Author's response to reviews

Title: Who is the research subject in cluster randomized trials in health research?

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Version: 2 Date: 19 April 2011

Author's response to reviews: see over
Reviewer's report

Title: Who is the research subject in cluster randomized trials?

Version: 1 Date: 10 January 2011

Reviewer: Charlie Goldsmith

Reviewer's report:

In general this second paper is well done. Here are series of suggestions designed to improve the manuscript.

Thank you. We address each reviewer comment below.


Done.

2. P 2, paragraph 2, l 10. Suggest rewriting as […] unless at least one of these conditions is met.]. I do not think you mean exactly one.

Done.

3. P 3, p 3, l 2. Replace [significant] by [important]. Leave significant for its statistical context.

Done.


Done.

5. P 3, p 3, l 4. Suggest replacing [will fail to] by [may not].

Done.
6. P 4, p 4, l 3. Rewrite as […] towards smokers.]. Leave out the space.

Done.

7. P 4, p 4, l 3. Delete the second [either].

Done.

8. P 6, p 4, l 2. Delete [in order] in front of [to] as the words are redundant in English. Also P 12, p1, l 6; and P 18, p 2,l2; and P 19,p 3, l 1.

Done.

9. P 8, p 1, l 1. Replace [Medial] by [Medical].

Deleted.

10. P 8, p 1, l 3. Replace [fail to] by [do not].

Sentence has been changed.

11. P 9, p 3. Suggest replacing the bullets by the numbers from 1 to 6 as this is the way they are referenced in the subsequent paragraph as well as on P 13.

Done.

12. P 10, p 2 ff. Would it be useful to reinforce that your recommendations are for human subjects and not for other types? You could comment about other types of subjects, but possibly in the discussion.

We have added “human” before “research subjects” in a number of places throughout the text. In particular, “human” has been added to the abstract, introductory paragraph, and Box 1.

13. P 12, p 2, l 2. Replace [e] by [be].

Done.

Done.

15. P 18, p 2. Suggest where you might like to have Box 1 located.

[INSERT TEXT BOX HERE] has been added to the text file.

16. P 26, p 1, l 5. Suggest dropping [only] as it implies an unstated expectation.

Done

17. P 27, p 4, l 2. Delete space after [messaging] before the [,].

Done

18. P 27 ff. Why not put a Y for Yes or N for No for each of the 4 criteria next to each possible subject type in each example?

We agree that it is useful to specify the reasons why each possible subject type in each example is or is not a research subject. However, we felt that repeating the criteria for each possible subject type in each example would be cumbersome. We have made modifications to the text of the resolution of each example to relate our conclusions regarding each possible subject type to the criteria in box 1.

19. P 32 ff. The number of authors listed is not consistent. Sometimes there as many as 9 authors for reference 36 and sometimes it is 3 et al for reference 5 when indeed there are 9. Trials could publish them all. A random sample of 10 references was checked for accuracy of citation. This reviewer also likes to see the issue number as without it sometimes makes the obtaining of a reference to be checked or read more difficult; so this reviewer like to see them included.


24. P 35, R 23. There is a more recent version published in 2005. Is there merit to having the latest one?


27. P 35, R 28 needs to include more in the citation.
28. P 36, R 32. This R could not be verified.
29. P 36, R 35. Include the rest of the authors.
30. P 36, R 36, l 3. Insert [(1)] after [6].
31. P 37, R 40, l 3. Insert [(1)] after [42].
32. P 37, R 41. Include the date of publication.

The corrections to the references have all been made.
With respect to reviewer’s note 24 (reference 23), the reference is specific to the 1974 version of the US Federal Regulations.
With respect to reviewer’s note 28 (reference 32), the reference may be verified here: (http://ajp.psychiatryonline.org/cgi/content/abstract/116/6/522).
Reviewer's report
Title: Who is the research subject in cluster randomized trials?
Version: 1 Date: 24 January 2011
Reviewer: David Osrin
Reviewer's report:
This is an important paper that I looked forward to reading. It will be useful for readers involved in cluster randomized controlled trials and I will use it myself. I have no suggestions for major revision.

Thank you. Reviewer comments are each addressed in turn below.

Discretionary revisions
I have no doubt that the sequence of decisions made by the authors was based on exhaustive knowledge, but the paper transmits a feeling of executive choice. The authors consider existing guidelines and then propose a definition of a research subject that is smart and makes one think (p12). I guess this is one way of doing it. They could have approached the definition from a philosophical viewpoint, such as utilitarianism, but they didn’t. Could they add a sentence or two explaining why they did what they did?

The reviewer is correct that many problems in bioethics may be addressed by appealing to a particular moral theory, such as utilitarianism or deontological moral theory. Subsequent papers on informed consent and the analysis of harms and benefits do use this approach. In this case, however, the answer to “Who is a research subject” does not stem from one particular moral theory. Rather, we rely on the philosophical method of reflective equilibrium. The methods section has been substantially revised to better describe this methodology.

The authors’ definition of a research subject is framed as a proposition. Presumably, a good way to approach this would be to treat it as a potentially falsifiable hypothesis: can we think of a context in which the proposition would fail? The authors choose to use supportive evidence, which doesn’t feel particularly critical. Is it possible to think a little about non-supportive situations?

In addition to the supporting arguments used in developing this definition of research subject, this definition seems to fit with our common intuitions about who should be treated as a research subject—and who should not. The additional material in the methods section on “reflective equilibrium” now reinforces this point.

There are two particular instances in the text in which the definition helps to clarify who is not a research subject: individuals about whom non-identifiable data is collected, whose privacy interests are not jeopardized (in the criticism of the Australian national guidelines, p. 13); and, patients whose physician is the subject of an experimental intervention and who do not otherwise receive interventions, interact with investigators or contribute private information, as no welfare, privacy or other interests are jeopardized (pp. 18-20). This is not precisely the kind of
contradictory evidence that the reviewer is referring to, but it does indicate that our definition of research subject is able to discriminate between subjects and non-subjects in a way that refines existing intuitions on the issue. The utility of the definition of research subjects in discriminating between subjects and non-subjects has been clarified in the text.

The writing tends toward the repetitive, probably for the sake of clarity, but from a reader’s perspective a little lumberingly. I’m sure the authors could get several hundred words off the paper with no detriment. Examples include:
P7. “The Common Rule offers the following criteria that identify a research subject. A research subject, according to the Common rule, is a…”
P14. “However, the reference to environmental manipulation is potentially a broad term, and requires further examination to determine what kinds of environmental manipulations is insufficiently explicit and requires further elucidation.”

A number of revisions have been made that shorten the length of the paper. Specifically, redundant text has been deleted from pages 7, 8, 11, 13, 14, 17, 20 and 28.

As a general reader I was unfamiliar with the term ‘principled definition’, introduced on p14. Could the authors add a sentence to explain the implications of a principled definition?

We agree that the term “principled definition” is problematic, and have either deleted “principled” substituted “comprehensive and broadly generalizable”.

P15. I find the reductio ad absurdum of the LHC clever but unhelpful here. It is the middle ground that triallists are worried about: fluoridation of water, changes to health services.

Some members of the target audience, particularly North American regulators and ethics committee members, hold a concrete, literal interpretation of the US regulation. We believe it is necessary to illustrate that a literal interpretation is untenable. We then go on to address the application of our definition to more practical, realistic cases, including the four example CRTs.

The later suggestion that individuals would be covered under regulatory criteria for a waiver of informed consent (p21 and p26) is important. Could the authors say a little more about such waivers? I’m interested in their mechanics and sources and other readers will be too.

A brief discussion has been added to page 21, outlining typical regulatory requirements for a waiver of consent. Readers are also referred to the forthcoming paper addressing consent issues in CRTs.

I approve of the inclusion of the discussion of random allocation. Something
about random allocation worries those who are intrinsically wary of RCTs, and it’s good to address this head on.

Thank you.

P14 Examples: challenges in identifying the research subject in CRTs. I don’t think we need the (a) and (b) here.

Deleted.

I think the examples on p14 would look good in a box, which could be followed by a similar box detailing the examples on p27-29.

We see some merit in this idea. However, we leave it to the editorial team as to whether placing the examples in a box or leaving them in the text is the preferred approach. Examples were used within the text of other papers in this series, and a consistent approach should be adopted.

P23. “Whether intervention assignment is random or non-random is a moot point.” I suggest not using the expression ‘moot point’ since it has two meanings: in North America, an irrelevance (the meaning here); in the UK, a contested point (not the meaning here).

Thank you. We were unaware of this definition of “moot”. “A moot point” has been changed to “irrelevant”.

There are grammatical mistakes throughout, including in the abstract.

Grammatical and typological errors have been corrected.
Reviewer's report
Title: Who is the research subject in cluster randomized trials?

Version: 1 Date: 1 February 2011

Reviewer: Elina Hemminki

Reviewer's report:

I have both substance and technical comments. The first mentioned are subjective, and cannot be taken into account if the authors disagree. However, the authors could argue their own view clearer.

We thank the reviewer for her thoughtful comments. We address each of them in turn, below.

Substance comments

1. I understood that the authors share the current ethics principles, which ethics committees in many countries use. Many of them, however, may not easily apply to many CRTs, and I had hoped for a more critical / reflective opinion. The current paper is one of a series. The content of the other papers was not available, and it is possible that the other issues will be discussed in the other papers. Particularly I was thinking of informed consent and the distinction between care and research. It might be good to add a short list and description what the other papers deal with and how they may relate to the definition of a research subject.

We have added a sentence outlining the content of the series in the final sentence of the first paragraph of the introduction.

2. A large number of CRT are made to compare service delivery (including preventive activities), which could be delivered without research. I.e. the option for research would not be “not giving the intervention”, but taking it into practice right away. This questions the logic of participant protection as now presented: which one is better? The definition for separating research and care (p.10) is not valid, particularly in CRT. All care is not just for one patient (example: infectious diseases, children vs. parents, availability of resources) and some research may be care at the same time. Clinician investigators are fine in many CRTs.

The reviewer is taking issue with the distinction between research and medical care that we cite on p10. This is not our own development, but rather a widely accepted conclusion that grounds the historical development of research ethics guidelines, and is enshrined in many national and international research ethics guidelines, including the Declaration of Helsinki.
We use the distinction between research and clinical practice to get at the essential feature of a research subject, in that the research subject’s interests may be compromised purely for scientific purposes, which is not the case in medical practice. The conclusion—that research subjects are individuals whose interests may be compromised for research purposes in a way that would not happen in ordinary practice—is equally applicable to other research fields.

While the distinction between research and practice entails a requirement that CRTs in health services research be reviewed by a research ethics committee, it does not necessarily follow that cumbersome restrictions be placed on such research. In fact, the clarity that this paper provides on who is—and who is not—a research subject, protects researchers from overregulation. Later in the series, we will also argue for the widespread use of waivers of consent that will facilitate the completion of important research while adequately protecting subjects’ interests.

3. For example, their view of classifying new service delivery as an individual patient intervention is potentially dangerous. Currently service delivery methods are often taken into practice without evidence.

We agree that it is common to adopt novel service delivery methods without high quality evidence. We believe—and we think we agree with the reviewer on this point—that it is important that such policy decisions are supported by high quality evidence.

However, with respect to the ethical challenges related to CRTs that evaluate novel modes of service delivery, the modes of service delivery being evaluated are experimental interventions. We attempt to clarify the belief that although service delivery interventions are not direct patient interventions, they are experimental interventions whose risks and potential benefits need to be evaluated by research ethics committees.

4. This being so, it is very important that any new research regulation suggested, should not impede CRT (for the above purpose). I would like to have comments on the impact of this new definition, how it will influence the interest and possibilities to do CRT and to get evidence base health care. It may be that their future articles show that other solutions, such as waivers, solve the research threat. But many/some countries do not have the possibility of a waiver: if someone is defined as a research participant, informed consent is needed (see also Helsinki declaration).

As we state in the text, the definition we propose for identifying research subjects may, in fact, facilitate the conduct of many CRTs. We make the point that many cluster members (such as citizens of a community participating in a CRT or patients in a healthcare institution participating in a CRT) may not be research
subjects, thereby streamlining the ethics review process.

We do point out that a waiver of consent may be an alternative in some cases. The 2002 CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, which is a commentary on the Declaration of Helsinki, provide internationally applicable guidelines for the use of a waiver of consent in specified circumstances. We agree that it would be ideal if all countries enacted research regulations permitting a waiver of consent. The waiver found in the CIOMS guidelines constitutes a potential avenue for seeking a waiver for studies conducted in countries that do not have a waiver regulation of their own.

5. They largely use Anglo-American laws for analyzing the current rules. The rules are not the same in many other countries. The limitation and its potential impact should be acknowledged.

In the introductory paper to the series, we set out an ethical framework that is universal, and broadly generalizable to any country or regulatory jurisdiction.

We used US and Australian regulations as the starting point for our analysis because—as we state in the text—they are the only guidelines that include a definition of “research subject”. If international guidelines such as Helsinki or the CIOMS guidelines included a definition of research subject, we would have gladly included them as well.

Our aim was to develop a principle that investigators, regulators and ethics committees could use to identify research subjects in CRTs (and other types of research) that is broadly generalizable, and we believe we have achieved this aim.

Technicalities
1. The paper is long and written like a story. As a health professional, I found it difficult to read, particularly as many of the concepts and words are not common English, but words with special meaning. I suggest a different structure, allowing readers to read only parts of the text, by their choice, and still get the authors’ point. This could be done by imitating the structure of medical reporting: background, previous literature, etc, current definition, its history, problems of current definition, new suggestions, arguments for the new suggestion etc. Some readers are not interested in the history or variation in different rules, but want to know what is now suggested and what follows from that.

We feel that the current structure of the paper is sufficiently similar to the structure that the reviewer suggests. The current section headings are also sufficiently descriptive to allow a reader to choose to examine particular sections in more or less detail.

2. The paper could also be shorter, and it could be made clearer by using tables.
A number of revisions have been made to make arguments more concise and shorten the overall length of the paper. Specifically, text has been deleted from pages 7, 8, 11, 13, 14, 17, 20 and 28.

3. At places, the text goes: there is nothing, but actually there is something, and actually there is one thorough good example (e.g. current definition of research subject). That style is difficult for the reader. Go more straight/ reverse the order.

This is a good suggestion for improving the conciseness of our arguments. In particular, the section “Regulatory definitions of ‘research subject’”, beginning on p.7 has been shortened in light of the reviewer’s suggestion.

Details
1. The word “intervention” is used, as far as I understood, to mean an activity made within research. As this word also has a more narrow meaning (“experiment”), not covering “data collection intervention” (data collection by interview or from documents), I suggest changing the term.

We respectfully disagree. Research involving human subjects—experiments, if you will—involves two different types of interventions: experimental interventions (those that are being evaluated and control interventions), as well as the data collection interventions that are used solely to answer the study’s scientific question. The distinction between experimental interventions and data collection interventions is morally relevant in that they offer a different relationship of risks and potential benefits to subjects, and must be considered separately during the ethics review process. We believe that this distinction must be preserved in our paper.

2. There are some misspellings/extra words, so a proof-reading is needed.

Done.