Reviewer's report

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

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Reviewer: Jesse Berlin

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Major Compulsory Revisions

The cases you present are reasonably compelling, and the idea of the clinically-integrated trial is (at least from my perspective) an attractive idea. As payers increasingly require evidence of comparative effectiveness of marketed products, and as the focus on safety continues to intensify, large practical randomized trials seem to present a great opportunity to obtain answers to a range of important questions. Your paper goes a long way toward helping the reader understand the nature of those questions.

A few points could benefit from clarification or more detail.

1. Page 10: I’m not sure this is a major point, but the model you propose for “me too” and rare disease treatments implies that the usual approach to payment for treatment will apply. One might argue (and colleagues of mine have made this point to me in discussions of large, simple studies), that the major barrier to conducting such studies is participant retention. What incentive is there for the subject to remain enrolled in the study, particularly over longer-term follow-up? My colleagues have argued that paying for treatments (in all trial arms) is key to retaining study subjects. In studies in which a change of therapies is permitted in case the randomized treatment is not effective or not tolerated, the trial might then need to pay for the second therapy, as well. Some discussion of alternative approaches to payment (which admittedly gets away from being strictly clinically-integrated) would be helpful.

2. On a related point to the first item, consider a trial of two antipsychotics. The same argument probably applies to studies in other areas of psychiatry or neurology. Typically, at least according to the CATIE study, a large proportion (I think it’s 75%) of patients (schizophrenics) change drugs by the end of a year. In a situation like that, the randomization at the beginning of the study ensures that the groups are similar at the start of follow-up, but one is no longer making a “pure” comparison of the two original drugs. Instead, the comparison is between a treatment strategy defined as “start with drug A” with a strategy defined as “start with drug B.” In an effectiveness study, such a comparison is informed by switches that occur due to lack of efficacy. In a safety study, unless switching occurs because of a specific adverse effect being studied, there is limited information on relative long-term safety of the two drugs. I would urge you to
consider including some discussion of this seeming dilemma. Does it mean this type of design doesn’t lend itself to long-term safety studies?

3. The paper would be far more convincing if you could provide an example (or two) of the sort of design you’re proposing having been used in practice. This would counter the arguments along the lines of “great idea, but can it actually be done?”

4. It’s really more of a suggestion than a mandatory change, but you might consider adding a table outlining the situations in which your proposed design would be appropriate. If there’s a way to contrast those situations with those for which the traditional trial is better suited, that would be an even more informative table. You really have elements of such a table already embedded in the text of the paper. I’m suggesting consolidating those elements into a summary form.

Page 6, top: Can you document the cost of $5,000 to $8,000 per patient? Is that for drug studies? Surgical studies? Publicly funded? Intensively monitored? At the least, you should provide a reference for those figures.

Page 7, item 5: Why require (or even recommend) a minimization routine? Shouldn’t a large enough trial with simple randomization ensure balance of covariates between treatment arms? On this same item, could (should) one consider randomization of surgeons to procedures (i.e., cluster randomization)? That approach would have the advantage of letting each surgeon become expert in a particular procedure. Along that same line of discussion, you might want to comment on the broader questions related to the learning curves for each surgeon. Where on the learning curve would one want to conduct trials of surgical procedures? Should the trial include patients early in each surgeon’s experience, or should we wait until the surgeon has reached a kind of “steady state?”

Page 10, first paragraph: You mention questionnaire results being sent to the patient’s physician. That seems inconsistent with a study of routine care, as typically those physicians would not be getting questionnaire results.

Page 10: One point you might want to mention, perhaps under “barriers,” is a feature of studies of treatments for rare diseases. At least in some (maybe many?) settings, the patient and physician community is fairly closely knit. Once a therapy has been “proven” in a clinical trial, this closeness of the community would make it very difficult to conduct a second study of the same therapy. This places even more pressure on investigators to get the details of the study correct the first time, as there may not be a second chance.

Page 11: I’m personally sympathetic to the suggestion that data be made available to investigators, but strongly suspect that there may be legal barriers to such data sharing. You may want to note this in your discussion. The problem, as I understand it, relates to the nature of many clinical trial agreements with sites about release of individual patient data. Even the so-called “limited data sets,” from which a standard set of identifiers has been removed, may not meet HIPAA
requirements for de-identification.

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

**Quality of written English:** Acceptable

**Declaration of competing interests:**

I am a full time employee of Johnson & Johnson Pharmaceutical Research and Development. I know of no specific conflicts generated by this methodologic paper.