Ethics review of COVID-19 human challenge studies: a joint HRA/WHO workshop

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ABSTRACT (299/300 words)

This report of a joint World Health Organization (WHO) and United Kingdom (UK) Health Research Authority (HRA) workshop discusses the ethics review of the first COVID-19 human challenge studies, undertaken in the midst of the pandemic. It reviews the early efforts of international and national institutions to define the ethical standards required for COVID-19 human challenge studies and create the frameworks to ensure rigorous and timely review of these studies.

This report evaluates the utility of the WHO's international guidance document, '*Key criteria for the ethical acceptability of COVID-19 human challenge studies'* (WHO Key Criteria) as a practical resource for the ethics review of COVID-19 human challenge studies. It also assesses the UK HRA's approach to these complex ethics reviews, including the formation of a Specialist Ad-Hoc Research Ethics Committee (REC) for COVID-19 Human Challenge Studies to review all current and future COVID-19 human challenge studies. In addition, the report outlines the reflections of REC members and researchers regarding the ethics review process of the first COVID-19 human challenge studies. Finally, it considers the potential ongoing scientific justification for COVID-19 human challenge studies, particularly in relation to next-generation vaccines and optimisation of vaccination schedules.

Overall, there was broad consensus that the WHO Key Criteria represented an international consensus document that played a powerful role in setting norms and delineating the necessary conditions to be considered for the ethical acceptability of COVID-19 human challenge studies. Workshop members suggested that the WHO Key Criteria could be practically implemented to support researchers and ethics reviewers, including in the training of ethics committee members. In future, a wider audience may be engaged by the original document and potential additional materials, informed by the experiences of those involved in the first COVID-19 human challenge studies outlined in this document.

HIGHLIGHTS (3 bullet points, 85 characters (including spaces), each)

- *Human challenge studies are not usually undertaken during a pandemic*
- *WHO Key Criteria provided practical guidance for ethics review of COVID-19 studies*
- *Complex ethics reviews require novel approaches to research ethics frameworks*

INTRODUCTION (MANUSCRIPT 2987/ 5000 words)

The coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has had an extraordinary impact on global public health and socioeconomic stability (1, 2). It has claimed millions of lives and placed extreme strain on health care systems worldwide (3, 4). Human challenge studies, in which research participants are deliberately exposed to infectious pathogens, have played a significant role in vaccine and therapeutic development and the study of host-pathogen interactions (5). However, human challenge studies are not usually undertaken with a novel pathogen in the midst of a pandemic. The COVID-19 pandemic galvanised the global scientific community, resulting in several rapid advances including the availability of highly efficacious vaccines within a year of the identification of SARS-CoV-2 (6). With these developments, the scientific justification for COVID-19 human challenge studies has evolved, with the potential aim of human studies shifting from first generation vaccine development to other purposes such as i) testing next generation vaccine candidates and therapeutics; ii) definition of immune correlates of protection to be used as surrogate endpoints in future trials, iii) improving understanding of the pathogenesis of, immune response to, and transmission of SARS-CoV-2 and iv) characterizing vaccine responses to variants of concern. This report of a joint World Health Organization (WHO) and United Kingdom (UK) Health Research Authority (HRA) workshop reviews the early efforts of international and national institutions to define the ethical standards required for COVID-19 human challenge studies during the pandemic as well as the experience of researchers who are now conducting such studies.

WHO KEY CRITERIA

In May 2020, the World Health Organisation (WHO) published an outline of key criteria for the ethical acceptability of COVID-19 human challenge studies (WHO Key Criteria) (7). This document aimed to provide guidance to scientists, research ethics committees, institutional review boards, funders, policy makers, and regulators in deliberations regarding SARS-CoV-2 challenge studies by identifying (especially salient) conditions that would need to be satisfied in order for such studies to suitably address key ethical concerns.

The WHO Working Group for Guidance on Human Challenge Studies in COVID-19 was tasked with developing this guidance and was formed as a sub-working group of the International Working Group on Ethics and COVID-19. Additional expertise was co-opted for this working group, including experts involved in a pre-existing WHO initiative to develop broader guidance on ethical issues in human challenge studies.

Eight interconnected ethical criteria were highlighted as key considerations to be addressed for COVID-19 human challenge studies (in addition to other usual research ethics criteria and local requirements) (7). In brief, SARS-CoV-2 human challenge studies:

1. Must have strong **scientific justification.**
2. Must have a reasonable expectation that the **potential benefits of the study outweigh the risks**, particularly in comparison to alternative scientific methods.
3. Should be informed by **consultation and engagement** with the public as well as relevant experts and policy-makers.
4. Should involve close **coordination** between researchers, funders, policy-makers and regulators.
5. Should undergo appropriate **site selection** to ensure research is conducted in places where it can be performed to the highest scientific, clinical and ethical standards.
6. Should ensure that **participant selection** criteria limit and minimize risk.
7. Should have **expert review** by a specialized independent committee.

8. Must involve rigorous **informed consent.**

UK SPECIALIST RESEARCH ETHICS COMMITTEE

In mid-2020, the National Health Service (NHS) HRA formed a Specialist Ad-Hoc Research Ethics Committee (Specialist REC) to consider UK applications for ethics review of COVID-19 human challenge studies. The Specialist REC was formed of eighteen experienced members from existing RECs from a range of professional backgrounds and nationalities (twelve from England, three from Scotland, two from Wales and one from Northern Ireland). The committee included twelve expert members (people with relevant formal qualifications or professional experience that can help the REC understand particular aspects of research proposals) , three lay members (people who reflect the currency of public opinion and are not employed in health or care professions or whose primary professional interest is not health- or care-related research) and three lay "plus" members (lay people who are not and have never been i) health care professionals; ii) involved in the conduct of clinical research other than as a participant; or iii) a chairperson, member or director of a health service body or body which provides health care), with this balance of lay and expert members required by law under clinical trial regulations (8). The UK Specialist REC was recognised by UKECA (United Kingdom Ethics Committee Authority). The HRA provided this group of Specialist REC members with specific training, the development of which was informed by the WHO Key Criteria.

COVID-19 HUMAN CHALLENGE STUDIES

The UK was the first and remains the only country in the world to commence COVID-19 human challenge studies (9). The UK Specialist REC reviewed and approved "*A Dose Finding Human Experimental Infection Study in Health Subjects Using a GMP-produced SARS-CoV-2 Wild Type Strain*" (COHVIC), the first SARS-CoV-2 human challenge study. This study was led by researchers from Imperial College London in partnership with hVIVO (a contract research organization that specialises in human challenge studies) and funded by the Royal Free Hospital NHS Foundation Trust. COVHIC is a virus characterisation study. Using

controlled doses, the aim of the research team was to discover the smallest amount of virus that causes SARS-CoV-2 infection in ≥ 50% of those challenged. The study was conducted sequentially in small groups of healthy young people, aged between 18 and 30 years. Up to 90 volunteers were planned to be involved (10). This study was submitted to the Specialist REC as separate elements, including the screening process to select potential participants and the dose finding procedure. The screening process was reviewed in November 2020 when it received a Provisional Opinion. A favourable opinion was then given in December 2020. The dose finding procedure was reviewed in December 2020 when it received a Provisional Opinion, with a Favourable Opinion given in February 2021. Potential participants were already being screened for the study by February 2021. The first sentinel group was challenged in March 2021 and the last participant in the study discharged from quarantine in July 2021.

The Specialist REC has also subsequently reviewed and approved "*A Dose Finding Experimental Human Infection Study with SARS-CoV-2 in Healthy Volunteers with Previous, Microbiologically Confirmed SARS-CoV-2 Infection*" (COV-CHIM01), a dose-finding infection study led by researchers from the University of Oxford, funded by the Wellcome Trust. The aim of this study was to establish the lowest dose of the SARS-CoV-2 challenge strain which could cause infection in 50% ± 10% of people who have previously been naturally infected. This study will be conducted sequentially in small groups of healthy young people aged between 18 and 30 years who have previously been naturally infected with SARS-CoV-2 and will include up to 64 volunteers (11). The SARS-CoV-2 challenge strain and inclusion/ exclusion criteria (apart from prior SARS-CoV-2 infection) for both COHVIC and COV-CHIM01 were deliberately aligned across the studies to aid the generalizability of SARS-CoV-2 human challenge study findings.

JOINT HRA/WHO WORKSHOP

In July 2021 a workshop was convened between members of the WHO Working Group for Guidance on Human Challenge Studies in COVID-19, the HRA, the UK Specialist REC and COVID-19 human challenge study investigators. This workshop provided opportunities for feedback on the WHO Key Criteria and to reflect on the UK Specialist REC and researcher experience of the ethics review of the first COVID-19 human challenge studies.

UK SPECIALIST RESEARCH ETHICS COMMITTEE EXPERIENCE

Overall, the participants agreed that the WHO Key Criteria document is a valuable tool providing an ethical framework for the review of COVID-19 human challenge studies. In particular, lay members of the panel who were not previously familiar with human challenge studies found that having an international reference document available to navigate the complexities of ethics review for this scientific research approach was useful and reassuring. By contrast, some participants with previous experience with human challenge studies indicated that they were already comfortable reviewing COVID-19 human challenge studies and aware of the need to address requirements such as those enumerated in the WHO Key Criteria.

The HRA approach of creating the UK Specialist REC for COVID-19 Human Challenge Studies as a dedicated national committee for the assessment of COVID-19 human challenge studies to ensure rigorous and timely review is in accord with criterion seven of the WHO Key Criteria (7), which recommends the formation of specialized independent committees with high levels of expertise. In addition to individuals with relevant expertise, the UK Specialist REC also included a significant proportion of lay members. This composition ensured the committee had broad representation, including relevant experts as well as people from outside the healthcare sector who reflected the currency of public opinion. In addition, in order to reduce potential bias in favour of a human challenge model, the committee was purposively made up of some members who did not have human challenge study experience. This composition was selected to ensure the panel included members who would be open to critiquing the

human challenge model. In order to provide appropriate background on human challenge studies to members without human challenge study experience, the HRA developed a specific COVID-19 human challenge studies training module informed by the WHO Key Criteria. The UK Specialist REC members all acknowledged that this training was particularly valuable for both education and team-building in the early preparatory stages after the committee was established. Now that the UK Specialist REC and HRA training materials have been deployed, this committee will be able to rapidly review future COVID-19 human challenge studies and will contribute to enhanced local capacity for human challenge study review for future pandemic preparedness.

The Specialist REC had a number of important priorities that needed to be balanced during the assessment period, including training of committee members, rigorous ethics review of available information, and timely assessment to avoid undue delay in starting potentially beneficial research. To expedite the review of the study, the project was separated into discrete elements for assessment, including review of the screening procedure, dose finding procedure, and the protocols to evaluate drugs/vaccines.

The UK has a well-established regulatory system comprising over 60 coordinated committees and approximately 1000 trained members and a variety of expert committee members, researchers and regulators with significant experience in human challenge studies established over decades. Therefore, the generalizability of the UK's experience to other settings may be limited. However, given the urgency, risk, and uncertainty involved with undertaking the first-in-human COVID-19 human challenge study, a highly experienced and well-resourced setting was arguably the best environment for the initial COVID-19 human challenge studies. This setting aligns with the recommendations of criterion five in the WHO Key Criteria, which states that these studies should be situated where the research can be conducted to the highest scientific, clinical and ethical standards (7). As the only country in which COVID-19 human

challenge studies have been performed, insights from the UK Specialist REC experience will be valuable for RECs who may review similar studies in other settings in the future.

RESEARCHER EXPERIENCE

Overall, researchers observed that the WHO Key Criteria built confidence and provided reassurance regarding the potential international acceptability of COVID-19 human challenge studies. It also provided consensus guidelines regarding the key ethical elements to be addressed in the studies in preparation for ethics review. The researchers found that interactions with the UK Specialist REC provided a forum for debate and promoted confidence in the study design and protocols, in addition to providing robust ethics review.

The structure and facilitatory model of the UK research ethics committee reviews enabled timely review of initial submissions and amendments in the face of a rapidly changing scientific and public health landscape. By separating the review of the study into separate elements, including review of the participant screening procedure, dose finding procedure, and protocols to evaluate drugs/vaccines, there were multiple opportunities for meetings between researchers and the UK specialist REC, with three rounds of review undertaken for both the COHVIC and the COV-CHIM01 studies in total. These meetings provided additional opportunities for amendments to be presented and discussed and the risks and benefits of the studies to be reassessed as the scientific and public health settings of the pandemic evolved. This facilitatory structure represents a model of good practice for ethics review of certain novel, complex or sensitive study designs, particularly where the associated scientific and public health settings pertaining to the study are rapidly evolving.

In addition to the UK Specialist REC, the researchers' work was supported by a wide array of academics and experts via the pre-existing Human Infection Challenge for Vaccines (HIC-Vac) network (an international network of researchers who are developing human infection challenge studies to accelerate the development of vaccines, funded by the Medical Research

Council (UK)), the UK MHRA (Medicines and Healthcare products Regulatory Agency), the HRA and the UK government. This broad coordination between researchers, policymakers and regulators is consistent with criterion four of the WHO Key Criteria, which states that COVID-19 challenge study research programmes should involve close coordination between researchers, funders, policy-makers and regulators. This co-ordination of key stakeholders and research activities may arguably help to ensure that the potential public health benefits of the research are optimized (7). Researchers reflected that this broad national support provided rigorous review and oversight, although the involvement of such a large collaborative group had trade-offs with regard to the rate of progress of the studies and the ability to rapidly share important findings of the research with the wider international community. For example, the involvement of public health agencies in such work requires that considerations must be made regarding how to incorporate the communication of preliminary research findings into the wider public health strategy and health promotion messages.

Public engagement work performed by the researchers included extensive consultation with policymakers and experts, as well as broad community engagement comprised of online surveys and focus groups. This work demonstrated broad support of COVID-19 human challenge studies in the UK population. Importantly, a human challenge advocacy group, 1Day Sooner, built substantial popularity and drew significant public attention during the period in which this stakeholder engagement took place and may have contributed to the shaping of public opinion on COVID-19 human challenge studies. As outlined in criterion three of the WHO Key Criteria, public consultation and engagement should inform COVID-19 human challenge research programmes (7). These consultation and engagement strategies need to be designed to target lay people as well as relevant experts including researchers, academics and policymakers. Multilevel communication strategies co-ordinated with specific public engagement activities are arguably key to the acceptability of COVID-19 human challenge studies. These activities would ideally involve experienced social scientists and be independent of the human challenge study research team. The independence of these

activities would remove the potential for perceived conflict of interest and bias when such activities are undertaken by the human challenge research team. Many of these activities could be undertaken in advance to ensure preparedness for future pandemics. However, these preparatory activities should be supplemented by consultations seeking public views on specific proposed research plans and should be regularly updated in light of emerging data.

PREPARING FOR THE FUTURE

Over the past 18 months, there have been significant changes relevant to the design, review and conduct of COVID-19 human challenge studies. The rapid improvement in knowledge about SARS-CoV-2 and interventions against it, as well as the evolution of the virus over time, has required researchers, regulators and policymakers to re-evaluate the scientific justification of COVID-19 human challenge studies on a regular basis. These developments have included the approval and rapid distribution of highly efficacious vaccines (6); the emergence of virus variants of concern (12, 13); the development of therapeutic agents (14); and the potential post-acute health impacts of COVID-19 (9, 15, 16). Amidst multiple developments in the COVID-19 pandemic, dynamic reassessment of whether the potential benefits of SARS-CoV-2 human challenge studies continue to outweigh risk is required.

Despite the availability of vaccines, COVID-19 human challenge studies still have potential scientific value, for example related to i) the assessment of new vaccines; ii) assessment of new therapeutics; iii) assessment of viral transmission; iv) detailed characterization of immune responses and correlates of protection; and v) assessment of the durability of post-infection and vaccine-induced immunity (9, 17). These rationales have recently been reviewed in detail by Rapeport et al and Nguyen et al (8, 15). Importantly, COVID-19 controlled human infection studies have distinct advantages over field studies for the detailed characterization of virological and immune responses to SARS-CoV-2, which will inform key scientific, clinical and public health questions (18). Compared to field studies, human challenge studies provide a level of control that is impossible to achieve in the field. Factors that can be carefully controlled

in human challenges studies include i) the infectious virus strain, dose and exposure; ii) participant characteristics; and iii) intensive biological sampling during all phases of infection. Of particular importance for next-generation vaccine development will be the identification of an *in vitro* immunological correlate of protection, which can be facilitated by the detailed characterization of immune responses that can be elucidated in this carefully controlled setting. Determining an immune marker that serves as a correlate of protection would potentially allow the likely efficacy of vaccines to be assessed by measuring the proportion of participants who develop this immune response, rather than measuring clinical efficacy through large, costly and time-consuming field trials. As a result, COVID-19 human challenge studies could potentially accelerate the development of next-generation COVID-19 vaccines, facilitate the optimisation of future vaccination schedules and assist with preparation for future vaccine challenges in a number of ways.

COVID-19 human challenge studies could also provide a platform for future vaccine candidates to be directly and rapidly compared to licensed vaccines, rather than undergoing large-scale comparative field studies. It is important to note that comparative field studies are rarely performed. Because vaccines are usually made by different companies, comparative field studies entail significant commercial risk and are therefore not a priority of commercial companies. While the expense involved in conducting large field studies is prohibitive to most independent researchers. It is also difficult to compare efficacy between field trials conducted by different investigators due to differences in trial design, population, public health settings and timing of the studies. Although COVID-19 human challenge studies offer a potential method to directly compare these vaccines, a significant potential barrier to this work would be the feasibility of accessing a healthy, unvaccinated population to recruit for these studies in the UK. It is expected that studies that aim to recruit a vaccine-naïve population would require additional community engagement and consultation work to be performed and significant revision of the current recruitment strategies.

COVID-19 human challenge studies could enable optimization of future vaccination strategies through the i) assessment of the durability of protection by challenging participants at pre-defined timepoints after natural infection or vaccination to inform the use and optimal timing for booster vaccine doses; ii) to compare novel vaccination schedules, such as heterologous vaccine combinations; and iii) assessing the incremental benefits of new vaccines compared to a baseline of previous vaccination/immunity. Finally, COVID-19 human challenge studies could be used to study vaccine efficacy against circulating SARS-CoV-2 variants of concern using challenge strains made using these variants (8, 15). Importantly, it must be acknowledged that there would be inevitable delays to commencing COVID-19 human challenge studies with novel variants of concern due to the lead time required to select and prepare the variant challenge strain according to regulatory standards for safe human administration. Despite these delays, understanding of vaccine breakthrough infection of one variant may be generalizable to other variants with similar viral mutations. Work is currently in progress on the first SARS-CoV-2 variant challenge strain. Imperial College London, funded by the Wellcome Trust has developed a SARS-CoV-2 delta variant human challenge strain that is likely to be ready for use by January 2022. Addressing these vaccine-related research questions are key priorities in mitigating the ongoing health, social and economic impacts of COVID-19 around the world.

Scientific progress has also enabled researchers to further mitigate risk to potential participants by utilizing real-time data of clinical outcomes in the proposed participant population (i.e. previously healthy young adults naturally infected in the UK) in risk assessments via the QCovid algorithm (19, 20). Such quantitative assessments can inform participant screening (to estimate individual absolute risk for hospitalization or death) and, if required, therapeutic interventions to reduce the likelihood of progression of disease in patients with COVID-19 (e.g. monoclonal antibodies (21, 22), corticosteroids (23, 24), non-steroidal immunomodulatory agents such as tocilizumab and baricitinib (25-28) and specific antivirals such as molnupiravir (29, 30)). Some REC members with prior experience in human

challenge studies reflected that malaria human challenge studies could be perceived as higher potential risk to participants than COVID-19 human challenge studies in the planned study population of healthy young adults. It is inevitable that SARS-CoV-2 will continue to evolve, as will the scientific understanding of individual and public health impacts of COVID-19, including preventative and therapeutic interventions. Human challenge studies will require regular reassessment and, in some cases, redesign to ensure that they continue to meet the rigorous ethical standards demanded of research involving healthy volunteers.

Future steps may include the development of COVID-19 human challenge studies in additional settings. In preparing for future ethics review of COVID-19 human challenge studies internationally, the workshop members identified several ways that the WHO Key Criteria could be adapted to improve implementation and engagement. In particular, the requirements outlined by the WHO Key Criteria could be made more accessible to a wider audience by i) translating the document into further languages; ii) producing associated documents to target specific audience (e.g. lay people, media and policy-makers); and iii) the addition of implementation materials (e.g. case studies) for multiple stakeholders (including research ethics committee members and researchers) as annexes. Initial training in the review of COVID-19 human challenge studies was identified as a valuable part of preparation for the UK Specialist REC. The addition of case studies to the WHO Key Criteria informed by the UK Specialist REC experiences would help provide material for this training and will provide examples for appropriate local or national resources to be created by groups in other countries preparing to review COVID-19 human challenge studies.

CONCLUSION

There has been explosion of scientific discovery related to COVID-19, with human challenge studies a potentially valuable component of ongoing research to improve our understanding of this important infectious disease. This workshop provided an opportunity to assess the performance of the WHO Key Criteria in practice and learn from the experience of the UK

Specialist REC that reviewed the first COVID-19 human challenge studies, along with COVID-19 human challenge researchers. Overall, the experience of workshop members suggested that the WHO Key Criteria was useful in a real-world setting by supporting researchers and ethics reviewers, including in the training of ethics committee members. There was broad consensus that the WHO Key Criteria represented an international consensus document that played a powerful role in setting norms and delineating the necessary criteria to be considered for the ethical acceptability of a COVID-19 human challenge study. Importantly, given the rapid pace of scientific discovery related to COVID-19 and the continuous evolution of SARS-CoV-2, the scientific rationale for COVID-19 human challenge studies will require regular reassessment to ensure that conducting research involving the intentional exposure of healthy volunteers to SARS-CoV-2 remains justified.

The ethics review structure implemented by the UK HRA for the review of the first COVID-19 Human Challenge Studies represented a model of good practice for ethics review of novel, complex and sensitive study designs. The two key elements of this structure included i) the formation of the Ad-Hoc Specialist REC for COVID-19 Human Challenge Studies, comprised of a specifically selected panel with broad and unbiased representation that was provided with specialized COVID-19 human challenge study training; and ii) a facilitatory review structure with studies separated into discrete elements, reviewed over multiple sessions, that both expedited the review and delivery of the study and accommodated the dynamic responses required in the context of the rapidly evolving scientific and public health landscape.

In future, a wider audience may be engaged by the original WHO Key Criteria document through supplementation with additional materials and ancillary documents, informed by the UK Specialist REC experience. The availability of international guidance as well as capacity building based on the UK experience may help to promote public confidence in this important type of research in other settings.

DECLARATIONS

All authors attest they meet the ICMJE criteria for authorship.

The authors declare no conflicts of interest.

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