so we reconsidered our strategy. We opted for a higher-level overview of themes so that we could include most of the work that we found. This unfortunately ends up feeling a bit superficial in places, given both manuscript word limits and how very heterogeneous the articles are. However, ultimately we are happy with the product, because we hope it can help set up shared language and broad concepts for future work, including more detailed work on some of the individual themes we identified.

P6, Results section

The inclusion criteria are clearly explained. The authors should add a little more detail about the articles that were excluded—what did they discuss, if not the process of informed consent? That is, explain why, if they showed up in the search results, what did they discuss that did not sufficiently address the criteria. Did they mention, but not discuss informed consent? Did they not involve pediatric participants?

Response: We have added a narrative sentence to this section that explains the most common reasons for exclusion after the initial screen. In summary, we excluded articles that did not include pediatric participants, articles that did not discuss the informed consent process, and articles that did not discuss consent processes in low or middle income countries.

Summary of guidelines and commentaries—general comment

It would be helpful to have some discussion of whether/how criteria such as “informed” and “voluntary” are supposed to be assessed according to these guidelines. This would help to ground the later discussion of more nuanced issues with these concepts from the literature.

Response: This is an important point. Interestingly the guidelines generally don’t help to operationalize these concepts, which is part of the need for the review and for ongoing work in this area we think. We’ve added a few sentences to this section address this point and provide some direct citations to guidelines.

P7, Lines 137 and 141, and other parts of article as well.

The use of “several” is not supported by the citation of two articles. I suggest either referring to additional reviewed articles, and/or adding “e.g.” to acknowledge others that were not cited, or avoiding use of “several” when only two examples are given.

Response: We’ve reviewed our word usage and, in most cases, changed “several” to a more appropriate descriptor.

P8, Line 156 (paragraph)

How is assent defined in these guidelines? Is the definition consistent across guidelines? Is it operationalized at all?

Response: Similar to the Reviewer’s other definitions question about, assent is not well operationalized either. We’ve added a sentence quoting additional text from the CIOMS guidelines to the relevant paragraph.

Page 11, Line 32 (rightmost column)—Are there any guidelines regarding the characteristics of the witness (e.g., identity, relationship to child, relationship to research)? Based on the comment in the discussion on p34, I am guessing not, but maybe note that here.

Response: There are not, what we’ve done to address this is add a few words to the end of the following sentence: “there is little specificity on how best to operationalize these core principles, such as how to formally document verbal consent or characteristics of a qualified witness.”

Page 13

Line 215—Again, are there any guidelines regarding the characteristics of the witness beyond literacy and training? Are there any details as to the content of training that could prepare a witness to secure real consent? While a trusted family member sounds like a good option, some consideration should be given to the burden on the family to provide their own advocate.

Response: We’ve clarified this question by adding a little more detail from the article under question as follows: “Kalabuanga and colleagues note, however, that witnesses may often impose their views on the consenting caregiver and their child, rather than encourage dialog and act as a safeguard, especially since they are often recruited in an ad hoc fashion (e.g., other literate patients or ancillary hospital staff).

Line 219—Remove “by” add “may”—This is an example where the authors added their own analysis and suggestions to the summary of articles—as noted in comments on the discussion, more of this kind of analysis and recommendation would increase the value of the article (but I also accept if that is not part of the intended scope).

Response:This was a badly written sentence. In addition to fixing the typo, we’ve also clarified that “authors” referred to the paper being summarized, not to our own opinion.

Response: We had thought that we would provide more “editorialization” when writing this review, but after we became more aware of the full scope and diversity of articles to review, we revised this plan and have adopted a more neutral, less editorial tone.

Page 14

Line 220—"but" to "by"

Response: We corrected the typo.

Line 232—What were some of these difficulties?

Response: We’ve expanded this sentence to provide more detail.

Line 238—How is successful informed consent assessed? Percentage of participants from whom consent was secured? Low dropout/high retention rates (which are affected by other factors)?

Response: We avoided addressing this question in the manuscript, because the details of how individuals teams assess informed consent is very heterogenous and it was difficult to provide a concise and useful summary. However, with the reorganization of Table 2, most of the articles that discuss these mechanics are now better grouped together and we hope this will allow the interested reader to more easily identify articles of interest to them if they want to investigate more specifics.

Page 15

Line 241—Unclear…when soliciting consent from male or female caregivers?

Response: We clarified this point in the text.

Also, does the study cited imply that the male’s authority is definitively overriding the woman’s inclination to consent?

Response: Yes, we clarified this as well be rewriting the sentence in question.

Gender dynamics should be discussed with greater nuance as there are more possibilities than the two noted here, for example, a woman may not want to have her child participate, but not feel empowered to refuse of her own volition, so she cites her husband’s refusal, or signals to him to refuse. Does this lack of nuance may simply reflect the narrow ideas of autonomy and gender dynamics projected on families by Western academia.

Response: Yes, this is primarily just a function of the fairly narrow Western biomedical lens through which the discussions of gender in these articles was discussed. We think it is an important qualifying point, and we’ve added a few sentences to the section on gender to emphasize this.

Line 257—This is a significant challenge, especially in situations where resources and access are limited. Did the reference that recommends “explicit attention to this dynamic while designing consent procedures” report any success in mitigating misconceptions? Do any of the articles reviewed discuss the role of incentives as a source of benefit?

Response: At the suggestion of Reviewer 1, we’ve made some clarifying edits in this paragraph which help address these questions in part.

Regarding the second question, the article did not document or discuss in any detail success mitigating these misconceptions, and so we’ve removed the sentences from the manuscript.

Regarding the last question in this paragraph, the primary discussion of incentives in the articles emerges in the discussion of how basic clinical care in a trial may be an undue incentive if health care access is poor. This issue is addressed in a later paragraph in this same section, and we've added the word "incentive" to the relevant sentence to make the linkage more obvious.

Page 16

Line 281—What constitute "appropriate early, equitable 282 benefit-sharing measures"?

Response: The authors of the manuscript do not elaborate. However, based on a close reading of this manuscript, we have added a concrete example which we think is in the spirit of their vague proposal.

Page 33/34—Discussion

The discussion nicely summarizes the major themes, offering some synthesis of the literature; however, more detailed analysis of the themes outlined would greatly improve its potential impact. This review could be very helpful to researchers if it were to more clearly extract the lessons or discuss details in the issues and challenges faced by researchers, from the reviewed literature. Basically, more detailed discussion would be valuable. That being said, that may broaden the scope of the paper beyond the authors' original intent, and not adding detail would not diminish the importance of the review as contributing to a structured discussion of the issue.

Response: We agree with the Reviewer that our manuscript feels a bit superficial in this regard. However, as mentioned above, our original plan to use a more in-depth case study format was disrupted by our discovery during the search process of a fairly large and very heterogenous group of published articles. Because of this, we've elected to stick with mapping out high-level themes. We anticipate that this will still be of value as it will help to frame the discussion and future work. It also allows us to remain within the journal format of short (~3000 word) review articles. Finally, we've added this as a limitation of our review in a concluding limitations paragraph.

P34 Line 340—"when authorities are approached first" would be more precise.

Response: We've made the suggested edit.

Table 2:

The summaries of articles included in Table 2 are invaluable as a briefly annotated bibliography, but there are some key themes in them that I think should be added to the main body of the article. One theme that could be addressed is the issue of recall and retention of information, which was noted in a few of the summaries, with Sarkar (54) also pointing out the need for continuous reinforcement of consent. Another (related to recall and retention) is "comprehension" of the purposes, methods, sampling, risks, benefits, etc. The authors referred to methods for probing comprehension and consent with adolescents, but the theme was represented in several of the articles in Table 2, and could be worth separate discussion. Part of this is noted in the discussion of therapeutic misconception on p33, L334, in theme (4), but I think that a discussion of comprehension of factors such as methods, required commitment, and right to withdraw could be separated.

Response:Reviewer 1 asked for some restructuring of the section on "Disclosing potential benefits and risks of participation in research" which clarifies some of these points. We've also added an additional sentence to that section about comprehension, information retention, and continuous reaffirmation of consent. We think this at least partly addresses these concerns without adding a new lengthy section to the manuscript. We also think that the reorganization of Table 2 will help interested readers better locate specific articles for more in-depth reading.

VERSION 2 – REVIEW

REVIEWER	Reviewer name: Elaine M. Bennett Institution and Country: Saint Vincent College. Latrobe, Pennsylvania. United States Competing interests: Reviewer has collaborated with the second author on a grant proposal that is unrelated to this topic.
REVIEW RETURNED	18-Oct-2018

GENERAL COMMENTS	The review comments were effectively addressed and the scope and limitations of the article are clearly acknowledged.