

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

Hugh Davies, On behalf of the HRA Specialist Research Ethics Committee

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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.



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- 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 their recruitment 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 importance⁵. 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 guidance¹ 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 than 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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Supplementary material

Deliberations structured on the WHO guidance.

1. Scientific justification

“SARS CoV-2 challenge studies must have strong scientific justification.”

Questions and deliberations

- i. What are the research questions and purposes?
- ii. Why is it important to seek answers to these questions?
- iii. Have these questions been answered already?
- iv. Will the chosen method answer the questions and contribute meaningful and valid information that will help disease prevention, management and treatment?
- v. Will results be applicable to the broader community (generalizability)?
- vi. Might the study detract from pandemic care?
- vii. How has transparency been ensured so results will be rapidly available?
- viii. Has there been independent review?
- ix. Has there been public involvement?

i. What are the research questions and purposes? The applicants answered:-

“20/UK/0002 is a dose finding, enabling study to develop a SARS COV 2 human challenge model.”

The committee accepted this position in conjunction with 1(ii).

ii. Why is it important to seek answers?

The committee felt this first, dose finding, study to be of extremely limited, if any, value. However if it were to enable future studies with possible benefit, there could be acceptable purpose. Hence, the committee wanted to know the exact data that these later studies would generate and how each would link to prevention and treatment of SARS COV 2 infection.

The applicants proposed further studies would: -

a) Establish the incubation period.

“The “incubation period” of COVID-19 is the time from coronavirus exposure to the beginning of symptoms and when people are most infectious. This human challenge study is the only way to accurately know how long the incubation period is and will be essential to improve Track and Trace efforts.

b) Allow study of asymptomatic infection.

Mild or asymptomatic infection in young people is probably a major driver of the pandemic and human challenge studies are the only way to obtain data about how infection and viral shedding occur in this group. This will immediately affect policy on length of self-isolation and prioritisation for vaccines for these people, if we show that they are major shedders of virus.

c) Determine how long people are infective.

This human challenge study will allow us to accurately measure how long people are infectious, from first exposure to the virus being cleared. This will determine exactly how long self-isolation (quarantine) periods should be after exposure.

d) Research risk of re-infection.

Based on what we know from similar viruses, some people can catch COVID-19 more than once. A human challenge study we are working on in Oxford will help

answer a number of important questions on re-infection, including how long people are protected after having had COVID-19; what makes people more at risk of re-infection; and whether re-infected people can spread the virus to others.

e) Help vaccine development.

..., using challenge studies, the most promising vaccine candidates could progress much quicker, having been strengthened by early evidence of efficacy, and the risk of a large-scale trial failing would be minimised. In addition, the human challenge study would validate the impact of immune markers that correspond with protection, strengthening the licensure package. The flipside of this is that if a novel vaccine fails in a head-to-head study comparing with one of the current vaccines, then progression to a costly and burdensome phase III trial would be avoided.

A key question that we will test for these vaccines is whether they stop people carrying and spreading the virus as well as preventing symptoms. Vaccines or antivirals that do nothing in healthy young adults are unlikely to work better in higher-risk populations (due to impaired immunity, kidney or liver function etc.), so can be de-prioritised in favour of those that do.”

f) Help development of anti-viral treatments.

This human challenge study will open the way for future testing of these.

g) Help manage variants

With regard to variants and mutation, despite changes in the newer strains, it is also important to emphasise that fundamentally these are all the same type of virus and many findings about the disease and the immunology will be generalisable. In addition, most antiviral drugs target parts of the virus that have remained largely unchanged, so the value of rapid early testing of new treatments using the existing challenge virus is unlikely to be affected by strain variation in the near term.

However, with unreliable transmission in the community, it may not be possible to test these quickly enough in field trials. In such an event, the human challenge programme will provide a simple and rapid method to test new vaccines against emerging strains.

The next step is therefore to manufacture a new challenge strain that matches what manufacturers use to re-engineer their vaccines. With our experience, we can now produce a novel challenge agent more quickly than before but without this current study, human challenge development would have to start from scratch and testing of modified vaccines greatly delayed.

In addition, follow-on studies (that will be subject to separate applications for ethical review) can give clear answers to questions that cannot be sorted out by field trials in a meaningful timeframe, including:

- Whether new vaccines/vaccine regimes are as good as/better than existing ones*
- o How to optimise the delivery of vaccines to ensure the most effective protection for the greatest number of people using one or two dose approaches can thus be resolved.*

- o Testing vaccines adjusted for mutant viruses (variants) using human challenge in a “bridging study” could bypass the need for more phase III trials and allow emergency authorisation of updated vaccines.*

- o What protects people from re-infection after having previously had COVID-19.*

- o *Very quick proof-of-concept studies are possible using human challenge that will bring these treatments on-line sooner.*
- h) *Identifying correlates of protection (i.e. the immune markers that are responsible for protection against SARS-CoV-2) is a powerful reason for running these studies in young adults as they are the benchmark for optimal immune responses. These can then be translated to higher-risk populations by immune bridging studies, where the immune markers that are shown to be responsible for protection in young adults can be used to accurately predict protection in higher-risk groups.*
- i) *Contribute to pandemic management*
 - o *On its own, this study will provide answers with important short-to-medium term public health impacts, specifically:*
 - o *Measuring virus coming out of the nose will show when and how much infectious virus is shed.*
 - o *Only a challenge study can accurately measure asymptomatic infection.*
 - o *Can the vaccine prevent asymptomatic infection? This could immediately alter public health strategy as it is considered that asymptomatic infection is driving the continuation of the pandemic.”*

iii. Have these questions been answered before?

The committee accepted that, from the evidence presented, these questions had not yet been satisfactorily answered.

iv. Will the chosen method and follow-on studies answer these questions (meet the stated purpose) and contribute meaningful information that will help disease prevention and treatment?

The committee accepted expert opinion in support of this study and that proposed methods would answer the questions posed with regards to the aims in 1(ii) .

v. Will results be applicable to the broader community (generalizability)?

The committee debated the broader generalisability of study results when the volunteers were young, healthy and of low risk and wanted reassurance that this research would be relevant to the broader population. The applicants responded: - *“While young healthy adults may not fully recapitulate high risk groups, they provide a benchmark for optimal protective immunity and are highly suitable for antiviral and monoclonal antibody testing. People in this age group are also likely to be the main drivers of continuing pandemic transmission once older adults are vaccinated.”*

vi. Has there been Independent review and review of prior work?

The scientific quality of the research had been reviewed within the Sponsor's organisation, by the study team at hVIVO while two independent reports were provided. Further support was provided by the Dept of Health, Vaccine Task Force and the Wellcome Trust.

vii. Has there been public involvement?

See 3(ii)

viii. Would the study detract from pandemic care?

Volunteers would be cared for, separately in the accredited isolation research unit at the RFH. For care of any volunteer who fell seriously ill see 2(ii). The committee asked whether the study should be timed to ensure that clinical care would be available should a volunteer fall seriously ill (i.e. Outside any surge of infection in the community). See 2(iii).

ix. How has transparency been ensured so results will be rapidly available?

In line with the HRA transparency policy the committee wanted reassurance that the results would be openly available once the study was completed. The applicants responded: -

“this is an academically-led study with the primary purpose of advancing scientific and medical knowledge.”

2. Risks and benefits

“It must be reasonable to expect that the potential benefits of SARS- CoV-2 challenge studies outweigh risks.”

Questions posed:

- i. What are the quantified risks?
- ii. Is care of volunteers acceptable including rescue medication?
- iii. Is the timing of the study acceptable?
- iv. Will viral containment meet current agreed standards?
- v. Is the quality of the infecting agent adequately ensured?
- vi. How are CT scans justified?
- vii. Are doses acceptable?
- viii. Are there a trial steering committee and Data Monitoring Committee?
- ix. Is payment to volunteers acceptable and not undue influence?
- x. Are compensation arrangements in place and acceptable?
- xi. Has expert review been satisfactorily conducted?
- xii. Has public consultation been undertaken?

i. What are the quantified risks?

Data presented to the committee:

- Acute consequences:

Age has been a major factor in severe outcome of COVID-19 in all series published so far (3). In one large meta-analysis by the Imperial group of data from China, it was estimated that the infection-mortality rate (95% confidence interval) in 20-29 year olds was 0.0309% (0.0138–0.0923), and in 30-39 year olds was 0.0844% (0.0408–0.185) (4). Recent analysis of severe outcomes from several European countries using denominators estimated by seroprevalence data showed the following in young adults <30 years old.

- Risk of death following infection: 1.2-6.1 per 100,000 (0.0012-0.0061%)
- Risk of ICU following infection: 0.9-4.5 in 10,000 (0.009-0.045%)
- Risk of hospitalization following infection: 0.8-3.9 per 1,000 (0.08-0.39%)

Data from the Office of National Statistics UK from the 16 weeks between 7th March and 26th June 2020 covering the peak of the first pandemic wave show an estimated absolute risk of death in those aged 15-24 years of 0.5 in 100,000 (0.0005%) and those aged 25-34 of 1.6 in 100,000 (0.0016%).

Additionally, the qCOVID living risk prediction algorithm provides an absolute risk of COVID-associated hospitalization in a White British 30 year old woman with no risk factors as 1 in 5076 (0.0197%).

- Ethnicity and acute consequences

The applicants' public and participant inclusion and engagement as well as reviews by experts in BAME health highlighted two opposing views: (1) that inclusion and diversity should be maximized, and (2) that BAME people should not be subjected to any increased risk before those with no documented risk had been through the study procedures.

"To take these views into account and since this increase in risk was not identical across ethnicities, it was felt that a regularly updated personalised risk assessment (qCOVID) would be a better way to balance inclusivity with safety."

- Long-term complications of COVID-19.

Data from the COVID Symptom Study (King's College London, September 2020, personal communication, Claire Steves) using self-reported symptom data from a mobile phone app to analyse the frequency and duration of symptoms related to COVID-19 shows that in 629 individuals in the 18-30 year old age group with PCR-confirmed SARS-CoV-2 infection and who were non-smokers, had a BMI<25, had no co-morbidities and consistently logged into the app. The most frequent symptoms were fatigue (78%), headache (74%), loss of smell (61%), sore throat (59%) and cough (48%). On average, these symptoms lasted no more than 5 days although some rare individuals experienced loss of smell and fatigue for up to 4 months before resolution. Nevertheless, fatigue had resolved in 75% of individuals after 11 days or fewer and 90% of individuals after 19 days or fewer, and loss of smell in 75% after 9 days or fewer and 90% after 14 days or fewer. Further analysis of the overall dataset has allowed the development of a risk prediction system for "long COVID", which has shown relatively lower risk in younger individuals with <5 symptoms (5).

ii. Is care of volunteers acceptable including rescue medication?

The committee was satisfied by detail provided and further reassured that, should a volunteer become seriously ill, care would be available at the Royal Free Hospital with its ITU facilities.

The committee was particularly concerned about the off license use of Remdesivir as rescue therapy, given there was no clear evidence of benefit in similar groups. This possible value was extrapolated from animal work and there was no human data on this pre-emptive use. The applicants provided hypothetical reasons to support this and responded: -

"The investigators remain convinced of the need to administer early treatment with Remdesivir as an additional safety measure, at least during the initial dose escalation phase. As there is currently no data on clinical outcomes of low-dose viral challenge in this setting, we are taking a highly conservative approach during these early cohorts. Remdesivir has been shown to be an extremely safe and well-tolerated drug. Phase I clinical trials of Remdesivir (which were carried out in the young adult age group) showed that the drug was safe even at much higher doses than the current standard of care and no safety issues associated with Remdesivir have been observed in any placebo-controlled trials to date."

..from published data we conclude that Remdesivir treatment will cause little harm and may limit lung involvement, if this were to occur in the controlled infection setting.”

iii. Is the timing of the study acceptable?

The committee queried whether it would be more appropriate to carry out the research after Spring 2021 given current pressure on ITU facilities, feeling that contingencies must be established to provide for clinical capacity in case a participant became unwell while the care of NHS patients must not be compromised. The applicants responded: -

“Procedures have been solidified to make sure there is clinical capacity to take care of our study participants in case they need rescue therapy. A panel of leaders of the North Central London (NCL) Adult Critical Care Network advise that CRITCON levels may not provide the resolution needed to address this concern and instead suggested that the Chief Investigator, Principal Investigator and clinical team seek their approval before initiation of each challenge group as follows:

- Using their direct access to daily capacity data across the network, plus local and national projections, ...the panel will provide an evidence-based opinion on clinical capacity at the start of each challenge group as well as the weeks to come and advise whether it is safe to commence.*

- This will also include review of non-ITU bed state and radiology capacity.*

- This decision will be recorded in the Trial Master File and no dosing will take place without a favourable opinion from this panel.*

This process has been adopted.”

iv. Does viral containment meet current agreed standards?

The committee accepted that this would be run in an established, accredited isolation unit with appropriate precautions and facilities.

v. Is the quality of the infecting agent was adequately ensured?

The committee received a Qualified Person (QP) declaration for the challenge virus, which explained that the QP had reviewed the challenge virus documentation and confirmed its compliance with the principles of GMP (GMP itself cannot be applied).

Further: -

“We agree that it is best practice to manufacture challenge viruses to GMP. We can confirm that our challenge virus has been manufactured in accordance with GMP in a state-of-the-art brand new high containment manufacturing facility. The specific manufacturing process and release testing of the SARS-CoV-2 challenge virus have been reviewed by the MHRA and confirmed suitable.”

vi. How is the use of CT scans justified?

The committee queried the role and value of the CT scans and their associated radiation dosage. The applicants responded: -

“the CT scan was included in the model to assess whether the infection of young adults using this system would lead to pulmonary changes. It was expected that most participants would have a mild form of the disease and therefore there would be no lower airway changes, however if there were some changes the team would need to consider whether it was appropriate to continue using the model; this would be another read out to assess safety.

Involvement of the lungs during COVID-19 is one of the most important measures of disease severity in patients ...The only way to objectively measure lung involvement

in COVID-19 is by radiology... Chest X-ray is not sensitive enough to detect mild changes in patients...CT scan is therefore the only way to detect these lung changes and two scans are necessary to pick up all instances as they can appear both early and late.

Lung changes may predict symptoms and the model may be made safer by prevention of lung changes e.g., by retaining pre-emptive therapy or reducing virus dose

.. we have been able to further reduce the radiation dose of each CT scan by 50%. This means that participants will at most be exposed to ~3mSv even with two CT scans."

vii. Are proposed doses acceptable?

The committee accepted expert advice on this.

viii. Is there a trial steering committee and Data Monitoring Committee?

The committee accepted details on this.

ix. Is payment to volunteers acceptable?

The applicants wrote that: -

"the usual compensation calculation based on the London Living Wage and time spent in the unit would be provided."

The committee accepted the principle of payment and felt the level of remuneration was fair.

x. Are compensation arrangements acceptable?

The volunteers would be expected to contract COVID 19 and suffer some symptoms and symptoms. Compensation would have to cover adverse events beyond these minor symptoms and signs while in the isolation unit. The applicants replied *"along with additional compensation for longer term effects the sponsor had taken out an additional insurance policy to cover for potential practical disruptions to normal life and potential loss of earnings. Participants would be at liberty to claim for this if any issues were experienced."*

xi. Has expert review been satisfactorily conducted?

See 3(i).

xii. Has public consultation been undertaken?

See 3(ii).

3. Consultation and engagement

"SARS-CoV-2 challenge research programmes should be informed by consultation and engagement with the public as well as relevant experts and policy-makers."

Questions posed: -

- i. Has expert independent review been sought?
- ii. Has public consultation been undertaken and is this appropriate to the needs of the ethnic population (BAME)?

Questions and deliberations

i. Has expert review been sought?

The applicants replied.

“The Vaccine Taskforce Human Challenge Board, chaired by the Deputy Chief Medical Officer, includes members from government, Wellcome Trust, MRC and leading universities, including members of the Joint Committee for Vaccination and Immunisation (JCVI). They continually engage with a strong collaborative network of global experts (including University of Oxford, Royal Free, UCL, Imperial, University of Southampton, hVIVO and WHO Advisory Group on Human Challenge).

ii. Has public consultation been undertaken and is this appropriate to the needs of the ethnic population (BAME)?

The applicants wrote: -

“An extensive programme of public engagement was conducted to support the development of this study. This comprised a survey of 2,137 people through YouGov, targeted survey of 350 people and 9 online focus groups between 15th and 21st October 2020.

The wide-reaching survey showed that there was overall agreement that a human challenge study with coronavirus should take place in the UK, but flagged practical concerns related to quarantine (which will be carefully explained to potential participants during the consent process). Many felt that the health risks to young people were small and un-concerning, the societal benefits outweigh the risks and they would feel positive contributing to science.

Some common points of discussion included needing clear and detailed explanation of the risks; concerns about long COVID; worries about needing time off work or being able to work effectively from the unit; mental health consequences; and protecting vulnerable people. Each of these will be addressed specifically during the consent process.

Further study specific PPI was then carried out, including a focus group with individuals from BAME backgrounds, where the risk profile and perceived risk of participation were discussed.

A focus group involving individuals who had taken part in previous challenge studies looked at consent processes. A draft version of the information sheet had been reviewed by this group and feedback had been provided.

Public engagement activities will continue, and a communication strategy is being developed between Imperial, hVIVO, Royal Free Hospital and the funder.”

See also 2(i) and 6(i).

4. Coordination

“SARS-CoV-2 challenge study research programmes should involve close coordination between researchers, funders, policy-makers and regulators.”

Question and deliberation

i. Has there been engagement with government and regulators?

The applicants wrote: -

“the team had been engaging with the MHRA about where human challenge data would fit in in terms of new vaccines along with reengineered vaccines...The Vaccine Taskforce Human Challenge Board, chaired by the Deputy Chief Medical Officer, includes members from government, Wellcome Trust, MRC and leading universities, including members of the Joint Committee for Vaccination and Immunisation (JCVI). They continually engage with a strong collaborative network of global experts (including University of Oxford, Royal Free, UCL, Imperial, University of Southampton, hVIVO and WHO Advisory Group on Human Challenge).

“

5. Site selection

"SARS-CoV-2 challenge studies should be situated where the research can be conducted to the highest scientific, clinical and ethical standards."

Questions posed: -

- i. Is site selection satisfactory and facilities appropriate?
- ii. Do the applicants have the necessary expertise and experience?
- iii. Does the team work under appropriate legal, institutional, and professional accountability?

Questions and deliberations

i. Is site selection satisfactory and facilities appropriate?

The study would be conducted in a unit equipped to handle such an infecting agent (The Royal Free Hospital, London) and this was accepted.

ii. Do the applicants have the necessary expertise and experience?

The applicants wrote: -

"The collaborative team we have formed for this study combines viral challenge study experts from academia, industry and government that are collectively among the most experienced viral challenge team worldwide.

For example, just hVIVO and Imperial combined have safely inoculated over 4000 people with influenza virus, Respiratory Syncytial Virus and Human Rhinovirus with populations covering both healthy adults aged 18-74 and asthmatics."

iii. Does the team work under appropriate legal, institutional and professional accountability?

These were described and the committee accepted the answers provided.

6. Participant selection

"SARS-CoV-2 challenge study researchers should ensure that participant selection criteria limit and minimize risk."

Questions posed:

1. Are participants at least risk?
2. Is there fair selection?
3. Is there fair approach to volunteers?
4. Is there assessment of physical and mental health?
5. Is there contact with the Health Care Practitioner?
6. Is there protection against over volunteering?

Questions and deliberations

i. Are participants at least risk?

See also 2(i).

The applicants wrote:

"it was felt that a personalised risk assessment (QCOVID) would be the best way to balance inclusivity with safety and the recruitment approach should be responsive to the most up-to-date data."

Given the advice that QCOVID was not recommended for individual clinical decisions, the committee debated this and discussed it with the researchers. It was agreed ultimately that, despite this advice, QCOVID was the most suitable instrument.

ii. Is there fair selection?

The committee believed that there should be risk based selection with no unfair discrimination but understood that current evidence was that those of BAME origin were at some increased risk. In discussion the committee accepted that the analysis by the Office of National Statistics and the OpenSAFELY <https://www.opensafely.org/> and ISARIC 4C studies (<https://isaric4c.net/>) of hospitalized patients have all concluded that the majority of the increased risk seen (particularly in Black and South Asian groups) was related to socioeconomic factors including greater exposure due to disproportionately being in front-line jobs. However, there remained some element of increased risk in BAME individuals that was still unexplained. The applicants reported: -

“ public and participant inclusion and engagement as well as reviews by experts in BAME health highlighted two opposing views: (1) that inclusion and diversity should be maximized, and (2) that BAME people should not be subjected to any increased risk before those with no documented risk had been through the study procedures. To take these views into account and since this increase in risk was not identical across ethnicities, it was felt that a personalised risk assessment would be a better way to balance inclusivity with safety and the recruitment approach should be responsive to the most up-to-date data. The QCOVID risk scoring tool is an independent, validated risk assessment algorithm that integrates age, sex, ethnicity, geography, body mass index and co-morbidities to provide an individualised estimate of absolute mortality and hospitalisation risk. This provides an objective absolute risk of death and hospitalization based on the best available UK epidemiologic data. The tool is CE marked and will be recalibrated with up-to-date data every 3-6 months.

By setting a risk threshold, the potential risks associated with particular participant features (such as ethnicity, sex or BMI) may be balanced holistically and certain risk factors mitigated by other characteristics such as younger age).

iii. Is there fair approach to volunteers?

This had been reviewed and approved at a prior meeting.

iv. Is there assessment of physical and mental health?

This was reviewed and the proposed methods accepted.

v. Is there contact with the Health Care Practitioner (HCP)?

This was reviewed and agreed would be an important part of mitigating risk. Changes to the correspondence with the HCP were requested.

vi. Is there protection against over volunteering?

The TOPs over volunteering database that would identify previous enrolment into phase I clinical studies would be used: <https://www.hra.nhs.uk/about-us/committees-and-services/the-over-volunteering-prevention-system/>

7. Expert review

“SARS-CoV-2 challenge studies should be reviewed by a specialized committee.”

The members of this committee were from Research Ethics Committees in the UK recognised to review both Clinical Trials of Investigational Medicinal Products (CTIMPs) and Phase 1 studies in healthy volunteers. Selection also focussed on those with experience of vaccine studies. Membership ensured a balance of expert and lay members in accordance with the relevant legislation and guidance and representation across the four nations. Those appointed to the committee were invited to two remote workshops on HICS conducted on Zoom and provided a current reading list. The committee also had access to other expertise and resources.

8. Informed consent:

“SARS-CoV-2 challenge studies must involve rigorous consent processes.”

Questions posed: -

- i. Is there a framework of consent processes?
- ii. Are volunteers presented with the clear key facts?
- iii. Is the consent interview recorded?
- iv. Is there an assessment of understanding?
- v. Is there fair time for consent?
- vi. Do those seeking consent have appropriate expertise and training?
- vii. Has there been public involvement in consent processes?

Questions and deliberations

- i. **Is there a fair framework of consent processes?**
A schedule was provided and accepted.
- ii. **Are volunteers presented with the clear key facts?**
A Key Fact Summary sheet to introduce the study was developed and accepted.
- iii. **Is the consent interview audio or video recorded?**
This was a suggestion made by the committee and accepted.
- iv. **Is there an assessment of understanding?**
The committee was reassured by
 - Use of a Key Fact Summary Sheet
 - An improved PIS
 - A break in procedures for volunteers to discuss the possibility of volunteering with others.
 - An itemised Informed Consent Form referring to “key facts”.
 - An MCQ quiz (that had to be passed) to assess understanding .
- v. **Is there fair time for consent?**
The committee was reassured on this.
- vi. **Do those seeking consent have appropriate expertise and training?**
This was presented and accepted.
- vii. **Has there been public involvement in consent processes?**
The Participant Information Sheet (PIS) and Informed Consent Form (ICF) had been submitted for broader comment (see also 3(ii)). We accepted that these groups thought it to be of good quality, the right length and level of detail and recommendations had been acted upon. Further advice was offered by one committee member.

9. Evaluating alternative study design¹

Questions posed: -

- i. What alternative designs might answer the research questions and meet the research purpose?

¹ Not a WHO category but the committee felt this of vital importance and would recommend its addition.

ii. Why should the study be conducted in the UK?

i. **What alternative designs might answer the research questions and meet the research purpose? Couldn't field studies (investigating naturally acquired infection) provide answers to the research questions?**

The committee understood that as infection rates fell, field studies would be more time consuming and difficult but looked into the exact data that different studies would generate and how each would link to the aims of prevention and treatment of SARS COV 2 infection.

The applicants responded: -

"Field studies are slow, expensive and complicated by differences in the populations in which they are carried out. Controlled direct head-to-head comparisons to compare new vaccines against existing ones are only feasible using human challenge. Furthermore, even with limited vaccination, pandemic waves will wax and wane unpredictably in those regions due to factors such as seasonal changes and public health measures. As a result, many more volunteers will need to be immunised with a vaccine candidate of unknown efficacy in a field trial than a challenge study (exposing more people to risk) and results will be much slower to obtain.

In addition, questions have been raised about the ethics of running vaccine trials in low and middle income settings (LMICs) for the benefit of more wealthy countries. This has proven highly problematic with some local communities, who have been concerned about exploitation, quality of study conduct, and uncertain benefit to themselves.

Importantly, where a vaccine has already been shown to be safe and effective in a phase III study, human challenge studies can also be used to quickly bridge when the vaccine is reformulated either in response to viral mutation or, for example, changes in manufacturing to improve supply chain. Thus, emergency use authorisation could be given to a reformulated vaccine after a rapid, small challenge study (as has been done recently with the conjugated typhoid vaccine)."

The committee accepted this position.

ii. **Why should this study be located the study in the UK?**

The applicants answered: -

"we believe that it is essential to run this first ever SARS-CoV-2 human challenge study in the UK as it is the only place with the facilities, expertise, experience and coordinated approach necessary to establish the model safely. The collaborative team we have formed for this study combines viral challenge study experts from academia, industry and government that are collectively among the most experienced viral challenge team worldwide. However, having established the safety profile, required virus dose and suitable endpoints to monitor infection, challenge models for all subsequent use can be set up, including potentially in other countries.

Based on our experiences setting up challenge studies in low- and middle-income countries (LMICs), it has only been possible to obtain public support and ethical approval to extend these studies once the model had been shown to be safe in a high-resource setting such as the UK"

The committee accepted this position.

Supplementary material

Deliberations structured on the WHO guidance.

1. Scientific justification

“SARS CoV-2 challenge studies must have strong scientific justification.”

Questions and deliberations

- i. What are the research questions and purposes?
- ii. Why is it important to seek answers to these questions?
- iii. Have these questions been answered already?
- iv. Will the chosen method answer the questions and contribute meaningful and valid information that will help disease prevention, management and treatment?
- v. Will results be applicable to the broader community (generalizability)?
- vi. Might the study detract from pandemic care?
- vii. How has transparency been ensured so results will be rapidly available?
- viii. Has there been independent review?
- ix. Has there been public involvement?

i. What are the research questions and purposes? The applicants answered:-

“20/UK/0002 is a dose finding, enabling study to develop a SARS COV 2 human challenge model.”

The committee accepted this position in conjunction with 1(ii).

ii. Why is it important to seek answers?

The committee felt this first, dose finding, study to be of extremely limited, if any, value. However if it were to enable future studies with possible benefit, there could be acceptable purpose. Hence, the committee wanted to know the exact data that these later studies would generate and how each would link to prevention and treatment of SARS COV 2 infection.

The applicants proposed further studies would: -

a) Establish the incubation period.

“The “incubation period” of COVID-19 is the time from coronavirus exposure to the beginning of symptoms and when people are most infectious. This human challenge study is the only way to accurately know how long the incubation period is and will be essential to improve Track and Trace efforts.

b) Allow study of asymptomatic infection.

Mild or asymptomatic infection in young people is probably a major driver of the pandemic and human challenge studies are the only way to obtain data about how infection and viral shedding occur in this group. This will immediately affect policy on length of self-isolation and prioritisation for vaccines for these people, if we show that they are major shedders of virus.

c) Determine how long people are infective.

This human challenge study will allow us to accurately measure how long people are infectious, from first exposure to the virus being cleared. This will determine exactly how long self-isolation (quarantine) periods should be after exposure.

d) Research risk of re-infection.

Based on what we know from similar viruses, some people can catch COVID-19 more than once. A human challenge study we are working on in Oxford will help

answer a number of important questions on re-infection, including how long people are protected after having had COVID-19; what makes people more at risk of re-infection; and whether re-infected people can spread the virus to others.

e) Help vaccine development.

..., using challenge studies, the most promising vaccine candidates could progress much quicker, having been strengthened by early evidence of efficacy, and the risk of a large-scale trial failing would be minimised. In addition, the human challenge study would validate the impact of immune markers that correspond with protection, strengthening the licensure package. The flipside of this is that if a novel vaccine fails in a head-to-head study comparing with one of the current vaccines, then progression to a costly and burdensome phase III trial would be avoided.

A key question that we will test for these vaccines is whether they stop people carrying and spreading the virus as well as preventing symptoms. Vaccines or antivirals that do nothing in healthy young adults are unlikely to work better in higher-risk populations (due to impaired immunity, kidney or liver function etc.), so can be de-prioritised in favour of those that do.”

f) Help development of anti-viral treatments.

This human challenge study will open the way for future testing of these.

g) Help manage variants

With regard to variants and mutation, despite changes in the newer strains, it is also important to emphasise that fundamentally these are all the same type of virus and many findings about the disease and the immunology will be generalisable. In addition, most antiviral drugs target parts of the virus that have remained largely unchanged, so the value of rapid early testing of new treatments using the existing challenge virus is unlikely to be affected by strain variation in the near term.

However, with unreliable transmission in the community, it may not be possible to test these quickly enough in field trials. In such an event, the human challenge programme will provide a simple and rapid method to test new vaccines against emerging strains.

The next step is therefore to manufacture a new challenge strain that matches what manufacturers use to re-engineer their vaccines. With our experience, we can now produce a novel challenge agent more quickly than before but without this current study, human challenge development would have to start from scratch and testing of modified vaccines greatly delayed.

In addition, follow-on studies (that will be subject to separate applications for ethical review) can give clear answers to questions that cannot be sorted out by field trials in a meaningful timeframe, including:

- Whether new vaccines/vaccine regimes are as good as/better than existing ones*
- o How to optimise the delivery of vaccines to ensure the most effective protection for the greatest number of people using one or two dose approaches can thus be resolved.*

- o Testing vaccines adjusted for mutant viruses (variants) using human challenge in a “bridging study” could bypass the need for more phase III trials and allow emergency authorisation of updated vaccines.*

- o What protects people from re-infection after having previously had COVID-19.*

- o *Very quick proof-of-concept studies are possible using human challenge that will bring these treatments on-line sooner.*
- h) *Identifying correlates of protection (i.e. the immune markers that are responsible for protection against SARS-CoV-2) is a powerful reason for running these studies in young adults as they are the benchmark for optimal immune responses. These can then be translated to higher-risk populations by immune bridging studies, where the immune markers that are shown to be responsible for protection in young adults can be used to accurately predict protection in higher-risk groups.*
- i) *Contribute to pandemic management*
 - o *On its own, this study will provide answers with important short-to-medium term public health impacts, specifically:*
 - o *Measuring virus coming out of the nose will show when and how much infectious virus is shed.*
 - o *Only a challenge study can accurately measure asymptomatic infection.*
 - o *Can the vaccine prevent asymptomatic infection? This could immediately alter public health strategy as it is considered that asymptomatic infection is driving the continuation of the pandemic.”*

iii. Have these questions been answered before?

The committee accepted that, from the evidence presented, these questions had not yet been satisfactorily answered.

iv. Will the chosen method and follow-on studies answer these questions (meet the stated purpose) and contribute meaningful information that will help disease prevention and treatment?

The committee accepted expert opinion in support of this study and that proposed methods would answer the questions posed with regards to the aims in 1(ii) .

v. Will results be applicable to the broader community (generalizability)?

The committee debated the broader generalisability of study results when the volunteers were young, healthy and of low risk and wanted reassurance that this research would be relevant to the broader population. The applicants responded: - *“While young healthy adults may not fully recapitulate high risk groups, they provide a benchmark for optimal protective immunity and are highly suitable for antiviral and monoclonal antibody testing. People in this age group are also likely to be the main drivers of continuing pandemic transmission once older adults are vaccinated.”*

vi. Has there been Independent review and review of prior work?

The scientific quality of the research had been reviewed within the Sponsor's organisation, by the study team at hVIVO while two independent reports were provided. Further support was provided by the Dept of Health, Vaccine Task Force and the Wellcome Trust.

vii. Has there been public involvement?

See 3(ii)

viii. Would the study detract from pandemic care?

Volunteers would be cared for, separately in the accredited isolation research unit at the RFH. For care of any volunteer who fell seriously ill see 2(ii). The committee asked whether the study should be timed to ensure that clinical care would be available should a volunteer fall seriously ill (i.e. Outside any surge of infection in the community). See 2(iii).

ix. How has transparency been ensured so results will be rapidly available?

In line with the HRA transparency policy the committee wanted reassurance that the results would be openly available once the study was completed. The applicants responded: -

“this is an academically-led study with the primary purpose of advancing scientific and medical knowledge.”

2. Risks and benefits

“It must be reasonable to expect that the potential benefits of SARS- CoV-2 challenge studies outweigh risks.”

Questions posed:

- i. What are the quantified risks?
- ii. Is care of volunteers acceptable including rescue medication?
- iii. Is the timing of the study acceptable?
- iv. Will viral containment meet current agreed standards?
- v. Is the quality of the infecting agent adequately ensured?
- vi. How are CT scans justified?
- vii. Are doses acceptable?
- viii. Are there a trial steering committee and Data Monitoring Committee?
- ix. Is payment to volunteers acceptable and not undue influence?
- x. Are compensation arrangements in place and acceptable?
- xi. Has expert review been satisfactorily conducted?
- xii. Has public consultation been undertaken?

i. What are the quantified risks?

Data presented to the committee:

- Acute consequences:

Age has been a major factor in severe outcome of COVID-19 in all series published so far (3). In one large meta-analysis by the Imperial group of data from China, it was estimated that the infection-mortality rate (95% confidence interval) in 20-29 year olds was 0.0309% (0.0138–0.0923), and in 30-39 year olds was 0.0844% (0.0408–0.185) (4). Recent analysis of severe outcomes from several European countries using denominators estimated by seroprevalence data showed the following in young adults <30 years old.

- Risk of death following infection: 1.2-6.1 per 100,000 (0.0012-0.0061%)
- Risk of ICU following infection: 0.9-4.5 in 10,000 (0.009-0.045%)
- Risk of hospitalization following infection: 0.8-3.9 per 1,000 (0.08-0.39%)

Data from the Office of National Statistics UK from the 16 weeks between 7th March and 26th June 2020 covering the peak of the first pandemic wave show an estimated absolute risk of death in those aged 15-24 years of 0.5 in 100,000 (0.0005%) and those aged 25-34 of 1.6 in 100,000 (0.0016%).

Additionally, the qCOVID living risk prediction algorithm provides an absolute risk of COVID-associated hospitalization in a White British 30 year old woman with no risk factors as 1 in 5076 (0.0197%).

- Ethnicity and acute consequences

The applicants' public and participant inclusion and engagement as well as reviews by experts in BAME health highlighted two opposing views: (1) that inclusion and diversity should be maximized, and (2) that BAME people should not be subjected to any increased risk before those with no documented risk had been through the study procedures.

"To take these views into account and since this increase in risk was not identical across ethnicities, it was felt that a regularly updated personalised risk assessment (qCOVID) would be a better way to balance inclusivity with safety. "

- Long-term complications of COVID-19.

Data from the COVID Symptom Study (King's College London, September 2020, personal communication, Claire Steves) using self-reported symptom data from a mobile phone app to analyse the frequency and duration of symptoms related to COVID-19 shows that in 629 individuals in the 18-30 year old age group with PCR-confirmed SARS-CoV-2 infection and who were non-smokers, had a BMI<25, had no co-morbidities and consistently logged into the app. The most frequent symptoms were fatigue (78%), headache (74%), loss of smell (61%), sore throat (59%) and cough (48%). On average, these symptoms lasted no more than 5 days although some rare individuals experienced loss of smell and fatigue for up to 4 months before resolution. Nevertheless, fatigue had resolved in 75% of individuals after 11 days or fewer and 90% of individuals after 19 days or fewer, and loss of smell in 75% after 9 days or fewer and 90% after 14 days or fewer. Further analysis of the overall dataset has allowed the development of a risk prediction system for "long COVID", which has shown relatively lower risk in younger individuals with <5 symptoms (5).

ii. Is care of volunteers acceptable including rescue medication?

The committee was satisfied by detail provided and further reassured that, should a volunteer become seriously ill, care would be available at the Royal Free Hospital with its ITU facilities.

The committee was particularly concerned about the off license use of Remdesivir as rescue therapy, given there was no clear evidence of benefit in similar groups. This possible value was extrapolated from animal work and there was no human data on this pre-emptive use. The applicants provided hypothetical reasons to support this and responded: -

"The investigators remain convinced of the need to administer early treatment with Remdesivir as an additional safety measure, at least during the initial dose escalation phase. As there is currently no data on clinical outcomes of low-dose viral challenge in this setting, we are taking a highly conservative approach during these early cohorts. Remdesivir has been shown to be an extremely safe and well-tolerated drug. Phase I clinical trials of Remdesivir (which were carried out in the young adult age group) showed that the drug was safe even at much higher doses than the current standard of care and no safety issues associated with Remdesivir have been observed in any placebo-controlled trials to date.

..from published data we conclude that Remdesivir treatment will cause little harm and may limit lung involvement, if this were to occur in the controlled infection setting."

iii. Is the timing of the study acceptable?

The committee queried whether it would be more appropriate to carry out the research after Spring 2021 given current pressure on ITU facilities, feeling that contingencies must be established to provide for clinical capacity in case a participant became unwell while the care of NHS patients must not be compromised. The applicants responded: -

"Procedures have been solidified to make sure there is clinical capacity to take care of our study participants in case they need rescue therapy. A panel of leaders of the North Central London (NCL) Adult Critical Care Network advise that CRITCON levels may not provide the resolution needed to address this concern and instead suggested that the Chief Investigator, Principal Investigator and clinical team seek their approval before initiation of each challenge group as follows:

- Using their direct access to daily capacity data across the network, plus local and national projections, ...the panel will provide an evidence-based opinion on clinical capacity at the start of each challenge group as well as the weeks to come and advise whether it is safe to commence.*

- This will also include review of non-ITU bed state and radiology capacity.*

- This decision will be recorded in the Trial Master File and no dosing will take place without a favourable opinion from this panel.*

This process has been adopted."

iv. Does viral containment meet current agreed standards?

The committee accepted that this would be run in an established, accredited isolation unit with appropriate precautions and facilities.

v. Is the quality of the infecting agent was adequately ensured?

The committee received a Qualified Person (QP) declaration for the challenge virus, which explained that the QP had reviewed the challenge virus documentation and confirmed its compliance with the principles of GMP (GMP itself cannot be applied).

Further: -

"We agree that it is best practice to manufacture challenge viruses to GMP. We can confirm that our challenge virus has been manufactured in accordance with GMP in a state-of-the-art brand new high containment manufacturing facility. The specific manufacturing process and release testing of the SARS-CoV-2 challenge virus have been reviewed by the MHRA and confirmed suitable."

vi. How is the use of CT scans justified?

The committee queried the role and value of the CT scans and their associated radiation dosage. The applicants responded: -

"the CT scan was included in the model to assess whether the infection of young adults using this system would lead to pulmonary changes. It was expected that most participants would have a mild form of the disease and therefore there would be no lower airway changes, however if there were some changes the team would need to consider whether it was appropriate to continue using the model; this would be another read out to assess safety.

Involvement of the lungs during COVID-19 is one of the most important measures of disease severity in patients ...The only way to objectively measure lung involvement

in COVID-19 is by radiology... Chest X-ray is not sensitive enough to detect mild changes in patients...CT scan is therefore the only way to detect these lung changes and two scans are necessary to pick up all instances as they can appear both early and late.

Lung changes may predict symptoms and the model may be made safer by prevention of lung changes e.g., by retaining pre-emptive therapy or reducing virus dose

.. we have been able to further reduce the radiation dose of each CT scan by 50%. This means that participants will at most be exposed to ~3mSv even with two CT scans."

vii. Are proposed doses acceptable?

The committee accepted expert advice on this.

viii. Is there a trial steering committee and Data Monitoring Committee?

The committee accepted details on this.

ix. Is payment to volunteers acceptable?

The applicants wrote that: -

"the usual compensation calculation based on the London Living Wage and time spent in the unit would be provided."

The committee accepted the principle of payment and felt the level of remuneration was fair.

x. Are compensation arrangements acceptable?

The volunteers would be expected to contract COVID 19 and suffer some symptoms and symptoms. Compensation would have to cover adverse events beyond these minor symptoms and signs while in the isolation unit. The applicants replied *"along with additional compensation for longer term effects the sponsor had taken out an additional insurance policy to cover for potential practical disruptions to normal life and potential loss of earnings. Participants would be at liberty to claim for this if any issues were experienced."*

xi. Has expert review been satisfactorily conducted?

See 3(i).

xii. Has public consultation been undertaken?

See 3(ii).

3. Consultation and engagement

"SARS-CoV-2 challenge research programmes should be informed by consultation and engagement with the public as well as relevant experts and policy-makers."

Questions posed: -

- i. Has expert independent review been sought?
- ii. Has public consultation been undertaken and is this appropriate to the needs of the ethnic population (BAME)?

Questions and deliberations

i. Has expert review been sought?

The applicants replied.

“The Vaccine Taskforce Human Challenge Board, chaired by the Deputy Chief Medical Officer, includes members from government, Wellcome Trust, MRC and leading universities, including members of the Joint Committee for Vaccination and Immunisation (JCVI). They continually engage with a strong collaborative network of global experts (including University of Oxford, Royal Free, UCL, Imperial, University of Southampton, hVIVO and WHO Advisory Group on Human Challenge).

ii. Has public consultation been undertaken and is this appropriate to the needs of the ethnic population (BAME)?

The applicants wrote: -

“An extensive programme of public engagement was conducted to support the development of this study. This comprised a survey of 2,137 people through YouGov, targeted survey of 350 people and 9 online focus groups between 15th and 21st October 2020.

The wide-reaching survey showed that there was overall agreement that a human challenge study with coronavirus should take place in the UK, but flagged practical concerns related to quarantine (which will be carefully explained to potential participants during the consent process). Many felt that the health risks to young people were small and un-concerning, the societal benefits outweigh the risks and they would feel positive contributing to science.

Some common points of discussion included needing clear and detailed explanation of the risks; concerns about long COVID; worries about needing time off work or being able to work effectively from the unit; mental health consequences; and protecting vulnerable people. Each of these will be addressed specifically during the consent process.

Further study specific PPI was then carried out, including a focus group with individuals from BAME backgrounds, where the risk profile and perceived risk of participation were discussed.

A focus group involving individuals who had taken part in previous challenge studies looked at consent processes. A draft version of the information sheet had been reviewed by this group and feedback had been provided.

Public engagement activities will continue, and a communication strategy is being developed between Imperial, hVIVO, Royal Free Hospital and the funder.”

See also 2(i) and 6(i).

4. Coordination

“SARS-CoV-2 challenge study research programmes should involve close coordination between researchers, funders, policy-makers and regulators.”

Question and deliberation

i. Has there been engagement with government and regulators?

The applicants wrote: -

“the team had been engaging with the MHRA about where human challenge data would fit in in terms of new vaccines along with reengineered vaccines...The Vaccine Taskforce Human Challenge Board, chaired by the Deputy Chief Medical Officer, includes members from government, Wellcome Trust, MRC and leading universities, including members of the Joint Committee for Vaccination and Immunisation (JCVI). They continually engage with a strong collaborative network of global experts (including University of Oxford, Royal Free, UCL, Imperial, University of Southampton, hVIVO and WHO Advisory Group on Human Challenge).

“

5. Site selection

"SARS-CoV-2 challenge studies should be situated where the research can be conducted to the highest scientific, clinical and ethical standards."

Questions posed: -

- i. Is site selection satisfactory and facilities appropriate?
- ii. Do the applicants have the necessary expertise and experience?
- iii. Does the team work under appropriate legal, institutional, and professional accountability?

Questions and deliberations

i. Is site selection satisfactory and facilities appropriate?

The study would be conducted in a unit equipped to handle such an infecting agent (The Royal Free Hospital, London) and this was accepted.

ii. Do the applicants have the necessary expertise and experience?

The applicants wrote: -

"The collaborative team we have formed for this study combines viral challenge study experts from academia, industry and government that are collectively among the most experienced viral challenge team worldwide.

For example, just hVIVO and Imperial combined have safely inoculated over 4000 people with influenza virus, Respiratory Syncytial Virus and Human Rhinovirus with populations covering both healthy adults aged 18-74 and asthmatics."

iii. Does the team work under appropriate legal, institutional and professional accountability?

These were described and the committee accepted the answers provided.

6. Participant selection

"SARS-CoV-2 challenge study researchers should ensure that participant selection criteria limit and minimize risk."

Questions posed:

1. Are participants at least risk?
2. Is there fair selection?
3. Is there fair approach to volunteers?
4. Is there assessment of physical and mental health?
5. Is there contact with the Health Care Practitioner?
6. Is there protection against over volunteering?

Questions and deliberations

i. Are participants at least risk?

See also 2(i).

The applicants wrote:

"it was felt that a personalised risk assessment (QCOVID) would be the best way to balance inclusivity with safety and the recruitment approach should be responsive to the most up-to-date data."

Given the advice that QCOVID was not recommended for individual clinical decisions, the committee debated this and discussed it with the researchers. It was agreed ultimately that, despite this advice, QCOVID was the most suitable instrument.

ii. Is there fair selection?

The committee believed that there should be risk based selection with no unfair discrimination but understood that current evidence was that those of BAME origin were at some increased risk. In discussion the committee accepted that the analysis by the Office of National Statistics and the OpenSAFELY <https://www.opensafely.org/> and ISARIC 4C studies (<https://isaric4c.net/>) of hospitalized patients have all concluded that the majority of the increased risk seen (particularly in Black and South Asian groups) was related to socioeconomic factors including greater exposure due to disproportionately being in front-line jobs. However, there remained some element of increased risk in BAME individuals that was still unexplained. The applicants reported: -

“public and participant inclusion and engagement as well as reviews by experts in BAME health highlighted two opposing views: (1) that inclusion and diversity should be maximized, and (2) that BAME people should not be subjected to any increased risk before those with no documented risk had been through the study procedures. To take these views into account and since this increase in risk was not identical across ethnicities, it was felt that a personalised risk assessment would be a better way to balance inclusivity with safety and the recruitment approach should be responsive to the most up-to-date data. The QCOVID risk scoring tool is an independent, validated risk assessment algorithm that integrates age, sex, ethnicity, geography, body mass index and co-morbidities to provide an individualised estimate of absolute mortality and hospitalisation risk. This provides an objective absolute risk of death and hospitalization based on the best available UK epidemiologic data. The tool is CE marked and will be recalibrated with up-to-date data every 3-6 months.

By setting a risk threshold, the potential risks associated with particular participant features (such as ethnicity, sex or BMI) may be balanced holistically and certain risk factors mitigated by other characteristics such as younger age).

iii. Is there fair approach to volunteers?

This had been reviewed and approved at a prior meeting.

iv. Is there assessment of physical and mental health?

This was reviewed and the proposed methods accepted.

v. Is there contact with the Health Care Practitioner (HCP)?

This was reviewed and agreed would be an important part of mitigating risk. Changes to the correspondence with the HCP were requested.

vi. Is there protection against over volunteering?

The TOPs over volunteering database that would identify previous enrolment into phase I clinical studies would be used: <https://www.hra.nhs.uk/about-us/committees-and-services/the-over-volunteering-prevention-system/>

7. Expert review

“SARS-CoV-2 challenge studies should be reviewed by a specialized committee.”

The members of this committee were from Research Ethics Committees in the UK recognised to review both Clinical Trials of Investigational Medicinal Products (CTIMPs) and Phase 1 studies in healthy volunteers. Selection also focussed on those with experience of vaccine studies. Membership ensured a balance of expert and lay members in accordance with the relevant legislation and guidance and representation across the four nations. Those appointed to the committee were invited to two remote workshops on HICS conducted on Zoom and provided a current reading list. The committee also had access to other expertise and resources.

8. Informed consent:

“SARS-CoV-2 challenge studies must involve rigorous consent processes.”

Questions posed: -

- i. Is there a framework of consent processes?
- ii. Are volunteers presented with the clear key facts?
- iii. Is the consent interview recorded?
- iv. Is there an assessment of understanding?
- v. Is there fair time for consent?
- vi. Do those seeking consent have appropriate expertise and training?
- vii. Has there been public involvement in consent processes?

Questions and deliberations

- i. **Is there a fair framework of consent processes?**
A schedule was provided and accepted.
- ii. **Are volunteers presented with the clear key facts?**
A Key Fact Summary sheet to introduce the study was developed and accepted.
- iii. **Is the consent interview audio or video recorded?**
This was a suggestion made by the committee and accepted.
- iv. **Is there an assessment of understanding?**
The committee was reassured by
 - Use of a Key Fact Summary Sheet
 - An improved PIS
 - A break in procedures for volunteers to discuss the possibility of volunteering with others.
 - An itemised Informed Consent Form referring to “key facts”.
 - An MCQ quiz (that had to be passed) to assess understanding .
- v. **Is there fair time for consent?**
The committee was reassured on this.
- vi. **Do those seeking consent have appropriate expertise and training?**
This was presented and accepted.
- vii. **Has there been public involvement in consent processes?**
The Participant Information Sheet (PIS) and Informed Consent Form (ICF) had been submitted for broader comment (see also 3(ii)). We accepted that these groups thought it to be of good quality, the right length and level of detail and recommendations had been acted upon. Further advice was offered by one committee member.

9. Evaluating alternative study design¹

Questions posed: -

- i. What alternative designs might answer the research questions and meet the research purpose?

¹ Not a WHO category but the committee felt this of vital importance and would recommend its addition.

ii. Why should the study be conducted in the UK?

i. **What alternative designs might answer the research questions and meet the research purpose? Couldn't field studies (investigating naturally acquired infection) provide answers to the research questions?**

The committee understood that as infection rates fell, field studies would be more time consuming and difficult but looked into the exact data that different studies would generate and how each would link to the aims of prevention and treatment of SARS COV 2 infection.

The applicants responded: -

“Field studies are slow, expensive and complicated by differences in the populations in which they are carried out. Controlled direct head-to-head comparisons to compare new vaccines against existing ones are only feasible using human challenge. Furthermore, even with limited vaccination, pandemic waves will wax and wane unpredictably in those regions due to factors such as seasonal changes and public health measures. As a result, many more volunteers will need to be immunised with a vaccine candidate of unknown efficacy in a field trial than a challenge study (exposing more people to risk) and results will be much slower to obtain.

In addition, questions have been raised about the ethics of running vaccine trials in low and middle income settings (LMICs) for the benefit of more wealthy countries. This has proven highly problematic with some local communities, who have been concerned about exploitation, quality of study conduct, and uncertain benefit to themselves.

Importantly, where a vaccine has already been shown to be safe and effective in a phase III study, human challenge studies can also be used to quickly bridge when the vaccine is reformulated either in response to viral mutation or, for example, changes in manufacturing to improve supply chain. Thus, emergency use authorisation could be given to a reformulated vaccine after a rapid, small challenge study (as has been done recently with the conjugated typhoid vaccine).”

The committee accepted this position.

ii. **Why should this study be located the study in the UK?**

The applicants answered: -

“we believe that it is essential to run this first ever SARS-CoV-2 human challenge study in the UK as it is the only place with the facilities, expertise, experience and coordinated approach necessary to establish the model safely. The collaborative team we have formed for this study combines viral challenge study experts from academia, industry and government that are collectively among the most experienced viral challenge team worldwide. However, having established the safety profile, required virus dose and suitable endpoints to monitor infection, challenge models for all subsequent use can be set up, including potentially in other countries.

Based on our experiences setting up challenge studies in low- and middle-income countries (LMICs), it has only been possible to obtain public support and ethical approval to extend these studies once the model had been shown to be safe in a high-resource setting such as the UK”

The committee accepted this position.

