Author's response to reviews

Title: When is informed consent required in cluster randomized trials in health research?

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Author's response to reviews: see over
Response to reviewers' reports
July 28, 2011

Reviewer's report #1
Title: When is informed consent required in cluster randomized trials in health research?
Version: 1 Date: 26 June 2011
Reviewer: Valentino Manase Lema

Reviewer's report:
The article is of great importance to health research especially in the developing world. Ethical issues remain thorny and of major concern. The article raises very pertinent issues especially for the developing world where most such studies will be conducted.

- Thank you. Our recent review of a random sample of 300 published cluster randomized trials (2000-2008) found that 255 (85%) were conducted in developed countries and 45 (15%) were conducted in developing countries (BMJ 2011; 342: d2496).

I have issues with any study being conducted in the developing world without proper informed consent process. As a researcher and someone who has served on ethics committee I do not agree that informed consent can be done away with for CRT. All efforts should be made to get informed consent of all participants, otherwise a study involving human subjects should not be carried out.

- We agree with the reviewer that the ethical conduct of research requires a proper informed consent process. We argue that informed consent is a key moral requirement for the conduct of human subjects research. As we explain, the function of informed consent is to allow prospective research subjects to adopt the ends of the study as their own, thereby (partially) justifying exposing subjects to risk for the benefit of others. The rest of our paper is an exploration of what is a proper informed consent process in a cluster randomized trial.

As we explain, CRTs pose difficult challenges for informed consent that have not been adequately considered by national or international ethics guidelines. There are two main reasons for this. First, in a single CRT the units of randomization, experimentation, and observation may differ meaning it is unclear from whom consent is required. Second, when a CRT involves a cluster-level intervention, refusal of consent may be meaningless if cluster members are unable to avoid the intervention and, if the cluster size is large, it may not be feasible to obtain informed consent of all cluster members.

Referring to prior work, we argue that when a cluster level intervention only has an indirect effect on cluster members (for instance, a knowledge translation intervention directed at health care providers may only indirectly affect patients), cluster members may not be research subjects in that they are not exposed to risk for the benefit of others. If they are not research subjects and are not exposed to risk for the benefit of others, the informed consent of such individuals is not required.
When a cluster-level intervention means that refusal of consent is meaningless or, due to cluster size, cannot be feasibly obtained, the study cannot proceed without additional moral justification. International ethics guidelines allow for a waiver of consent in such cases only if study participation poses no more than minimal risk. We explain how this position is consistent with the above described moral purpose of consent:

"Since informed consent is key to justifying exposing research subjects to risk for the benefit of others, waiving the informed consent requirement can only be contemplated in cases in which the risk involved is insignificant. When a study poses more than minimal risk, the lack of informed consent would amount to using research subjects as mere means to an end. Thus, when informed consent cannot be obtained and study procedures expose subjects to more than minimal risk, we believe a study cannot proceed ethically."

In the second section we argue that informed consent is not required for randomization of clusters when this occurs prior to individual cluster members being approached (at the earliest opportunity) for informed consent. Here, of course, informed consent of cluster members is still required; the claim is simply that consent to randomization is not part of the consent process. In the third section we consider what the scope of consent ought to be in such cases—a question hitherto not considered in the literature. In the fourth section, we argue that passive consent is not an valid substitute for informed consent. In the fifth section, we argue that health care professionals have a prima facie moral obligation to participate in research but that their informed consent is still required.

In short, our paper begins with the moral purpose of consent and explores just what is a proper informed consent process in the face of the difficult challenges posed by CRTs.

I do not buy the assertion that providing complete information in CRT may lead to bias of study results/findings! The same can be said with regards to reliability of authenticity of study findings in cases where informed consent was not obtained in advance.

- Thank you for raising this point. We have expanded our discussion of informed consent and bias in CRTs, and now describe two kinds of bias related to informed consent and we have added a reference to substantiate this point. It now reads, in part:

"CRTs commonly evaluate interventions aimed at modifying the behavior of cluster members. Knowledge of the nature of interventions in other arms of the trial, including the control arm, may at times plausibly be thought to change people's behaviors and consequently bias the outcome of the study (i.e., response bias). For example, consider a CRT evaluating an intervention to improve physician uptake of clinical practice guidelines. If physicians in the control group are informed of the details of the study intervention, they may change their behavior in accord with the practice guidelines, thus biasing the estimate of the intervention effect towards the null hypothesis [26]. In the worst case scenario, the study may conclude that an effective intervention is ineffective; on the other hand, if the bias is modest, the observed effect may still be of clinical interest and hence, influence policy."
Separate from response bias, selection bias can be introduced in a CRT when patients are required to provide informed consent for data collection after randomization of their health professionals [27]. Selection bias does not arise when all patients—or a random subsample in each arm of the study—consent; however, when there are different propensities to consent in the intervention and control arms of the study (e.g., when knowledge of, or exposure to, the experimental or control interventions influences the likelihood that patients consent to data collection) this can lead to imbalances between the trial arms which can bias the estimate of the intervention effect in an unknown direction and make the trial results uninterpretable.

It is important to appreciate the fact that such studies will be carried out in developing countries and funded by multinationals from the developed world. For whose interest are the studies being conducted? Why should the researchers not invest in obtaining informed consent at all times? Would such processes be acceptable in the developed world? I guess NOT! as in-fact shown by the reference to the USA where it is stated in the article that each state may vary what has been recommended. This to me is a another way of saying that it is okay for other countries but not the USA!

- The reviewer raises an important point. Research in developing countries is conducted against a backdrop of global inequalities in the distribution of health and health care. Unscrupulous study sponsors or researchers may attempt to exploit these inequalities and conduct research that is primarily for their own pecuniary interests, or for the primary benefit of the sponsor country. We take up this important issue in another paper in the series, "How ought vulnerable groups be protected in CRTs?", as described in the introduction to the series (http://www.trialsjournal.com/content/12/1/100).

We would like to make clear, however, that our finding are universal in scope and apply to developed and developing countries equally. The discussion of waiver of informed consent is focused on U.S. federal regulations that permit waivers of consent in the United States. State law may in principle block the use of a waiver of informed consent, but this is true of legislation in any country. We are unaware of any State law that in fact prohibits a waiver of consent, but we have not systematically reviewed State legislation.

All the examples given in the article are on studies carried out in developing countries and by non-developing country researchers I guess. It therefore supports the above assertion.

The article opens a pandora box on a critical issue - research in developing world funded by the developing world!

- We chose examples that illustrate well the challenges in obtaining informed consent in CRTs. The Guidelines Trial aimed to increase the uptake of evidence-based obstetrical guidelines in Argentina and Uruguay and illustrates well a study intervention directed at health care providers that only indirectly effects patients. The malaria prevention trial conducted in Pakistan is a good example of a cluster-level intervention (insecticide spraying of dwellings) that would be difficult for those refusing consent to avoid. The umbilical
stump care trial in Nepal is a clear case in which it would have been impossible to seek the informed consent of cluster participants before clusters were randomized.

In all three cases, we argue that informed consent is, in fact, required for some of the people in the study and for some study procedures. In the Guidelines trial, we argue that informed consent ought to be obtained from health care providers. In the malaria prevention trial we state that "researchers should have obtained informed consent for screening subjects and taking blood for peripheral smears". In the umbilical stump care trial we argue that the informed consent of all women in the trial is required and that "the informed consent document should have been tailored to the trial arm to which a particular cluster was allocated".

Further, in each of these cases the trial was designed to address a question of considerable importance to the health of local patients or public health. None, insofar as we are aware, involves any substantial worry of corporate influence.

The comments notwithstanding, I feel the article is worth publishing if only to stimulate further discussion on the subject!

- Thank you.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests: I declare that I have no competing interests.

Reviewer's report
Title: When is informed consent required in cluster randomized trials in health research?
Version: 1 Date: 27 June 2011
Reviewer: Charlie Goldsmith

Reviewer's report:
In general, this manuscript is well done. However, there are a few suggestions that will hopefully improve the manuscript for readers.

- Thank you.

1. P(age) 1, second to last author. Is there a reason why her email address is NOT underlined?

- Done.

2. P 8, p(aragraph) 2, l 8. Suggest dropping [in order] in front of [to] as the words are redundant in English. Also P 28, p 2, l 2.
3. P 11, p 1. Try to reword your text to be gender neutral. You always place the male before the female. Is this intentional? So in l 2 suggest replacing [he or she] by [the person]. Likewise on l 4 suggest replacing [his or her] by [their] and on l 5 replacing [him- or herself] by [themselves]. Other variations can also work but still keeping gender out of the language when it is NOT needed. There are many more in the rest of the manuscript; however, they will not be noted.

- Done throughout the paper.

4. P 11, p 3, l 3. While here you place a description of the study interventions as desirable information to disclose, later you suggest it is not needed. Should you not be consistent? See P 19, p 3, l 8 is in conflict with this because of possible bias. Also P 24, p 2, l 7 and 8 as well as what follows.

- The paragraph on page 11 summarizes requirements for informed consent as found in a variety of current national and international guidelines. The documents generally require that study interventions should be described in the informed consent process. However, these requirements are not absolute. Most of these guidelines contain a provision for a waiver of consent allowing a research ethics committee to "approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent" provided certain conditions are met. Thus, with justification, an informed consent procedure may not include a description of some or all study interventions. We have added text clarifying this point: "As discussed in detail below, a number of these guidelines allow for a waiver of consent [12,13,15]. Accordingly, when a research ethics committee concludes that it is not feasible to obtain consent and study participation poses only minimal risk, it may approve a consent procedure which does not include, or which alters, some or all of these requirements, or it may waive the requirement to obtain consent."

On page 19, we have clarified our position on bias and waiver of consent. As noted above we have expanded our discussion of bias. We point out that investigators ought first to explore other means to avert selection bias. We further point out that the bar for research ethics committee approval of such requests ought to be high. Generally, these cases will involve a request for an alternation of one or more of the disclosure requirements as opposed to a request to waive the requirement to obtain consent; thus, even when granted, informed consent will be sought from prospective subjects. The section now reads as follows:

"Researchers can sometimes avoid or mitigate the risk of selection bias through careful planning of study procedures and execution [27]. For example, identification and recruitment can be completed before randomization if possible, or done by someone blind to the randomization status of the group. When such steps are inadequate, researchers may apply for a waiver of consent. There is no specific regulatory guidance defining when concerns for study validity might outweigh obligations to obtain informed consent. Generally, we believe that research ethics committees ought to adopt a restrictive stance on granting waivers of consent. When
applying for a waiver of consent, investigators should provide evidence that complete disclosure would so bias the study findings as to make the study practically uninterpretable. When compelling evidence exists, the research ethics committee may approve an alteration of the consent procedures to ensure subjects are blinded to the exact nature of the interventions. Thus, these cases will involve an alteration of one or more of the disclosure requirements, rather than waiving altogether the requirement to obtain consent. Research ethics committees should not grant a waiver of consent in the absence of compelling evidence."

On page 24, we attempt to define the ethical requirements of informed consent when clusters are randomized before study subjects are approached for participation. This is not a circumstance that any of the national or international guidelines we refer to above has anticipated. Accordingly, we appeal to the moral purpose of informed consent for our analysis. We argue that in order to make a responsible decision people must be provided with detailed information on the consequences of agreeing to and declining study participation. Typically in an individually RCT, randomization occurs after consent and thus the pertinent consequences include the study procedures in all of the trial arms. Hence, informed consent must include a description of study procedures in all trial arms. However, when subjects are approached for consent after clusters have been randomized the pertinent consequences do not include study procedures in trial arms to which their cluster has not been allocated. Thus, we argue, informed consent need only include a description of the study interventions in the arm to which their cluster has been allocated (and, of course, the other elements of consent). We have added a sentence to this section clarifying the relationship between our proposal and a waiver of consent: "It is important to recognize that "tailored consent" is not a waiver of consent; rather, it is full disclosure in these circumstances as defined by the moral purpose of informed consent". Finally, in the discussion of tailored consent and bias we point out that: "It should be noted, however, that concerns about selection bias are not affected by this proposal."

5. P 12, p 3, l 19. Since data is a plural word, suggest replace [is] by [are].

- Done. The document was searched for other mismatches between the word 'data' and a verb.

6. P 13, p 3, l 14. What is the time frame for incidence here? Is should always be clear, and is usually stated. Also P 13, p 3, l 13. Also P 18, p 3, l 5.

- Done. The term "annual incidence" is now used in each case.

7. P 17, p 2, l 14. This would be a good place to provide an example of such a state.

- Done. California is listed as an example.

8. P 18, p 1, l 16. Suggest replacing [population] by [group]. Few investigators get a chance to study a population. There may be a target population, however nobody ever successfully accesses all of the members, it is usually a sample.
9. P 19, p 3, l 11. This needs to be properly discussed. Not all bias is bad. It can be over or under estimate an effect, however, if the magnitude is underestimated and still be of clinical interest, the effect can still influence a policy. However, if bias makes an effect seem important when it is not by overestimating the effect, then that makes it invalid. This depends on the measurement properties of the tool used to measure the outcome of clinical interest. This also is needed on P 20, p 1, l 11 to justify the waiver here.

- Thank you for this suggestion. As described above, we have modified the text to indicate that the type of bias resulting from contamination of the intervention effect will tend to be towards the null, and thus, will not necessarily invalidate the trial results. We added that a more serious form of bias can arise when patients are required to provide consent to data collection after randomization of their health professionals. This form of bias can threaten the internal validity of the trial. We have added a reference to substantiate this point.

10. P 21, p 1, l 3. Suggest replacing [failing] by [inability]. The word failing is too strong as it implies it MUST be done. For a subject, they may not want to consent so how can it be a failure?

- Done. The document was checked for other instances of the inappropriate use of the words 'fail' or 'failure'.

11. P 21, p 2, l 3. Suggest replacing [significant] by [important]. If this is meant to imply it is statistically significant; you need to say what is the referent category. If this is an opinion, then the word important is more suitable.

- Done. The document was searched for other inappropriate uses of the word 'significant'.

A random sample of 10 R(eference)s was checked for citation accuracy.


- Done. This change was made for all references to documents available on websites. All references were carefully checked. Reference 16 and 28 were duplicate and hence reference 27 was removed. A new reference was inserted addressing the issue of bias, discussed above. All website addresses were reconfirmed. All article references were checked on PubMed for accuracy.

13. P 34, R 6 and 7, l 3. Add [London ON] at the end of each. I was not able to verify these.

- Done for reference 6. We have changed reference 7 as the paper has now been published in Trials.

14. P 35, R 9 should have authors listed as [Faden RR, Beauchamp TL, King NMP].

- Done.
Reviewer's report #3
Title: When is informed consent required in cluster randomized trials in health research?
Version: 1 Date: 7 July 2011
Reviewer: Inmaculada de Melo-Martin

Reviewer's report:
The purpose of this paper is to address the questions from whom, when, and how must informed consent be obtained in cluster randomized trials CRTs in health research. The authors use the moral purpose of consent –respect for persons-- as a conceptual foundation to answer those questions. The title and abstract are appropriately informative, the paper is clear, and the arguments are compelling. It provides a good overview of some of the main concerns that arise in relation to informed consent when conducting CRTs.

- We are very grateful to the reviewer for her kind words about the paper. Thank you.

Level of interest: An article of importance in its field
Quality of written English: Acceptable
Statistical review: No, the manuscript does not need to be seen by a statistician.
Declaration of competing interests:
I declare that I have no competing interests.