Author’s response to reviews

Title: Protecting intellectual property associated with Canadian academic clinical trials - approaches and impact

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Author’s response to reviews: see over
Dr Gordon Doig  
Trials Editorial Office  

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Dear Dr Doig  

Commentary:  
Protecting intellectual property associated with Canadian academic clinical trials – approaches and impact  
Sue Ross, Laura Magee, Mark Walker, Stephen Wood  

On behalf of my co-authors and myself, I submit our revised commentary, taking into account the thoughtful comments of the reviewers. Changes are highlighted in the revised manuscript.  

Reviewer 1  
Dr Webb made very insightful comments that identified a number of non sequiturs that occurred in our paper, as well as raising some issues we had not previously considered. Our responses to each comment follow below:  

This is a well-written, thoughtful, and interesting manuscript that identifies an area of interest to readership of the Journal. I feel that there are some potential areas of additional discussion that warrant consideration for inclusion within the manuscript.  

Major Points  
1. Responsibility to complete a trial lies with the investigators who have proposed to conduct the trial. This is a shared responsibility to the community of clinicians who may avail themselves of the results of the study as well as a responsibility to the body that has funded the trial. If investigators feel that their interests in completing the trial are best served by open access, is there any reason why they should not provide open access. Similarly, if investigators
feel, for whatever reason, that their interests in completing the trial are best served by restricted access, is there any reason why they should not be able to restrict access. If there is a difference in the real impact of these approaches, on trial productivity and completion, the investigators that use the system that offers advantage will out-compete the investigators who opt for the other model. I think an argument can be constructed that investigators should be open to choose the method that makes sense to them, and that it should not be the role of funding bodies to specify the model of access. My personal view is that restricted access will be wholly counterproductive, but I could be wrong- let those who hold a countervailing view have their opportunity to prove me wrong.

This is a very significant point – investigators should certainly be able to choose the approach that they feel offers them an advantage in undertaking and completing their trial. We have added a comment to the final paragraph (the take home message of the paper) that stresses this point. We have retained the comment about funding agencies making statements about open access to protocols because of their use of public funding and contribution to public good as mentioned by Dr Webb in point 5 below (page 11, final paragraph).

2. A central issue in this paper is concern that the IP in a protocol will be expropriated by others. There may be a range of alternative solutions that allow open access, but reduce the risk of expropriation that could be considered and discussed. It is possible that investigators who work within a clinical trials network (particularly a network with terms of references that cover issues related to IP and its protection) may be offered at least partial protection as a consequence of the capacity of the network to prevent other researchers from conducting the same or similar study in the same location. This obviously won’t stop expropriation by investigators in other countries. Open access, to some extent, can prevent expropriation of a trial concept, as if an expropriated project is submitted for funding, the grant panel that considers the application is more likely to be aware of the preceding study if it has submitted itself to open access in other locations should be searching for existing studies. Sometimes, protection against competition from the same trial being conducted elsewhere can be achieved by the infrastructure that is necessary to conduct a trial being unique to the group that is conducting it, i.e. if your group of investigators is the only group who can feasibly do the trial there is no reason to promote restricted access.

We agree that the main concerns associated with IP are to do with the possibility of expropriation of ideas – concerns which are the province of institutional legal departments. We had certainly not discussed alternative suggestions to protect IP, including collaborative trials networks, and specialised or unique trials infrastructures. These trial infrastructures will serve to protect the IP in both “open” and “closed” access settings. We have added those excellent ideas (page 6, paragraph 1; page 9, paragraph 2.) (These suggestions tie in with point 6 below.)

3. I feel the risk of expropriation and value of IP in a protocol may be both over-estimated by the authors. There are few clinical questions that are unique and so, I presume, there is no reason why different investigator groups should not consider developing trials to answer the
same research question. Perhaps, if there is something unique and novel about the proposed methods there may be a rationale for restricted access, but the idea of randomly allocating patients to different interventions and then measuring outcomes has, after all, been around for a while.

We agree that the issue of IP and protection are over-emphasised in the “closed” access approach used to protect protocols, and this was the reason we wrote our commentary. In the section about the origin of NDAs, we pointed out that industry trials usually include proprietary information that would merit NDAs (page 5, bottom paragraph). We also commented on the difficulty of finding exclusive IP within a trial protocol that uses well established and valid trial methods, and questioned the need for NDAs and a “closed” approach in that type of trial (page 4, bottom paragraph).

We have added a paragraph that discusses the benefits of multiple investigator groups undertaking similar research studies, and the potential negative impact of NDAs in areas of important clinical debate (page 9, paragraph 3).

4. An additional potential defense against expropriation, that might be considered, for those who advocate open access could be better processes for establishing provenance of the trial concept. For example, clinical trial registration sites could collect information on the history of how the trial was developed and when and to whom it was submitted for funding prior to final funding success. At least then, if there were claims of expropriation, there is a documented record of who proposed what when.

This is an interesting suggestion. Unfortunately it seems that registries have a long way to go before they can even rigorously collect information on the actual protocol, changes to the protocol or ongoing progress of trials.

5. It could also be argued that there is societal advantage associated with open access (and perhaps this is an argument for funding bodies to have a role). Many of these are outlined in the manuscript, but, it could be argued, that if a trial is expropriated and conducted, because it was available via open access, then there is likely to be more (possibly better) evidence in the public domain to provide better definitive information to clinicians who care for patients, i.e. the original investigators might be harmed but, so what, patients end up with better care.

We agree that replication of research may lead to societal benefit, although we had neglected to discuss this. We have added a section to the table, included a comment in the discussion (page 8, top paragraph), and a paragraph that discusses the benefits of multiple investigator groups
undertaking similar research studies, and the potential negative impact of NDAs in areas of important clinical debate (page 9, paragraph 3).

6. The IP of trial can be substantially more than the protocol. Particularly in resource constrained environments, as is common for investigator-led trials, the protocol is only part of the IP, with other aspects of trial management (operationalisation, ie how trial management get sites to participate and follow the protocol) being as or more important than the protocol. These comments tie in with point 2 above. We have added a comments about operationalisation of protocols (page 6, paragraph 1; page 9, paragraph 2.)

7. I wonder if the issue of the potential enforceability of NDAs should be discussed. While legal remedies are available are NDAs enforceable and, if so, what realistic prospect of obtaining damages is there and what sort of damages would be possible.

We have commented that it is not evident what legal remedies might be applied (page 8, bottom paragraph).

8. It was not clear to me if the model of restricted access that is discussed in the manuscript includes ongoing restriction of access to the protocol after completion of recruitment and publication. If so, I think this is difficult to justify but it may be useful if the manuscript could clarify this.

This is a good point. We have added a brief comment on page 7, paragraph 3, that NDAs generally apply to restricted access prior to sites signing a sub-contract with the lead site. For the purpose of the analysis, we have assumed that a similar degree of restriction is applied to access to the protocol in “closed” access settings, after they have agreed to participate in the study. We have also added a footnote to the table.

Minor Points

1. I’m not sure I accept the logic within or the logical connection between the first threes sentences in the background- grant funding is competitive but is their compelling information that the difficulty of competition is worsening. Not sure that the reputation of institutions is dependent on ownership and management of IP, as distinct from the academic productivity and the quality of infrastructure provided by an institution to its faculty members.

Thanks for pointing out that the first two paragraphs of the paper did not flow or even make much sense. The paragraphs have been revised and restructured. A recent report from CIHR (Canadian federal funding agency) reported that over a ten year period, the number of applications to the operating grant program increased by 80%, while the success rate for applications decreased from 34% to 22%. We have cited this report to support our assertion that the environment is increasingly competitive (page 4, paragraphs 1 & 2).
2. Line 55, IP can be accorded legal protection, but not sure that is valid to say it should.

This statement was removed in the revision of the second paragraph of the paper (page 4, paragraph 2).

3. Publication of trial protocol can still occur with restricted approach, would just occur close to completion of recruitment.

Thanks, the relevant sentence has been changed to say that early publication of the protocol would be incompatible with the restricted approach (page 10, paragraph 2).

4. Not sure that I agree that the “Need to adhere strictly to protocol and publish study as designed, or publish amendments affecting design or analyses” is a disadvantage. If changes to study design occur these should be formalised by changes in protocol with, in the system of open access, publically available trail of changes.

Thanks for picking us up on this point. We agree that adhering to a protocol is the goal of all rigorous trialists. We also agree that this paragraph was badly written, and have revised it to capture better what we meant to say (page 11, paragraph 2).

Reviewer 2

This is a well written commentary. I recommend Accept as is.

Thanks for this comment.

We have made one additional significant change to our paper. Several months after our paper was submitted for publication, we learned that the PI of the FACT study had persuaded his research administration office to remove the requirement for NDAs to be signed by potential sites before they were permitted access to the study protocol. His reasons were exactly those identified in our submitted paper – that the extra step required by interested sites was acting as a barrier to site recruitment. We therefore invited the FACT PI, Dr Mark Walker from Ottawa, to join us as an author on our paper, so that we could add his actual experience with NDAs to our theoretical perspective (page 7, paragraph 2, and page 11, paragraph 3). We believe that Mark’s input has further strengthened our paper.
We hope that you will agree that our paper is much improved by the changes we have made, and will now be able to publish our commentary. Please let us know if you require any additional information about our commentary.

Yours sincerely

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