Reviewer's report

Title: The clinically-integrated randomized trial: a novel method for conducting large trials at low cost

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Reviewer: Mike Clarke

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Since this is a discussion piece, I am content that all my comments are regarded as "Discretionary revisions".

This is a very interesting paper, setting out what you describe as the novel method of the “clinically integrated randomised trial”. I am always wary of people labelling anything as novel and I don’t believe this label adds much to the strength of your ideas and so you might like to consider removing it. If you wish to keep it, it probably needs justifying by evidence that you have searched for similar ideas in the past (for example, in the Cochrane Methodology Register or within existing randomised trials in the Cochrane Central Register of Controlled Trials). It would also be worth adding some discussion of how your design differs from mega-trials which have (for more two decades) relied on wide eligibility criteria and the recruitment of people in the presence of uncertainty, or the suggestion of people such as Tom Chalmers that randomisation should begin with the very first patient. Is the main difference the proposed use of the electronic patient records, which are only now becoming available (but are still not universally available)?

1. Introduction: can you include references to other work (perhaps written by you) on the scale of the problems faced by doctors when they recruit patients into trials?

2. Discussion, paragraph 1: you write that the clinical experience would be “virtually indistinguishable” from routine practice if a patient is in a clinically integrated trial, but won’t there still be a need to discuss the trial with the patient, obtain their consent and maintain their right to leave the trial at any time? Won’t this add to the clinical experience?

3. Discussion, paragraph 3: who would pay for the treatment, tests, etc in a clinically integrated trial? Would it be paid for in the same as in routine practice or would the health care in the trial be paid for in a non-routine way?

4. Discussion, paragraph 3: instead of “The costs of randomization are trivial”, it might be better to write “The costs of each additional randomization are trivial” since I expect that there would be non-trivial costs to set up the randomization programmes in the first place.

5. Discussion, Example 1, paragraph 1: if you wish to contrast the volume of
literature on surgery for prostate cancer, in addition to noting that there are 5 trials with 450 patients, you should include data on the number and size of non-randomized studies in the literature.

6. Discussion, Example 1, paragraph 2: you should give a reference for your statement that a typical estimate for costs is $5000 - $8000 per patient. You should also include an estimate of how much it would cost per patient within a clinically integrated trial.

7. Discussion, Example 1, step 1: do you have an estimate for the amount of time it will take to discuss the trial with the patient? Also, how long would you wish to leave her to make the decision after the trial has been explained to her? Would it be possible to rephrase the second sentence to make it clearer that the considerable doubt relates to which of the alternative techniques to use, rather than doubt about whether or not to do surgery at all. How confident are you that “all, or nearly all” patients will agree to take part in the randomised trial? Is it not likely that a significant proportion will not wish to be part of research?

8. Discussion, Example 1, step 5: have you considered the possibility of randomising patients to different surgeons, in an expertise based design (see Devereaux et al. Need for expertise based randomised controlled trials. BMJ 2005;330:88-91)?

9. Discussion, Example 1, step 6: it would be good if you added something here about whether the electronic medical record would make it clear that the patient had been randomised or simply note the treatment they had been allocated without indicating that this was the outcome of a randomisation.

10. Discussion, Example 1, step 8: do you believe that you can sufficiently de-identify data to protect privacy? For example, it might take only a few pieces of data to identify a person and these data might be vital to the analyses (eg their age, the date they were treated and the clinic they were treated in).

11. Discussion, Example 1, penultimate paragraph: it might be worth expanding this a little to note that some randomisations might be mutually incompatible. For example, one surgical procedure might be compatible with a drug randomisation, but the other procedure might not be.

12. Discussion, final paragraph: it might be worth expanding this a little to discuss how patients could opt out of specific randomisations. At the moment, this paragraph focuses on the wishes of surgeons.

13. Discussion, Example 2, first paragraph: is it true that “there are no treatments that have been proven to be effective” for rare diseases? Have no randomised trials been done that show a treatment is effective? Have no treatments been shown to be effective in robust non-randomised comparisons with, for example, the natural history of an illness?

14. Discussion, Example 2, second paragraph: expand “the drug is chosen at random” by adding “from among those that are known to be effective”.
15. Discussion, Example 2, last paragraph: you should expand this to discuss the need for worldwide agreement on which interventions to test. You might also wish to discuss the possibility of having multi-intervention randomised trials in which individual centres could decide to opt out of some of the interventions; and the ability to remove from the options any treatment that is found to be harmful during the trial.

16. Discussion, Example 3, first paragraph: are the typical costs of $1-2.5 million the costs of the two cited trials or of NIH trials in general?

17. Discussion, Example 3: have you considered including some test of understanding for patients after they have read the online material?

18. Discussion, Example 3: the online trial you suggest is attractive but it would be good if you expanded your discussion of this example to give better balance in the length of the article between the three examples. Some things to consider are: (1) how would loss to follow-up be minimised? (2) would an intention to treat analysis be possible? (3) how would you prevent malicious or accidental false entries? (4) would the lack of personal contact with the participants be problematic? and (5) would you regard this example as “clinically integrated” if it is done with such minimal clinical involvement?

19. Discussion, Incentives, first paragraph: if giving access to the raw data is an incentive for academics, is this because they would use these data to satisfy their own curiosity or would they be able to present and publish analyses, independently of the trial? Is it acceptable to share confidential medical information with all doctors in the trial? Would there need to be rules on whether the doctor/academic had to randomise a minimum number of patients in the trial before they get access to all the raw data for the trial? Might it be a dis-incentive to patients if they know that their medical data will be shared with potentially many people, above and beyond those directly involved in their care and the main organisation and analysis of the trial?

20. Discussion, Incentives, first paragraph: some of your criticism of “traditional trials” is based on the costs and you include cash amounts for these. I suggest, therefore, that you should also include your estimate for the costs of the “modest payment” to doctors in a clinically integrated trial.

21. Discussion, Incentives, second paragraph: the play the winner modification is attractive but I feel that it would be much more complicated to implement than set out in your paper, and it might be better to remove this text. As examples of the complexity: (1) would the analyses need to be stratified for the subgroup into which the next patient falls? (2) would analyse be done in “real time” (ie after each outcome is captured and just before each patient is randomised)? (3) how would you correct things if there was a mistake in the outcome recorded for a patient? (4) how will you cope with short and long term outcomes (eg you mention weight loss, is this over a short term or a long term? The patient might prefer a long term benefit but play the winner might need to use a short term -
potentially unstable - outcome)? and (5) what if a patient would prefer a lower risk of a rare adverse effect, rather than an increased benefit on the primary outcome, and interventions go in opposite directions for these outcomes - can the patient set their own play the winner preferences?

22. Discussion, Incentives, second paragraph: I disagree with the words that you put into the doctor's mouth for their explanation to patients. If the doctor says that "the chance" is that the patient will get the most effective treatment", do you believe that patients in a 1:1 trial would think that this means 60%, or closer to 90%? Furthermore, in the four arm trial you use as an example, if the balance switches from 25:25:25:25 to 30:25:25:20, "the chance" is still that the patient will not get treatment A: they have a 70% chance of getting something different. I would also be cautious about this dynamic approach to the allocation ratio because, if I had entered the trial and been allocated 6 months of treatment with B, but during the first couple of months, the evidence was favouring A, would I be allowed to re-randomise in the hope of getting A or to swap treatments?

23. Discussion, Barriers, first paragraph: where you mention that clinical integrated trials could be 10, 20 or 50 times bigger than "traditional trials", what is your basis for these figures? For example, do you believe that a trial that would have recruited 200 people might recruit 10,000? Also, how comfortable are you in relying on "trust" that no important preferences would lead to bias in the clinically integrated trials? Even a small bias will lead to a finding of statistical significance if thousands or tens of thousands of patients are recruited. For example, if there is a 5% bias in the clinically integrated trial and the true difference is a 1% harm, a "small" trial with no bias would not change practice, but a large clinically integrated trial with the bias might produce a statistically and clinically significant 4% benefit leading to practice change and harm for many patients. Having a large trial will not overcome the effects on the variance of cheating, if that cheating is in the same direction. In fact, doing a large trial in such circumstances is worse than a small trial since it will mathematical precision to the wrong answer.

24. Discussion, Barriers, second paragraph: where you write "many institutions" do you mean in the USA, another country or globally? Instead of "would only need to be done once", it might be better to write "would only need to be done once in each institution". At the end of the paragraph, if you feel it is necessary to write that the costs of the clinically integrated trial "would certainly not approach the many millions of dollars currently associated with large trials", you should still include at least a crude estimate for the costs of clinically integrated trials. For example, do you think it would be a few hundred thousand dollars, many hundreds of thousands, or a few millions?

25. Discussion, Barriers, third paragraph: you should add more discussion about the challenges of ethical approval for global trials. This is especially relevant given your use of the example of trials in rare diseases. Is it necessary to write "something which is rather out of character for bureaucracies"? The reason that local ethical committees might not wish to relinquish oversight is not as simple as being tied to bureaucratic processes, I am sure that some of these committees
feel that they are protecting the rights of people in their location from distant decision makers.

26. Discussion, Barriers, third paragraph: at the end of this, can you expand on what you mean by "matters of ethical oversight remain unclear"? For example, do you mean that you are uncertain or that people who would implement these trials are uncertain?

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Declaration of competing interests:**

I work on randomised trials and systematic reviews. Articles such as this can have an impact on attitudes to such research.