Reviewer comments

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Article title: Time required to initiate a clinical trial at the onset of the Canadian COVID 19 pandemic: an observational research-in-motion study

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Reviewer 1: Christopher Doig/Foothills Hospital, Critical Care Medicine

From my interpretation of their data, the major source of delay is from protocol receipt to REB (or contract) submission. As such, I might disagree with the statement in the discussion “Failure to adopt a model clinical trial agreement likely created the single greatest barrier to timely initiation of CATCO.” It’s a bit hard to criticize institutional bodies (such as legal) for delays in contract approval when the major delay seems to lie with the investigators responsible for the local site research. Would the authors care to provide any comment as to how to improve individual investigator accountability?

You bring up an excellent point. Some sites require submission to REB before submission to legal, others proceed in parallel, which adds inherent delay and variability seen. Appreciating this, one recommendation might be to allow parallel processes to occur so delay in one doesn’t cause delay for the other. There is a fairly big difference between community and academic sites, with the community sites having larger variability and longer start-up times.

We agree with your excellent comment and have updated our discussion to emphasize that it is not always the investigator or legal team that determines the duration of start-up time. “Although there were other factors at play that caused delays, such as the inability of some sites to proceed in parallel with the REB and legal submissions, lack of a model clinical trials agreement document before the pandemic started created a significant barrier to timely initiation of CATCO.”

I do agree that attempts to create a standardized template for contracts may be beneficial if the ‘back and forth’ represent major differences rather than simply local delays in review and approval. Given that the authors’ comment on ‘back and forth’ between individual sites and sponsors, do these authors have any anecdotal data from the CATCO principal investigators which might help understand difficulties in contract negotiations, and areas where templates may help (or not).

We unfortunately do not have granular data, but agree that it would help to understand difficulties in contract negotiations.

This is an excellent point, we agree with the reviewer that this usually makes a difference and gives some sites a ‘head start’. In this case, there was an incredibly short turnaround time from the request for proposal to announcement of funding. Aside from primary investigators and home institutions, most sites found out the opportunity to participate at the same time. Therefore, we are not able to explore this hypothesis (although we think this makes sense most of the time).

(Minor) Discussions on provincial and national harmonization of REB processes may have begun prior to the H1N1 pandemic. For example, early attempts at harmonization in AB began in approximately 2003.

This statement in the discussion has been modified to the following: "The development of provincial clinical trials ethics organizations has greatly improved research ethics efficiencies over the last two decades."
The boxplots in Figure 2 preclude determining from the figure, the medians in the 'solid' boxes: I would suggest a different format to the figure (although the medians are present in the Tables, the boxplots should 'stand alone'). **The solid boxes have been modified in figure 2. The medians are now visible.**

Reviewer 2: Anh Pham/University of Alberta Faculty of Medicine and Dentistry

This manuscript discussed a highly essential but not always clear aspect of health research, especially in more urgent situations like the recent pandemic. The knowledge here is novel and necessary.

There is one minor point I think worth to discuss. Even though this is a descriptive manuscript, it would be nice to read more about barriers that caused delays at some sites. It is to open a future discussion(s) to reduce initiation time.

Thank you for your work. It is a very important study that could lead to multiple studies and changes in the field of RCTs.

Thank you for your review. You bring up a good point on barriers at specific sites. Unfortunately, we were unable to acquire that data in this study. We do feel that this is an excellent point for future study and would allow us to get into the richness of the site-to-site variation.

Reviewer 3: Boglarka Soos/University of Calgary, Department of Family Medicine

As mentioned in your discussion, this is a study with a sample size of one. The early pandemic created an environment where funding was readily available to study covid- 19, research related to the pandemic was fast- tracked, and health care providers may have been more willing to participate in a clinical trial. The timeframes described here may not be representative of clinical trials under other circumstances/pandemics. The title of the article should be updated to reflect this.

This is an excellent point. We have updated the title of the article to: "Time required to initiate a clinical trial at the onset of the Canadian COVID 19 pandemic: an observational research-in-motion study"

The strength of this paper is the discussion. I think increased commentary of the potential facilitators to creating a research-ready environment in academic clinics and learnings from different provinces would be compelling.

Thank you for highlighting this excellent point.

Appreciating the space requirements, the facilitators mentioned in the discussion include:
1. **Adoption of harmonized clinical trial agreements,**
2. **Greater inter-provincial coordination in research ethics review,**
3. **Streamlining of Health Canada regulations for low- risk clinical trials and**
4. **A transition towards funding durable research networks across health systems in Canada would address some of the challenges currently faced by clinical trials**