Author’s response to reviews

Title: Collaborative H1N1 Adjuvant Treatment (CHAT) Pilot Trial A Canadian Critical Care Trials Group Project in collaboration with the International Forum for Acute Care Trialists

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Response to Reviewer’s comments

This is a very interesting collaborative project. I wish you all the best in your undertaking.

Thank you for your thoughtful review.

[Text in italics = our responses, Text in bold = new text added to the protocol or moved under different sub headings]

1. Many readers remain confused between allocation concealment and blinding. In your paragraph on Study Randomization, I recommend you explicitly use the term Allocation Concealment to refer to the methods that will be used to maintain Allocation Concealment. I recommend the sentence “The site investigators, research coordinator, clinical pharmacist involved in the care of the patient and all other study personnel will remain blinded to treatment assignment.” Should be moved to the section on blinding.

   Thank you for this comment. We agree that clarification is required to ensure that allocation concealment is a pre-randomization phenomenon while blinding is a post randomization phenomenon in writing protocols.

   The text under ‘Study Randomization’ now reads:

   **To preserve allocation concealment**, participants will be randomized centrally. Randomization lists will be distributed by the study methods centre to the research pharmacies of participating centres. Stratified variable block randomization, based on centre alone, will be performed to take into consideration differences in patient characteristics at participating ICUs. Day one will be considered the day of study treatment initiation, which may or may not be the same day of randomization

   Additionally, we moved the text on “blinding” under the heading of ‘Study Treatment Overview’ (after the heading ‘Consent’)

   Using randomization lists provided by the study methods centre, research pharmacists will assign critically ill adults to once daily enteral administration of
rosuvastatin or matched placebo for 14 days. **Only the research pharmacy staff will be aware of the assigned treatment arm. The site investigators, research coordinator, clinical pharmacist involved in the care of the patient and all other study personnel will remain blinded to treatment assignment.** An oral placebo for nasogastric administration, identical in appearance (colour and consistency matched) to crushed rosuvastatin, will be prepared by Pharmacy 1 (Toronto, Canada) and supplied to the study sites. All other aspects of patient management will be left to clinician discretion as per pragmatic trial design. The Applied Health Research Centre of the Keenan Research Centre and Li Ka Shing Knowledge Institute (St Michael’s Hospital, Toronto, Ontario) will be the Study Methods Centre.

2. Section on Study Randomization: Please explicitly report all stratification variables.

   Given the need to ensure that this protocol can be implemented under pandemic conditions, we planned only to stratify on the basis of centre. This point is now clarified in the text as follows:

   **Stratified variable block randomization, based on centre alone, will be performed to take into consideration differences in patient characteristics at participating ICUs.**

3. Should the larger trial never eventuate, or the larger trial is manifestly different from the pilot feasibility trial, the clinical outcomes of the pilot feasibility trial must be published. Please stipulate your commitment to publishing the clinical outcomes of this pilot feasibility trial under these circumstances.

4. Please stipulate the circumstances under which the pilot feasibility data may not be pooled with the results of the larger trial.

   These are very important points to be stated explicitly in the protocol. Thank you. We have added the following text under the heading ‘Other Considerations’ to address both concerns:

   **The investigators plan to make changes to the larger study protocol based on their experience in implementing the pilot trial. Regardless, we will publish the findings of the CHAT Pilot Trial separately if recruitment ensues even if the study protocol is modified in important ways following conduct of the pilot trial or the planned larger trial never comes to fruition. Pilot trial data will be combined with data from the larger trial if recruitment ensues, study personnel (including the data analyst) remain blinded to treatment assignment and no important modifications are made to the study protocol following the pilot trial.**

Thank you.

Respectfully Submitted.

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