

Peer Review File

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Reviewer Comments

This is an interesting paper on a timely topic.

General comments:

This manuscript needs very substantial copy-editing / proofreading for grammar, and at times clarity, throughout.

Reply: Thanks a lot for your comments. We have invited proofread it and did substantially modify the grammar, and at times clarity, throughout.

Specific comments:

Comment 1: Page 2 line 55 – this reference should be updated. In addition, given that rate of vaccine research and emergency deployment, I recommend updating the remainder the paragraph – i.e. through to page 3 line 67

Reply: Many thanks for your suggestion. We updated the data in Page 2 line 56-57 and the relevant reference (page11, line 402-404).

Comment 2: Page 3 line 70 – in what way are CHIMS a hybrid model and what are they a hybrid between (they're not a hybrid between conventional and pandemic development models)

Reply: Thank you for your comments. Here the aim is to introduce different models have been proposed as a strategy for accelerating SARS-CoV-2 vaccine development. However, we really did not show it clearly. We modified according to your question in revised manuscript. (See page 3, line 69-70)

Comment 3: Page 3 lines 70-74- it's important to be clear and consistent with terminology – say that you are calling them CHIMS or human challenge studies and use one of those terms going forward.

Reply: Thank you very much for your suggestion. It is really very import to use one term to avoid making readers confused. We have modified the text in the revised manuscript. (See page 3, line70-91).

Comment 4: Page 3 line 72 – it's more accurate to say exposed to infection rather than infected – in some studies, for example, exposure will not lead to infection if an intervention being trialed is successful.

Reply: Many thanks. Here the “infected” is not an accurate description. We changed the text as advised. (See page3, line72)

Comment 5: Page 3 line 75-78 – I appreciate this is a quote but it’s not an accurate one and not worth repeating– CHIS shouldn’t be considered to be alternative to Phase III generally (for example often the questions they address are different to those in Phase III trials). Moreover there are extensive and ongoing Phase III vaccine trials in the context of COVID-19 which commenced prior to CHIS and the critical data they provide cannot be provided by CHIS.

Reply: Thank you very much for your constructive suggestion. The quote was deleted from revised manuscript. (See page3, line 71-76)

Comment 6: Page 3 lines 80-81 – there has been a huge amount of commentary – it would be valuable to itemise some of the key issues that have been identified and addressed in it, rather than just mention that it’s taken place.

Reply: Thank you for your suggestion. We have added “Human challenge study is not without risks, but every week that SARS-CoV-2 vaccine rollout is delayed will be accompanied by many thousands of deaths globally. Importantly, challenge studies are conducted against the background of competent volunteers’ informed consent, minimization of study risks, and high baseline risks of infection for participants. They do not violate participants’ individual rights on the altar of emergency response, but heed both individual rights and the global public health emergency. To further assess the potential of human challenge studies to speed vaccine development, researchers suggest that an expert group might be convened, including those with experience of human challenge studies of other pathogens, regulators, vaccine trialists, ethicists, potential participants, and relevant funding agencies, to plan if and how such studies might be taken forward ethically and expeditiously” in the revised manuscript. (See page3, line86-96)

Comment 7: Page 3 line 81 – ethical review is a key gatekeeper – there are many (regulators, funders etc.)

Reply: Thank you very much for your kind remind. We have modified this sentence to “The research ethics committee is one of the key gatekeepers” (see page 3, line 87).

Comment 8: Page 3 line 83 – here and throughout ‘ethic’ is not the appropriate word in this context – it is research/medical ethics, ethical etc.

Reply: Many thanks for your comments. We have modified the “ethic” to the appropriate word “ethics” or ethical throughout the paper.

Comment 9: Page 4 line 104-105 – it’s misleading to say in the abstract that the 15 interviewees were purposively selected if they were the only ones who provided contact details.

Reply: Thank you very much for your constructive comments. The description of sampling approach is really inconsistency in the section of abstract and methods. Actually, purposive sampling approach was used in our study. 15 of these REC

members were purposefully selected to participate in qualitative interviews according to the result of quantitative survey to reflect different opinions. we have modified in the abstract and methods (See Page2 line 31-32, page 4, line110-112).

Comment 10: Page 4 line 110 – what is a self-constructed questionnaire? It sounds like it was constructed by the research team.

Reply: Many thanks. The questionnaire was constructed by the research team. We have modified the text in manuscript. (Page 4 line 117).

Comment 11: Page 4 lines 120-122 – I don't understand this sentence.

Reply: Thank you for your comments. We might not describe it clearly. Here is the progress of how to develop the interview guides and the content of this interview. We have revised the text. "Interview guides were developed according to the domains of quantitative questionnaire, and modified it after a pilot interview. The main content of interview included reviewers' attitudes, views and suggestions on this controversial issue". (See page4, line 127-130)

Comment 12: Page 4 line 124 – what does this mean – do you mean sufficient data was collected to saturate the themes? Is it accurate to claim that interviews were stopped at 15 because no further data was needed, when in practice only 15 interviewees were available?

Reply: Thanks for your comments. Actually, fifteen interviewees were from participants who completed the quantitative survey. Interviews were stopped at 15 when themes were saturate. We have modified our text as advised (see Page 4, line 131-132)"

Comment 13: Page 4 line 136 – how were these rules? Perhaps they are better described as key themes (as they are in the results section – although there are only six there).

Reply: Thank you very much for your good suggestion. Here are the key themes rather than rules. And we feel so sorry to make a mistake of 7 themes. Indeed, there are 6 themes refined in our manuscript. We have revised the text in revised manuscript. (See page 5, line 143).

Comment 14: Page 5 – lines 173-175 – why did survey respondents think this was unreasonable? (was this only explored in the interviews?)

Reply: Thank you for your comments. Here, "half of the respondents (n=19, 52.8%) thought that it was unreasonable to choose healthy people between 20 to 45 years old as the study subjects" was the result of questionnaire survey. From the qualitative interview, this result was explained, that is "Opponents believed that, currently, it lacked sufficient knowledge of COVID-19, although people in this age group were in good health, the susceptible population groups in COVID-19 were uncertain, so the

people in this age group can't represent all the people."

Comment 15: Page 5 lines 214-217 – again was there space for a qualitative response in the survey to determine why this view was taken? Line 215 – susceptible to what?

Reply: Thank you. Qualitative findings further explained the result of survey. "In the interview, in terms of the selection of subjects, interviewees thought that they could not choose the vulnerable groups, not only because the living environment and psychological state of the vulnerable groups could not match well with the healthy people, but also harmed the rights and interests of the subjects. And it was contrary to ethics, there is discrimination, and infringes on their human rights. Some subjects believe that if some disadvantaged population were involved in such a human challenge study, it can only because the environment they lived were suitable for the study, rather than their identification as a vulnerable population." (See page 7, line 221-236). In addition, we have added "people who are susceptible to the virus" in page 7, line 219.

Comment 16: Page 7 line 222-223 what does this mean?

Reply: Thank you for your comments. We do feel very sorry to bring you the confusion. This means that some subjects believe that if some disadvantaged population were involved in such a human challenge study, it can only because the environment they lived were suitable for the study, rather than their identification as a vulnerable population. We have modified text in revised manuscript. (See page 7, line 225-228).

Comment 17: Page 7 quote beginning line 224 – I find this difficult to understand

Reply: Thank you for your comments. We do feel very sorry again to bring you the confusion. We have revised the text in the revised manuscript as "P6 (F, practiced 8 months in Research Ethics Committee): I think it absolutely cannot involve vulnerable groups in human challenge study. First of all, human challenge study is a very controversial study to make infection intentionally to do harm to subjects, which challenge ethics and morals even involving the normal and healthy people. If this is the young, healthy subject, its morbidity or mortality is the lowest, which still can get a moral defense to a certain extent. But if involving vulnerable people, ethical fairness and respect would be challenged. It must be resolutely avoided in the challenge experiment." (See page 7, line 229-236).

Comment 18: Page 7 line 240 – what is mental compensation?

Reply: Many thanks for your comments. More precisely, it should be mental injury compensation here. Anxiety might occur after being exposed to the infection, in this case, compensation can be used for counseling and therapy, or make things a little bit easier. Therefore, mental injury compensation should be provided to subjects. We gave further explanation in the revised manuscript. (See page 7, line 245-247).

Comment 19: Page 7 line 246 – how does a willingness to participate without compensation prove full informed consent has been given? What is the problem with tempting subjects? Undue inducement goes beyond temptation to making an offer that participants feel unable to decline.

Reply: We highly appreciate your constructive suggestions. It is important to make it clearer. We modified the text in revised manuscript. “The extra compensation may have a certain temptation to participate in such a study, which might break the fairness of ethics. Therefore, the decision of participation should be made based on willingness after full informed consent and without compensation.” (See page 7-8, line 251-254).

Comment 20: Page 8 lines 256-260 – here and in the discussion of compensation it is important not to conflate issues relating to voluntariness and free decision-making with issues relating to providing appropriate information and participants’ understanding. Both of these are needed for consent to be valid. For example, coercion (i.e. a threat) may have an impact on voluntariness while not impacting information provision and understanding.

Reply: Thank you very much for your comments. This is a key point to distinguish informed consent and compensation. We have modified in revised manuscript as “Interviewees believe that it was essential to ensure that the subjects were fully informed, consequently they can make decisions based on a fully understanding of the study and risks”. (See page 8, line 264-265).

Comment 21: Page 8 lines 264-265 – here it’s important to distinguish between consent and public consultation / engagement – both have been considered critical in the context of COVID-19 CHIS but they are very different processes conducted for different purposes (although the latter can inform the former).

Reply: Many thanks for your constructive comments. It is different between consent and public consultation / engagement. In this manuscript, we focused on the consent. Therefore, the sentence about public consultation / engagement was deleted in revised manuscript. (See page 8, line 265-269).

Comment 22: Page 8 – line 267 – did they disagree with all challenge studies or just in the context of COVID-19?

Reply: Thank you for your good question. We did not describe accurately in manuscript. They disagree with challenge studies in the context of COVID-19. We have revised the text. (See page 8, line 274).

Comment 23: Page 8 line 268-271 – this is unclear. Was it suggested in the survey and interview that CHIS be used to ‘skip’ Phase III trials as per the quote at the beginning of the paper? Because as noted there, that is not realistic.

Reply: Many thanks for your question. We did not describe the definition clearly before. Now we have changed the text in revised manuscript. (See page 8, line 276-278)

Comment 24: Page 8 line 284-285 – what does this mean – to allow them? Earlier in the paper you described the public concerns giving rise to commentary. This seems contradictory.

Reply: Thank you for your comments. It means that there was already a human challenge study conducted at that time, which illustrates that it issued pass

Comment 25: Page 9 line 296 – I would be cautious about making any claim of representativeness

Reply: We appreciated your constructive comments. We have modified our text as advised as “The perspectives and options in this study can represent the attitude towards human challenge studies to a certain degree. However, there might be different perspectives in other ethical reviewers.” (See page 9, line 300-302)

Comment 26: Page 9 line 309 – To be balanced it should also be noted that other COVID-19 vaccines were in Phase III trials before receiving EUA (emergency use authorisation)

Reply: Thank you very much for your suggestion. We have revised as suggested in revised manuscript, “But we should note that there were other COVID-19 vaccines in Phase III trials before receiving EUA (emergency use authorization).” (See page 9, line 307-308).

Comment 27: Page 10 line 342-352 – this are some very broad claims being made where in relation to China and Chinese scholars generally. Is the ‘we’ just referring to the authors? Is the ‘our scholars’ referring to all Chinese scholars?

Reply: Many thanks. “We” and “our scholars” refers to Chinese scholars who devote themselves to COVID-19 relevant medical research. We revised the wording. (See page 9, line 360-361).

Comment 28: Page 10 line 364 – It would also be useful to reflect on the limitations of the research posed by the researchers and participants being based at the same institution, and the participants undertaking ethical review of the research.

Reply: Thank you very much for your advice. We revised the content of limitations as advised. “Thirdly, even though the participants in this study had various backgrounds, all the participants were from the same institution, and the attitude of the personnel who conducted the ethical review of the study was not analyzed.” (See page 11, line 374-376).