UK Research Ethics Committee's review of the global first SARS-CoV-2 human infection challenge studies

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ABSTRACT

This paper describes the UK Research Ethics Committee's (REC) preparations and review of the global first SARS-CoV-2 human infection challenge studies. To frame our review, we used the WHO guidance and our UK Health Research Authority ethical review framework. The WHO criteria covered most issues we were concerned about, but we would recommend one further criterion directing RECs to consider alternative research designs. Could research questions be equally well answered by less intrusive studies? The committee met virtually, ensuring broad representation across the UK nations and also ensuring applicants could attend easily. We worked in collaboration with the applicants but while we recognise that such proximity might raise the accusation of 'collusion', we made every effort to maintain 'moral distance' and all decisions were made by the committee alone. Prior existing processes and policy facilitated training and review but even with this preparation, review took time and this could have hindered a rapid response to the emergency. Review for the various follow-on studies will now be speedier and once the pandemic has subsided, our group could be reconvened in future emergencies. In conclusion, we have tried to make decisions in good faith. We know there is controversy and disagreement and reasonable people may feel we have made the wrong decision. A more detailed analysis, built on the WHO guidance, is provided in online supplemental material.

PREPARATION

International guidance and national law require research proposals to be reviewed by an independent research ethics committee (REC), so when the UK government announced its support for SARS-CoV-2 human infection challenge studies (HICS), the UK Health Research Authority (HRA) convened a specialist ad hoc REC to undertake ethical review.

Expert and lay members of UK RECs recognised to review Clinical Trials of Investigational Medicinal Products or phase I studies in healthy volunteers, particularly those with experience of vaccine studies, were invited to join the ad hoc REC. They were then asked to attend two virtual HRA workshops before the first committee meeting.

These training meetings provided an opportunity for members to meet, discuss collective views and their approach to review. The first provided a background to HICS, while the second was designed to help the committee think through the questions that should be asked when reviewing SARS-CoV-2 HICS and the considerations that would then arise (to consider 'how to think' rather than 'what to think'). To facilitate this, an Oxford debate entitled 'This house believes that SARS CoV2 human challenge studies are inherently unethical' was conducted and after this, delegates reviewed a 'dummy' SARS-CoV-2 HICS as if in committee. Members were provided with articles from both sides of the argument for further reading.

REVIEW

We conducted our review using all resources available to us. We saw we could not, nor should not, work alone. Given the controversial nature of the study, it was essential that the design and review had meaningful and robust involvement of all with legitimate interest, both expert and lay (WHO criteria 3 and 4).[1] We were pleased to note the detailed public involvement the research team had undertaken.

We also realised very rapidly that, given the possible risks and burdens to the volunteers, we had to consider alternative research designs in depth. In essence we had to review more than one proposal. We asked, 'could studies of natural infection (field studies) answer research questions more safely and as reliably as an HICS?' To help us reach a decision, we wanted to know the exact data both types of studies would generate (benefits), their risks (harms) and how each would link to prevention and treatment of SARS-CoV-2 infection. With this we could base our decision on such a comparison.

Benefits and harms (WHO criteria 1 and 2)

The balance between benefits and harms was at the centre of our review. The benefits would need to be robust and valid answers to well defined, justified research questions. To ensure that this purpose would be met, we sought reassurance that the questions were indeed justified from expert and public groups and that the study methods would provide meaningful and valid answers through methodological and statistical analysis.

The first HICS we reviewed was to define the dose infectivity for further SARS-CoV-2 studies with wider therapeutic aims. Its acceptability, therefore, depended crucially on demonstrating purpose to these later studies. It could not stand on its own so we wanted to know exactly how these later projects would contribute to the understanding of SARS-CoV-2 infection, investigating correlates of immunity, vaccine development, public health management and advancing improvements in treatments.

We also wanted to be reassured that:

- The results could be generalised from these healthy volunteers to the broader population.
- Whether the studies were justified when there were vaccines of greater than 90% efficacy.

- These studies would continue to have value as new variants emerge.

Possible harms and their mitigation were the other part of this balance, not a unique consideration for HICS but of particular importance as volunteers could potentially be very sick. We looked closely at quantitative data on the risk of hospitalisation, admission to critical care, death and 'long COVID-19' (2-3).[2–4] When assessing the proposed measures to mitigate risk, we considered the proposed care and rescue treatments along with the expertise and experience of the whole team, both those conducting the research and those who would be caring for the volunteers.

Much discussion was given to the proposed rescue medication, remdesivir. We felt that the balance between the risks of SARS-CoV-2 infection and this treatment needed detailed consideration, particularly as there was extremely limited evidence for its efficacy in groups such as of these volunteers although we recognised that it was well tolerated in young people. There were hypothetical reasons for its use but no convincing data. We also explored whether the use of this medication would undermine the purpose of the research.

Given the pandemic surge that was happening when we reviewed the study, we considered whether it would be more appropriate to delay therecruitment until there was guaranteed critical care availability should the volunteers become ill.

Selection and consent (WHO criteria 6 and 8)

The applicants proposed using the qCOVID personal risk assessment tool (https://qcovid.org/) to ensure that volunteers would be at the least risk from SARS-CoV-2 infection. We accepted this after much discussion but, while recognising the increased vulnerability of BAME individuals (Black, Asian and Minority Ethnic - a demographic classification), we were also keen that they should not be discriminated against and unfairly excluded from participation.

Given the possible risks of harm, we saw robust consent procedures would be of crucial importance[5]. It would be vital to ensure any volunteer understood what he or she was agreeing to and the attendant risks. To ensure this, we required a clear consenting schedule, starting with an introduction to outline the key facts about the study followed by a more detailed discussion in which the participant information sheet could be used as a template for discussion with the participant. After a break allowing the potential participant to reflect and ask others, understanding would be checked by a consent quiz before signed consent was taken using an itemised informed consent form, matched to the introductory 'key facts'. We required this process was audio or video recorded.

DISCUSSION

We have now completed the review of one further SARS-CoV-2 human challenge study. Both were given a provisional opinion at the first meeting, then favourable after amendments were made and accepted. No vote was taken but dissenting voices on issues were recorded. Those who dissented accepted the committee's decision.

To frame our review, we used established guidance[1] and the UK HRA ethical review framework.[6] We found the WHO criteria a useful basis for deliberation, covering most of the issues we were concerned about and only two did not map well onto our UK framework, but these were more about the process of review rather the ethical/scientific considerations (criterion 4, 'Coordination' and criterion 7, 'Expert Review'). These could be considered as being covered by the formation of the specialist REC by the HRA. After our review, we would now recommend one further criterion, specifically directing RECs to ask and consider alternative research designs. This was a major consideration for us. Could research questions be equally well answered by less intrusive field studies?

Given the pandemic lockdown, we met virtually. This had benefit, ensuring broad representation across the UK nations and that applicants were easily able to attend. We were unanimous in our view that discussing the project with the applicants at the meeting was essential to our review. As just three examples, the use of remdesivir as a rescue medication, the evaluation of alternative designs and developing robust consent processes required discussion with the researchers over more than one meeting (and correspondence between these).

We worked in collaboration with the applicants and we recognise that such proximity might raise the accusation of 'collusion'. We made every effort to maintain 'moral distance' and all decisions were made by the committee alone. As an example, when we felt consent procedures were inadequate, the committee proposed one member should engage with the team to describe our concerns and suggestions. This was recorded in the minutes and the member took limited part in the subsequent debate and would not have participated if a vote had to be called.

What might we have done differently?

Even with prior preparation, review took time and, in the context of a pandemic where there is an argument for speed, this could have hindered a rapid response to the emergency. We need to continue to consider how our review might be conducted more speedily and streamlined for future emergencies.

Now the committee is established, we hope review for the various follow-on studies will be speedier and with time our procedures can be further refined and if we are 'mothballed' once the pandemic has subsided, our group could be reconvened in future emergencies.

In conclusion, we have tried to make a decision in good faith, using the evidence we could ascertain and listening to all others with fair interest. We know there is controversy and disagreement within and without our committee and reasonable people may feel we have made the wrong decision but we feel we have given the issue detailed consideration. We cannot know whether the possible benefits outweigh the risks but we will require regular reports. Meanwhile this article is an opportunity for us to hear other voices in this area. A detailed analysis is provided in the online supplemental material.

Correction notice Since this article first published online changes have been made. The postcode of the corresponding author has changed and the full collaborator list has been added.

Collaborators Miss Stephanie Ellis: Retired Civil Servant & Chair of Specialist Ethics Committee Dr Hugh Davies: Retired Consultant Paediatrician, past Research Ethics Advisor UK Health Research Authority Professor Iolo Doull: Consultant Respiratory Paediatrician Mr Chris Foy: Medical Statistician Dr Leo James: Independent Pharmaceutical Physician Dr Lucy Kershaw: Research Fellow in Imaging Science Dr Simon E. Kolstoe: Reader in Bioethics, University of Portsmouth Dr Tony Lockett: Medical Director Dr Thomas Woodcock: Retired Consultant – Intensive Care Unit Dr Ian Zealley: Consultant Radiologist Dr Kathrine Craig: Nurse, Chair Wales REC 1.Mrs Arlene Seaton: Retired Medical Publisher Dr Mauro Buraglio: Independent Consultant in Clinical Pharmacology and Clinical Development Dr Aaron Courtenay: Lecturer in Clinical Pharmacy Mr Lindsay Murray: Chartered Biologist/Scientist and Health & Safety Manager.Dr Fran Silverton: Statistician and Lecturer.

Contributors HD has written this article on behalf of the whole committee.

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Patient consent for publication Not required.

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Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information.

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