PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Informed consent in cluster randomised trials: a guide for the perplexed
AUTHORS	Nix, Hayden; Weijer, Charles; Brehaut, Jamie; Forster, David; Goldstein, Cory; Taljaard, Monica

VERSION 1 – REVIEW

REVIEWER	Flory, J Memorial Sloan Kettering Cancer Center
REVIEW RETURNED	16-Aug-2021

GENERAL COMMENTS	This is a lucid and helpful overview of an important topic, and helps to disseminate the important Ottawa Statement. This reviewer did identify (mostly minor) opportunities to clarify or more appropriately frame this work, as follows. There is considerable subjectivity to some of these critiques and I would urge the editor and authors to view them as suggestions rather than demands by this reviewer. Minor critiques: 1) This overview draws much of its authority from reference to the Ottawa statement. That being the case, it is worth highlighting for readers that authorship of this manuscript and of the Ottawa statement overlap significantly - this could be done briefly in the text, or perhaps in the acknowledgment section. 2) Abstract: the phrase 'intact social groups' is never clearly defined and intuitively does not seem right to me (eg, some cluster randomized trials [CRTs] have randomized units such as people on a particular insurance plan). In lay language I wouldn't say sharing an insurance plan creates an intact social group. Would suggest removing phrase. Or, if it's doing important conceptual work I don't appreciate, would explain in the main text. 2) Abstract - "Some argue - incorrectly - that cluster randomization ..." - I would word this a little more cautiously. Dismissing an ethical position as 'incorrect' in the abstract with no supporting argument sets too authoritative a tone for this topic. The authors are presenting a coherent framework for ethical reasoning about informed consent for CRTs, and in doing so make a compelling case for requiring informed consent in many of these studies, but I don't think should write as if they've 'proven' competing positions to be absolutely wrong. Page 5: Would clarify through a more specific example what kind of 'logistical challenges' the authors have in mind. It is important to

	be clear (unless this is what the authors mean) that logistical challenges does not include 'logistically challenging to approach individuals for informed consent'. Table 1: 'patients are not research participants ...unless...their private information is used' - here and elsewhere in the paper, it would be useful to researchers to clarify whether this does or does not require informed consent for a trial that passively collects outcome data from an electronic medical record, either as structured data or through chart review. Does the exception for medical record review mentioned on page 9 apply here? Or does the initial access of identifiable information trigger a need for informed consent, as on page 12? Page 8: "obtaining consent may be infeasible when consent is logistically challenging, for example due to excessive cluster size'. This seems a remarkable exception, if it allows researchers to argue that there are just too many individuals to contact. Why would this exception not also apply to very large individually randomized RCTs? (Eg, if I wanted to study a very rare safety outcome and had to randomize millions of individuals). Page 13. REC used without defining acronym first Page 16. Similar to the point earlier about large cluster size justifying a waiver, the argument here that cost might be the explicit justification for an informed consent waiver is remarkable, at least to a reviewer working in the US research oversight system. Are there examples of this being done? Is this issue specific to CRTs or are such waivers discussed for conventional trials as well? Page 18: The statement "Issues of informed consent are a function of the unit of the intervention in a study, not the unit of randomisation" is the last line of the abstract and the first line of the last paragraph of the paper, making it seem as though it is either the conclusion to which previous arguments in the paper lead, or else is just the most important single concept in the paper. It seems to be functioning more as a useful starting point that then helps the reader execute the three-step framework. Would clarify the role this idea plays in the framework presented here. Page 19: Would consider replacing 'guide to the perplexed' with a more prosaically informative subtitle, something like 'A framework for determining when it is required'

REVIEWER	Bower, Peter University of Manchester, NPCRDC
REVIEW RETURNED	27-Aug-2021

GENERAL COMMENTS	Comments for the editors The pitch for this paper is whether it adds significantly to previous pieces on this issue, and the practical focus here is a contribution – I am myself doing a cluster RCT and this was helpful in assessing that and thinking through the issues I had some minor comments, but I think this is a useful contribution and publishable with minor changes Thanks for the opportunity to comment on this paper. As someone currently embroiled in a cluster RCT, I thought this was a useful

	overview with some helpful practical advice on how to approach some of the tricky ethical issues in a structured fashion. The aim of the paper is 'to build upon the Ottawa Statement by providing a practical and useful framework to guide researchers and research ethics committees through consent issues in CRTs'. This suggests that the Ottawa statement needs additional detail and 'working through' to be useful. I think their case is reasonable and that this paper makes a useful contribution. The tables and 'decision rules' are useful I had some areas where I felt some additional clarification would be useful In applying their heuristics to my own current trial, I faced a real ambiguity concerning an ability to distinguish between CRTs in which the intervention is delivered to healthcare professionals and CRTs in which the intervention is delivered by healthcare professionals'? They highlight this complexity, and gave some examples, but I still struggled with the distinction (which seems very important). Could they provide additional guidance here? The reference to 'fiduciary duties' was not that helpful, and I did not find the comment about clinicians being free to make treatment choices very clear. What would be an example where they were not free? Would ALL pragmatic trials essentially meet those criteria of 'freedom'? I realise that this is a complex area, but any further clarity on this issue would be helpful – even if it is just more examples. Similarly, the statement about CARDSS, where the 'nature of the intervention required healthcare professionals in the trial to retain the ability to easily reidentify patient data' could benefit from more explanation. Was that specific to CARDSS, as I was not sure why that would be the case. Was it a patient safety issue, or a methodological one? A minor issue, but I struggled to understand why PICS was a CRT, and further explanation might be useful to make it clear why the trial took that approach. I think the authors make a reasonable simplification, when they state that 'it is common for one CRT to evaluate interventions with multiple components at multiple levels. However, for simplicity in this educational paper, we consider CRTs that exclusively evaluate interventions at a single level'. However, I thought it would be reasonable to say a little about what additional complexities are introduced with multiple levels. For example, would the 'lowest' level (i.e. individual interventions') essentially 'trump' other levels in terms of the stringency of the ethical requirements? That was my original thought, but they will have course given it far greater consideration than me. Did the paper have input from representatives from ethics boards? It would seem critical that the ideas and tools here had traction with those making decisions from that 'side of the fence'. I thought it was a shame that consideration of the issues in the specific context of the US was fairly informal, and that this was only done for the US. Could that have been done for the UK and Europe, or for a LMIC context? That seemed like a missed

	opportunity although I appreciate it is potentially significant additional work. In the introduction, there was a reference to the 'moral status' of individuals and groups and I was not really sure what was being discussed here. Was that required? I was not sure what that added

VERSION 1 – AUTHOR RESPONSE

Informed consent in Cluster Randomised Trials: a guide for the perplexed

Reviewer 1
Dr. J Flory, Memorial Sloan Kettering Cancer Center
Comments to the Author:
This is a lucid and helpful overview of an important topic, and helps to disseminate the important Ottawa Statement. This reviewer did identify (mostly minor) opportunities to clarify or more appropriately frame this work, as follows. There is considerable subjectivity to some of these critiques and I would urge the editor and authors to view them as suggestions rather than demands by this reviewer.

Thank you for your kind words and helpful suggestions.

Minor critiques:
1. This overview draws much of its authority from reference to the Ottawa statement. That being the case, it is worth highlighting for readers that authorship of this manuscript and of the Ottawa statement overlap significantly - this could be done briefly in the text, or perhaps in the acknowledgment section. [NOTE FROM THE EDITORS: For full transparency, it may be appropriate to mention this in the 'Competing interests' statement].

We have added the following statement to the Competing Interests disclosure: "CW, JCB, DF, and MT are authors of the Ottawa Statement on the Ethical Design and Conduct of Cluster Randomised Trials" (Competing Interests, Page 20, Line 45-46).

2. Abstract: the phrase 'intact social groups' is never clearly defined and intuitively does not seem right to me (eg, some cluster randomized trials [CRTs] have randomized units such as people on a particular insurance plan). In lay language I wouldn't say sharing an insurance plan creates an intact social group. Would suggest removing phrase. Or, if it's doing important conceptual work I don't appreciate, would explain in the main text.

We replaced "Intact social groups" with "intact groups" (Abstract, Page 2, Line 2; Introduction, Page 3, Line 3 and 32; CRTs of Individual-level interventions, Page 14, Line 27).

The key consideration here is that a cluster randomised trial allocates existing or naturally occurring groups - rather than separate individuals. The groups may be formed through a social or geographical connection, or based on a logistical consideration (e.g., people on a particular insurance plan). A defining feature is that membership in a group gives rise to a positive (intracluster) correlation among responses within a group. In a related design, the "individually randomized group treatment trial" which is not considered in this manuscript, individuals are randomly allocated to groups who then receive the intervention in a group-based setting.

3. Abstract - "Some argue - incorrectly - that cluster randomization ..." - I would word this a little more cautiously. Dismissing an ethical position as 'incorrect' in the abstract with no supporting argument sets too authoritative a tone for this topic. The authors are presenting a coherent framework for ethical reasoning about informed consent for CRTs, and in doing so make a compelling case for requiring informed consent in many of these studies, but I don't think should write as if they've 'proven' competing positions to be absolutely wrong.

We deleted the word “incorrect” and edited the abstract to summarise our argument in a less authoritative tone:
“Some argue that cluster randomisation is a reason not to seek informed consent from research participants… The objective of this paper is to clarify this confusion by providing a practical and useful framework to guide researchers and research ethics committees through consent issues in CRTs.” (Abstract, Page 2, Line 5-10).

4. Page 3: Would clarify through a more specific example what kind of 'logistical challenges' the authors have in mind. It is important to be clear (unless this is what the authors mean) that logistical challenges does not include 'logistically challenging to approach individuals for informed consent'.

We edited this paragraph to clarify that we were referring to logistical challenges in the delivery of the study intervention, not logistical challenges surrounding obtaining informed consent from participants:
“But CRTs can also be a useful design for evaluating individual-level interventions when there is a compelling reason not to use individual randomisation—such as… logistical challenges. For example… interventions of protocolized treatments, such as intravenous fluid resuscitation, may be logistically easier to deliver to patients using cluster randomisation… However, avoiding the need to seek informed consent is an inappropriate justification for adopting a cluster randomised design.” (Introduction, Page 3, Line 11-21).

5. Table 1: 'patients are not research participants ...unless...their private information is used' - here and elsewhere in the paper, it would be useful to researchers to clarify whether this does or does not require informed consent for a trial that passively collects outcome data from an electronic medical record, either as structured data or through chart review. Does the exception for medical record review mentioned on page 7 apply here? Or does the initial access of identifiable information trigger a need for informed consent, as on page 10?

We thank the reviewer for identifying this as an aspect of our paper that is unclear. The historical scope of the waiver of consent did not encompass randomised trials. Its scope was limited retrospective chart reviews and behavioural research: two types of non-randomised research activities. The Ottawa Statement expanded the scope of the infeasibility criterion for a waiver of consent to encompass CRTs of cluster-level interventions: We edited the text to clarify this issue:
“The waiver of consent was originally designed for retrospective review of medical records and behavioural research. Originally, it did not encompass randomised trials. Its scope was limited to retrospective medical record reviews and behavioural research: two types of non-randomised studies. When medical records are reviewed for research purposes outside of randomised trials, it is considered infeasible to track down each participant to obtain consent for the use of their data; a waiver of consent is generally acceptable so long as adequate confidentiality protections are in place.[14]… The Ottawa Statement expanded the scope of the infeasibility criterion for a waiver of consent to encompass cluster-level interventions in CRTs, in which cluster members have little or no choice but to be exposed to the intervention.” (CRTs of Cluster-level interventions, Page 7, Line 22-34).

6. Page 6: "obtaining consent may be infeasible when consent is logistically challenging, for example

due to excessive cluster size'. This seems a remarkable exception, if it allows researchers to argue that there are just too many individuals to contact. Why would this exception not also apply to very large individually randomized RCTs? (e.g., if I wanted to study a very rare safety outcome and had to randomize millions of individuals).

We agree that this is an inappropriate justification for a waiver of consent. This clause has been deleted (The Ottawa Statement Guidance on Informed Consent, Page 6, Line 16).

7. Page 11. REC used without defining acronym first

“REC” has been replaced with “research ethics committees” (CRTs of individual-level interventions, Page 12, Line 25).

8. Page 14. Similar to the point earlier about large cluster size justifying a waiver, the argument here that cost might be the explicit justification for an informed consent waiver is remarkable, at least to a reviewer working in the US research oversight system. Are there examples of this being done? Is this issue specific to CRTs or are such waivers discussed for conventional trials as well?

We agree with the reviewer that cost is an exceptional justification for a waiver of consent. Waivers of consent are, in our experience, rare in individually randomized trials for any reason. When they invoke cost, researchers are often referring to the limited research infrastructure at participating sites, including the lack of study coordinators to seek standard written consent from participants. In such circumstances, we believe that researchers should consider more cost-effective approaches to standard written consent, such as integrated or verbal consent. We believe these alternatives to be preferable to a waiver of consent as they reduce study costs, respect participant autonomy, and promote pragmatism. We have clarified the discussion as follows:
“Generally, cost is not a sufficient justification for a waiver of consent. If the cost of obtaining informed consent in a CRT is prohibitively expensive, then researchers should consider whether the study question can be answered with a different, less expensive design. The cost of seeking informed consent is a function of sample size and CRTs are statistically inefficient, requiring a larger sample size than an analogous individually randomised trial. Consequently, when evaluating an individual-level intervention, individual randomisation is typically more cost effective than cluster randomisation. Further, researchers should consider the use of pragmatic alternatives to standard written informed consent, such as integrated consent, verbal consent, or short form consent.[29] Healthcare professionals, as opposed to hired research staff, may be used to obtain informed consent from patients to avoid excessive costs.” (CRTs of individual-level interventions, Page 15, Line 7-17).

9. Page 16: The statement "Issues of informed consent are a function of the unit of the intervention in a study, not the unit of randomisation" is the last line of the abstract and the first line of the last paragraph of the paper, making it seem as though it is either the conclusion to which previous arguments in the paper lead, or else is just the most important single concept in the paper. It seems to be functioning more as a useful starting point that then helps the reader execute the three-step framework. Would clarify the role this idea plays in the framework presented here.

We agree. The notion that informed consent tracks the unit of intervention, not the unit of randomisation, is both a central point in this paper and a starting point from which trialists and researchers should execute the three-step framework. The abstract, introduction, and conclusion have been edited to reflect this understanding of our position.

Abstract: “In CRTs, it is the unit of intervention—not the unit of randomisation—that drives informed consent issues. We explicate a three-step framework for thinking through informed consent in CRTs: (1) identify research participants, (2) identify the study element(s) to which participants are exposed,

(3) determine if a waiver of consent is appropriate for each study element. We then apply our framework to examples of CRTs of cluster-level, professional-level, and individual-level interventions, and provide key lessons on informed consent for each type of CRT." (Abstract, Page 2, Line 10-16).

Introduction: "We argue that it is the unit of intervention—not randomisation—that drives issues of informed consent in CRTs. We offer a three-step framework to determine whether informed consent should be obtained from an individual in a CRT (Figure 1). First, are the individuals in question research participants? Second, if they are research participants, to what study element(s) are they exposed? And third, do the conditions for a waiver of consent obtain for each study element? In what follows, we review the Ottawa Statement guidelines on informed consent in CRTs. Then we apply our three-step framework to CRTs of cluster-level interventions, professional-level interventions, and individual-level interventions. For each type of CRT, key lessons are provided (Table 1) and an example is discussed in detail." (Introduction, Page 4, Line 22-30).

Conclusion: "This paper seeks to provide a three-step framework for thinking through these challenges: First, who are the research participants? Second, to what study element(s) are they exposed? And third, for each study element, is a waiver of consent appropriate? Applying this this framework to CRTs of cluster-level, professional-level, and individual-level interventions demonstrates that issues of informed consent are a function of the unit of the intervention in a study, not the unit of randomisation." (Conclusion, Page 16, Line 38-43).

10. Page 1: Would consider replacing 'guide to the perplexed' with a more prosaically informative subtitle, something like 'A framework for determining when it is required'

We acknowledge that titles are matters of aesthetic judgement and are open to reasonable disagreement. In our view, "a guide for the perplexed" is semantically equivalent to "a framework for determining when it is required." We think our title a more artful turn of phrase, but we are happy to leave the decision to the editors.

Reviewer: 2
Dr. Peter Bower, University of Manchester
Comments to the Author:
Comments for the editors
The pitch for this paper is whether it adds significantly to previous pieces on this issue, and the practical focus here is a contribution – I am myself doing a cluster RCT and this was helpful in assessing that and thinking through the issues. I had some minor comments, but I think this is a useful contribution and publishable with minor changes.
Thanks for the opportunity to comment on this paper. As someone currently embroiled in a cluster RCT, I thought this was a useful overview with some helpful practical advice on how to approach some of the tricky ethical issues in a structured fashion.
The aim of the paper is 'to build upon the Ottawa Statement by providing a practical and useful framework to guide researchers and research ethics committees through consent issues in CRTs'. This suggests that the Ottawa statement needs additional detail and 'working through' to be useful. I think their case is reasonable and that this paper makes a useful contribution. The tables and 'decision rules' are useful.
I had some areas where I felt some additional clarification would be useful.

Thank you for these kind words. It is gratifying to read that the paper was useful to you in thinking through a trial you are designing.

1. In applying their heuristics to my own current trial, I faced a real ambiguity concerning an ability to distinguish between CRTs in which the intervention is delivered to healthcare professionals and CRTs

in which the intervention is delivered by healthcare professionals'? They highlight this complexity, and gave some examples, but I still struggled with the distinction (which seems very important). Could they provide additional guidance here? The reference to 'fiduciary duties' was not that helpful, and I did not find the comment about clinicians being free to make treatment choices very clear. What would be an example where they were not free? Would ALL pragmatic trials essentially meet those criteria of 'freedom'? I realise that this is a complex area, but any further clarity on this issue would be helpful – even if it is just more examples.

We agree that the distinction between interventions that are delivered to versus delivered by healthcare professionals is particularly challenging. Indeed, our research team plans to explore this question in an independent, forthcoming paper. For the purposes of the paper under review, we offer several clarifications. First, we have added an example of a trial in which the intervention is entirely delivered by healthcare professionals: "For example, the REMCARE trial evaluated the effectiveness of group reminiscence therapy for people living with dementia and their family caregivers.[19] Researchers trained healthcare professionals to facilitate the group therapy sessions. The primary objective of the trial was to evaluate the effectiveness of the group therapy sessions, not healthcare professionals' ability to deliver the intervention. Because the intervention was delivered by the healthcare professionals, healthcare professionals are neither research participants nor is their informed consent required." (CRTs of professional-level interventions, Page 9, Line 17-23).

Second, we revised the section about the CARDSS trial to make it clear that, in the CARDSS trial, the intervention was entirely delivered to healthcare professionals: "In the CARDSS trial, all components of the intervention were delivered to the team of healthcare professionals" (CRTs of professional-cluster interventions, Page 9, Line 25-26)

Third, we revised the section about fiduciary duties to clarify that this argument applies only to CRTs of professional-cluster interventions that (1) are entirely delivered to healthcare professionals, and (2) promote the uptake of evidence-based behaviour. The notion of "fiduciary duties" seeks to clarify why patients may not be research participants when the study intervention seeks to promote the uptake of evidence-based practices by health providers. "Unlike healthcare professionals, patients may not be research participants in some CRTs of professional-level interventions that are entirely delivered to healthcare professionals… Knowledge translation interventions that are (1) entirely delivered to healthcare professionals and (2) promote the uptake of evidence-based behaviours do not interfere with the physician's individualised judgement on behalf of her patient.[8]" (CRTs of professional-level interventions, Page 9, Line 45-46; Page 10, Line 3-6).

2. Similarly, the statement about CARDSS, where the 'nature of the intervention required healthcare professionals in the trial to retain the ability to easily reidentify patient data' could benefit from more explanation. Was that specific to CARDSS, as I was not sure why that would be the case. Was it a patient safety issue, or a methodological one?

We thank the reviewer for identifying this ambiguity. In the CARDSS trial, a component of the study intervention included the opportunity to reidentify specific patients' data for discussion during the education sessions. This was not a patient safety issue per se. Instead, it was a component of the audit and feedback intervention, to allow healthcare professionals in the trial to learn more about how they should provide care in specific cases. The text has been edited to clarify this point: "The feedback included a written report and an in-person education session led by a researcher. Importantly, during the education sessions, healthcare professionals were given the opportunity to reidentify patient data to discuss the details of specific cases" (CRTs of professional-level intervention, Page 8, Line 37-40). "But one component of the feedback intervention required healthcare professionals in the trial to retain the ability to easily reidentify patient data so that they could discuss specific cases in detail" (CRTs of professional-level interventions, Page 10, Line 27-29).

3. A minor issue, but I struggled to understand why PICS was a CRT, and further explanation might be useful to make it clear why the trial took that approach.

This comment raises an excellent question. We too wonder about the choice to cluster randomise in the PICS trial. We have taken this as an opportunity to remind researchers and research ethics committees that cluster randomisation ought to be justified, and that those justifications need to be scrutinised: “Because individual-level interventions can be tested in individually randomised trials or CRTs, researchers need to justify the use of cluster randomisation. In turn, research ethics committees need to scrutinise these justifications, because cluster randomisation should never be chosen to avoid informed consent.

The researchers in the PICS trial provided two justifications for adopting a cluster randomised design. First, they argue that the protocolized nature of the study intervention makes cluster randomisation favourable: “Cardiac surgery is conducted in specialized centers using highly standardized procedures, an approach that lends itself to a cluster [randomised] design.”[22] Second, they argue that adopting a factorial cluster crossover design reduced the financial cost of the trial:

[A] trial randomizing individual patients would likely not be feasible due to financial constraints, considering the large sample size needed to power the study properly... In contrast, if the randomization occurs at the level of the health-care center, and therefore, the study intervention becomes the standard operating procedure for that center, the resources required are significantly reduced.[22]

The first justification may be acceptable. However, given that CRTs are less statistically efficient than individually randomised trials, it is unclear how adopting a cluster randomised design reduces costs. The cluster randomised design necessarily requires a larger number of patients to account for the intracluster correlation: approximately 10% more patients in the PICS trial. The investigators are likely comparing cluster randomisation without consent to an individually randomised design with consent.” (CRTs of individual-level interventions, Page 11, Line 2-25).

4. I think the authors make a reasonable simplification, when they state that ‘it is common for one CRT to evaluate interventions with multiple components at multiple levels. However, for simplicity in this educational paper, we consider CRTs that exclusively evaluate interventions at a single level’. However, I thought it would be reasonable to say a little about what additional complexities are introduced with multiple levels. For example, would the ‘lowest’ level (i.e. individual interventions’) essentially ‘trump’ other levels in terms of the stringency of the ethical requirements? That was my original thought, but they will have course given it far greater consideration than me.

In response to this helpful comment, we added to the introduction:
“When dealing with complex CRTs, the three-step framework presented here should be used to evaluate each study intervention and data collection procedure separately.” (Introduction, Page 4, Line 33-35).

5. Did the paper have input from representatives from ethics boards? It would seem critical that the ideas and tools here had traction with those making decisions from that ‘side of the fence’.

We agree that input from representatives from ethics board is invaluable for this kind of work. Accordingly, co-author David Forster is the Chief Compliance Officer of the Western Copernicus Group Institutional Review Board in the US and a member of the US Secretary of Health and Human Services Secretary’s Advisory Committee on Human Research Protections.

6. I thought it was a shame that consideration of the issues in the specific context of the US was fairly informal, and that this was only done for the US. Could that have been done for the UK and Europe, or for a LMIC context? That seemed like a missed opportunity although I appreciate it is potentially significant additional work.

We thank the reviewer for identifying this ambiguity. This section was meant to convey that additional work is required to translate our framework into national regulations around the world. We invoked the example of US regulations simply to demonstrate that this kind of work has been done in some places but has not been done elsewhere. Our point is that more translational work needs to be done: "Therefore, additional work is required to translate our framework for application with various national research regulations around the world.
One example of such translational work comes from the US. The Secretary's Advisory Committee on Human Research Protections (SACHRP) translated the Ottawa Statement recommendations to apply in the US regulatory context.[6] … There is a need for similar translational work to be done elsewhere to apply our framework to national research regulations." (Translating the Ottawa Statement into national regulatory contexts, Page 16, Line 15-34).

7. In the introduction, there was a reference to the 'moral status' of individuals and groups and I was not really sure what was being discussed here. Was that required? I was not sure what that added

This sentence has been rephrased to clarify that "moral status" refers to rights and interests, and obligations owed to people by others: "While the rights and interests of individuals have been broadly discussed and codified, CRTs involve groups of people, and the rights and interests of groups are not well understood." (Introduction, Page 3, Line 31-33). The purpose of this sentence is to convey that CRTs raise ethical issues that are not present in individually randomised trials.

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COI statements:
Reviewer: 1
Competing interests of Reviewer: None.
Reviewer: 2
Competing interests of Reviewer: I have no competing interests.