WHO GUIDANCE ON THE ETHICAL CONDUCT OF CONTROLLED HUMAN INFECTION STUDIES
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Alleviating the impact of infectious diseases on human health remains a key global health priority. In controlled human infection studies (CHIS), healthy volunteers are intentionally exposed to pathogens in a controlled environment, in order to promote understanding of the pathogenesis, transmission, prevention and treatment of infectious diseases in humans. Such studies may be conducted to gain insights into how pathogens infect human hosts and cause disease, to better understand immune responses to infection, or to evaluate the efficacy of vaccines and drugs designed to prevent and treat infectious diseases. CHIS have a long history and have made important contributions to the treatment and prevention of many infectious diseases of global health importance.

Although recognition of the potential value of CHIS is leading to such studies increasingly being conducted in a wider range of contexts, they remain a relatively unfamiliar research method. This guidance has been developed in response to requests to the World Health Organization (WHO) for guidance on ethical questions associated with CHIS, especially in the context of growing interest in conducting CHIS in endemic settings.

The concept of conducting research in which healthy volunteers are intentionally exposed to pathogens which can cause infection, and in some cases disease, can appear ethically counter-intuitive – particularly when natural infections with such pathogens can lead to severe adverse outcomes, including death. This was clearly evidenced during 2020, when CHIS received unprecedented public and social media attention following proposals to conduct CHIS to accelerate COVID-19 vaccine development pathways. Recent debates about the ethical acceptability of COVID-19 CHIS illustrate the diversity of stakeholder views: social acceptance of CHIS is influenced by a complex global landscape in which there are different levels of confidence in health-related research. This underscores the importance of carefully considering the consultative and trust-building approaches needed to inform CHIS research proposals. Consultation and engagement activities with the public, regulators and ethics review boards have been recognized as particularly important when CHIS involve factors such as novel models of infection, populations in which such research may be unfamiliar, higher levels of risk and/or burdens, risks to third parties, and/or outbreaks of novel pathogens, among others. Engagement and associated social science research have played an important role in settings where CHIS are unfamiliar and can play a key role in the development and conduct of research programmes seeking to address local health priorities and incorporating CHIS.

This guidance aims to inform well-considered and contextualized decisions about the ethical acceptability of proposed CHIS, including priorities for engagement and social science research to support deliberation and practice, and requirements for oversight and governance. When addressing ethical issues that should be considered during the planning, design, conduct and governance of CHIS, this guidance takes the position that CHIS are not, in themselves, an exceptional and morally distinct form of research, but instead fall within the continuum of health-related research conducted with human participants. As such, this guidance should be read in conjunction with relevant national and international ethics guidance and regulations for health-related research in humans.

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When applying this guidance, stakeholders involved in CHIS are encouraged to develop approaches that take into account their own local social, cultural, and political contexts. WHO is committed to providing countries with regulatory considerations in support of these efforts.

In addition to the guidance itself, included in the annexes are essential information on consent (Annex 1), a checklist for ethics committees (Annex 2) and eight case studies (Annexes 4 to 11), all designed to further assist with the implementation of this guidance.

Furthermore, during the development of this guidance, discussions began around the possibility of conducting CHIS in the context of COVID-19. As such, and building on the expertise and knowledge gained from this work, WHO formed a working group to produce guidance on the key criteria for the ethical acceptability of COVID-19 human challenge studies, which can be found in Annex 3. Lastly, Annexes 12 and 13 contain scoping reviews of engagement studies and social science studies on CHIS.
This guidance document was developed under the direction and coordination of Katherine Littler (Co-Lead of the Health Ethics and Governance Unit in the WHO Department of Research for Health), under the overall guidance of John Reeder (Director, the Department of Research for Health) and Soumya Swaminathan (Chief Scientist).

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>BCG</td>
<td>bacillus Calmette-Guérin</td>
</tr>
<tr>
<td>CHIS</td>
<td>controlled human infection studies</td>
</tr>
<tr>
<td>CHIVIM</td>
<td>controlled human influenza virus infection model</td>
</tr>
<tr>
<td>COVID-19</td>
<td>coronavirus disease</td>
</tr>
<tr>
<td>CZS</td>
<td>congenital Zika syndrome</td>
</tr>
<tr>
<td>FGD</td>
<td>focus group discussion</td>
</tr>
<tr>
<td>HAI</td>
<td>hemagglutinin inhibition</td>
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<tr>
<td>HIC</td>
<td>high-income countries</td>
</tr>
<tr>
<td>IDI</td>
<td>in-depth discussion</td>
</tr>
<tr>
<td>LMIC</td>
<td>low- and middle-income countries</td>
</tr>
<tr>
<td>NAI</td>
<td>neuraminidase inhibition</td>
</tr>
<tr>
<td>REC</td>
<td>research ethics committee</td>
</tr>
<tr>
<td>SARS-CoV-2</td>
<td>severe acute respiratory syndrome coronavirus 2</td>
</tr>
<tr>
<td>TB</td>
<td>tuberculosis</td>
</tr>
<tr>
<td>the USA</td>
<td>The United States of America</td>
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</table>
1. INTRODUCTION

In this guidance, the term ‘controlled human infection studies’ (CHIS) is used to encompass a subcategory of clinical research – also known as human challenge trials and voluntary infection studies – that seeks to answer specific questions regarding the mechanisms and treatment or prevention of infectious disease in humans. The boundaries between CHIS and other forms of biomedical research, such as Phase I trials of live-attenuated vaccines, may not always be clear. For the purposes of this guidance, CHIS are defined as:

Studies that involve the deliberate exposure of research participants to infectious agents for the primary purposes of:

a. developing models of infection or disease – that is, rigorous and reproducible methods of infecting participants with specific microorganisms and/or
b. generating knowledge about host-pathogen interactions (including pathogenesis and correlates of infection, transmission and immunity) and/or
c. testing (novel) vaccines and therapeutics and the exposure takes place in a controlled manner in which:
   a. the microorganism strain(s), and the timing, route, and/or dose of the infectious agent are known, and
   b. the risks and burdens associated with a resulting infection are often (relatively) minor, monitored, managed and minimized.

1. This definition focuses on deliberate exposure to infection, rather than deliberate infection. This is because, although all CHIS involve exposure to an infectious agent, in some studies such exposure will not always result in an infection.
1.1 DISTINCTIONS BETWEEN HISTORICAL DELIBERATE INFECTION STUDIES AND CHIS

Research in which participants are deliberately exposed to infection has a problematic history. A number of well-documented early examples of deliberate infection studies would be considered ethically unacceptable today, on multiple grounds (1–3). For example, the World War II research programmes of Germany and Japan incorporated the deliberate infection of thousands of subjects with pathogens, including anthrax, chlamydia, plague, tetanus and tuberculosis (4–5). Additional examples include the deliberate infection of vulnerable groups with bacteria causing syphilis and gonorrhoea in Guatemala during 1946–8, the deliberate infection of intellectually disabled children with hepatitis in the United States during the 1950s–1970s (6–7). Criticisms of such studies are not focused solely on the deliberate infection per se, but encompass multiple aspects of research design and conduct. These include unacceptably high levels of risk and harm, inadequate consent or lack of consent, inadequate infection control, recruitment of populations with heightened vulnerabilities without appropriate justification or protections, and the conduct of research with limited scientific validity.

In contrast, CHIS conducted in recent decades have been conducted in compliance with international norms of ethical research and enrolled tens of thousands of healthy volunteers with very few reported serious or lasting harms (2). Such research has been conducted with over 30 pathogens, using a range of infection models and research designs. These CHIS have provided unique insights into host-pathogen interactions, and accelerated development of beneficial interventions for a range of pathogens. For example, CHIS have played a key role in the development of recently approved and/or licensed vaccines for infectious diseases including typhoid (8), cholera (9), and malaria (10). Some examples of the wide range of pathogens and disease states that have been addressed in modern CHIS are listed in Table 1.
1. INTRODUCTION

### TABLE 1. Examples of pathogens and diseases addressed in modern CHIS (2, 11-13).

<table>
<thead>
<tr>
<th>Pathogens</th>
<th>Relevant disease states*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adenovirus, Human coronavirus 229E, Parainfluenza viruses, Rhinovirus</strong></td>
<td>Common cold</td>
</tr>
<tr>
<td>BCG (bacille Calmette–Guérin, a tuberculosis vaccine strain)</td>
<td>Tuberculosis</td>
</tr>
<tr>
<td>Campylobacter jejuni, Giardia lamblia, Rotavirus</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td>Candida albicans</td>
<td>Thrush</td>
</tr>
<tr>
<td>Chlamydia spp.</td>
<td>Pelvic inflammatory disease</td>
</tr>
<tr>
<td>Cryptosporidium spp.</td>
<td>Cryptosporidiosis</td>
</tr>
<tr>
<td>Cyclospora cayetanensis</td>
<td>Cyclosporiasis</td>
</tr>
<tr>
<td>Dengue virus</td>
<td>Dengue</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>Urinary tract infection</td>
</tr>
<tr>
<td>Francisella tularensis</td>
<td>Tularaemia</td>
</tr>
<tr>
<td>Haemophilus ducreyi</td>
<td>Chancroid</td>
</tr>
<tr>
<td>Helicobacter pylori</td>
<td>Peptic ulcer, gastric cancer</td>
</tr>
<tr>
<td>Influenza virus</td>
<td>Influenza</td>
</tr>
<tr>
<td>Lactobacillus spp.</td>
<td>N/A</td>
</tr>
<tr>
<td>Leishmania spp.</td>
<td>Leishmaniasis</td>
</tr>
<tr>
<td>Listeria spp.</td>
<td>Listeriosis</td>
</tr>
<tr>
<td>Necator americanus</td>
<td>Hookworm disease</td>
</tr>
<tr>
<td>Neisseria gonorrhoeae</td>
<td>Gonorrhoea</td>
</tr>
<tr>
<td>Neisseria lactamica</td>
<td>n/a</td>
</tr>
<tr>
<td>Norovirus</td>
<td>Viral diarrhoea</td>
</tr>
<tr>
<td>Parvovirus B19</td>
<td>Slapped cheek disease</td>
</tr>
<tr>
<td>Plasmodium falciparum, Plasmodium vivax</td>
<td>Malaria</td>
</tr>
<tr>
<td>Pneumococcus (Streptococcus pneumoniae)</td>
<td>Bacterial pneumonia, meningitis</td>
</tr>
<tr>
<td>Respiratory syncytial virus</td>
<td>Bronchiolitis, viral pneumonia</td>
</tr>
<tr>
<td>Salmonella paratyphi, Salmonella typhi</td>
<td>Typhoid fever</td>
</tr>
<tr>
<td>Sarcoptes scabiei</td>
<td>Scabies</td>
</tr>
<tr>
<td>Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)</td>
<td>Coronavirus disease 2019</td>
</tr>
<tr>
<td>Schistosoma mansoni</td>
<td>Schistosomiasis</td>
</tr>
<tr>
<td>Shigella spp.</td>
<td>Dysentery</td>
</tr>
<tr>
<td>Streptococci (non-pneumococcal)</td>
<td>Strep throat, rheumatic heart disease</td>
</tr>
<tr>
<td>Strongyloides spp.</td>
<td>Strongyloidiasis</td>
</tr>
<tr>
<td>Vibrio cholera</td>
<td>Cholera</td>
</tr>
</tbody>
</table>

*Note that some pathogens listed do not cause the disease state(s) listed, and/or the CHIS are designed so that the particular disease states do not occur among participants. However, the models with these infectious agents are intended to inform research aims related to the associated disease states.
Ethics as a discipline is concerned with questions about how individuals and institutions ought to act and the moral arguments in favour of and against alternative courses of action. All health-related research has an ethical dimension, and a number of international guidelines seek to provide universal ethical frameworks for evaluating the ethics of research (14, 15). The foremost consideration in such guidance is recognition of both the importance of conducting health-related research to generate knowledge and interventions to promote human health, and the need to ensure that the rights and interests of research participants are respected and protected.

In recent decades CHIS have been conducted in compliance with international norms of ethical research and have made important contributions to the treatment and prevention of many infectious diseases of global health importance. They have provided insights into how pathogens infect human hosts and cause disease, immune responses to infection, and the efficacy of vaccines and drugs. However, the concept of conducting research in which healthy volunteers are intentionally exposed to pathogens which can cause infection, and in some cases disease, can appear ethically counter-intuitive. Concerns have also arisen about whether the risks of exposure to specific infectious agents can be kept within ethically acceptable limits, particularly when natural infections with related pathogens can lead to severe adverse outcomes, including death (16). Such concerns may be compounded by historical examples of research involving deliberate infection which are widely cited as paradigmatic cases of unethical research (see section 1.1 above). In the context of such considerations, questions have arisen about whether CHIS should be considered to be morally distinct from other forms of research with healthy volunteers, and whether and how they can be ethically justified.

Clinical research with healthy volunteers, including first-in-human studies of novel pharmacological agents, and clinical trials of vaccines, may be associated with risks that the interventions being studied cause harm. This guidance takes the position that there are no morally compelling grounds for distinguishing between the types of risks and burdens in such clinical research and in CHIS designs. CHIS are therefore not, in themselves, a morally distinct form of research but instead fall within the continuum of health-related research conducted with human participants governed by relevant national and international ethics guidance and regulations. All such research can only be conducted when it satisfies research ethics standards, including those requiring that the potential risks and burdens of research are systematically identified, evaluated, minimized, and considered reasonable and justified in terms of the social and scientific value of the research.

This guidance addresses ethical considerations in CHIS in order to guide researchers, ethics committee members, regulators, funders and policymakers in their deliberations during the design, conduct and governance of CHIS. The ethical issues addressed are not unique to CHIS, but are particularly important to address and evaluate in decision-making processes relating to them. These include: issues associated with the selection of infectious agents and the design of models of infection and disease; potential justifications for conducting research involving deliberate exposure to infectious agents; potential risks of such research to participants and bystanders; and the obligations and responsibilities of researchers and decision-makers to ensure that such risks are effectively managed and minimized.
2.1 CORE VALUES

In addressing ethical issues that are particularly salient in the context of CHIS, this guidance draws on core values and principles that inform international norms and consensus standards of research ethics. One such core value is **respect for persons**, including the obligation to respect and protect the dignity, interests, agency, and human rights of research participants. Respect for persons highlights, for example, the importance of appropriate processes for recruitment, consent and compensation, and of avoiding undue constraints on participants’ freedom of movement.

A second core value centres on **minimization of suffering and the promotion of human health**; this forms the foundation for approaches to evaluating justifications for conducting CHIS, and the obligations and responsibilities that arise when such research is conducted.

Values relating to **social justice** and **global health justice** highlight the importance of fairness in the distribution of resources, opportunities and benefits and burdens of research. In terms of setting research priorities and facilitating research, they emphasize the need to conduct research to address the needs of populations experiencing greater burdens of infectious disease, and to implement fair research processes, including the sharing of research skills, resources and capacities. They also promote protection from potential harms of research and commitments to fair sharing of benefits.

Multiple ethical values are relevant to most of the issues discussed in this guidance. At times these point in differing directions, giving rise to tensions, which require careful deliberation and review. Important values in deliberations and decision-making about CHIS include **transparency, honesty, accountability** and **inclusivity**, highlighting the role of public engagement, participatory processes and social science research. **Equal respect** for persons entails a commitment to being sensitive and appropriately responsive to differing values, perspectives and concerns relating to CHIS. Consultation processes are particularly important where there may be heightened concerns about CHIS, for example due to the novelty of the model of infection or research setting, or because the study design is associated with higher levels of risk and/or burdens, or risks to third parties.

Finally, values relating to **responsible stewardship** of science and of research resources highlight the importance of ensuring appropriate governance frameworks and processes are in place to review, regulate and oversee CHIS, and ensure they are conducted ethically. Such stewardship also entails commitments to use finite research resources and the contributions of research participants responsibly.
To be ethically justifiable, all healthcare-related research with human participants must have appropriate scientific and social value. Recent CHIS have made considerable contributions to understanding of infectious diseases and to the development of effective vaccinations and treatments. CHIS have the capacity to address important research questions about pathogens capable of infecting humans, that are unfeasible, impractical or less expedient to address using other clinical research methods (see Box 1. Why might CHIS be proposed?). These include, for example, unique insights into asymptomatic host-pathogen interactions, particularly around the time of infection, and rapid preliminary evidence about the efficacy of potential vaccine candidates (see Box 2. Potential scientific and social value).

Box 1. Why might CHIS be proposed?

Researchers may propose to conduct CHIS for a range of reasons, including those listed below. The justifications for conducting CHIS, in terms of their expected scientific and social value, always require careful consideration and review on a case-by-case basis.

1. In some cases, CHIS may offer the **only feasible way** to address specific research questions, including questions about:
   - Mechanisms of early stages of infection and immune response (including prior to the development of symptoms of disease) (17,18)
   - The efficacy of interventions for diseases which currently have insufficient incidence levels and/or erratic outbreak patterns which limit the capacity to conduct Phase III vaccine trials (see Annex 9. Zika case study)
   - Diseases for which there are no alternative appropriate models available, such as non-human animal models (see Annex 8. Typhoid case study).

2. A CHIS is **a robust and rigorous way** to address a research question, for example:
   - Measurements of markers of infection or immunity may need to be validated against a well characterized model of infection (19,20).

3. A CHIS is the **most expedient way** to address a research question, for example:
   - Findings from CHIS may inform preliminary triage of vaccine candidates, accelerating the development of those likely to be the most effective (21) (see Annex 10. Malaria case study).

4. A CHIS is the **most cost-effective** way to address the research question:
   - A CHIS may enrol fewer participants and provide results within a shorter period of time than alternative research designs (9).

5. A CHIS is **a critical component** of a product development pathway:
   - CHIS alone are typically insufficient to demonstrate effectiveness of a novel intervention, but can provide pivotal evidence to support evaluations of efficacy in conjunction with other forms of research, such as field trials (9, 22).
As outlined in Box 1, CHIS may be conducted to address a wide range of research aims, from the development of models of infection, to the testing of novel interventions to address disease. In evaluating justifications for CHIS, it is important to recognize that, as with Phase I and II clinical trials, the results of research conducted with healthy volunteers from populations at low risk from the infection under study may sometimes have limited generalizability to populations where the infection is a major health problem. The generalizability of CHIS findings to wild-type infections may also be limited when CHIS employ specific, well-characterized infection strains, which have been selected to enable effective risk management and/or to enable specific research questions to be addressed as discussed below (see section 4. Research Design). Consequently, as in all healthcare-related research, assessments of the social and scientific value of CHIS should not focus solely on the generalizability of findings but also on the value of context-specific results.

In evaluations of the social value of research, the potential of research findings to directly inform approaches to addressing population health needs, such as by accelerating vaccine development, is a key consideration. In practice, CHIS may propose to address a broad range of research questions as part of a research programme, some of which, such as those focusing on understanding infection and immunity, may not have immediate implications for public health. During evaluations of the justifications for conducting CHIS it may be important to consider the social and scientific value of proposed CHIS not within the context of an isolated study, but in conjunction with its anticipated role in a programme of research, such as a product development pathway or informing a disease control strategy (see section 11.4, Product development and licensure).

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**Box 2. Potential scientific and social value**

Scientific value refers to the merits of a study in terms of generating reliable information in response to an unresolved research question, which can then inform further research or approaches to addressing health needs. The social value of research is assessed by considering the importance of the research question being addressed and the anticipated value, to society, of the information that the study will produce. CHIS can be associated with scientific and social value in many ways including:

1. **Enabling future research by developing models of infection:**
   - with rigorous and reproducible methods of infecting participants with specific strains of pathogens or other microorganisms
   - with relevant and generalizable endpoints of infection or disease
   - which meet appropriate quality control, safety and regulatory standards (23).

2. **Promoting understanding of immunology, pathogenesis and transmission in host-pathogen interactions including,**
   - investigating risks of transmission posed by infected individuals (24)
   - providing insights into microbial interactions in the human microbiome, including regarding the carriage of potential pathogens (25)
   - determining correlates of protection – that is, the types of immune responses a vaccine needs to elicit in order to protect against disease (26).

3. **Informing product development pathways including:**
   - the prioritization and de-prioritization of vaccine candidates for further study (27)
   - the design, testing and evaluation of novel interventions (28)
   - accelerating the research pathway required to inform the licensing of a new intervention (28)
   - comparing vaccine performance in endemic and non-endemic settings, including the impact of pre-existing levels of immunity (see Annex 10. Malaria case study).
Multiple aspects of CHIS research design influence the ethical acceptability of such studies. CHIS researchers select the infectious agent that participants will be exposed to (rather than studying a naturally acquired infection). CHIS designs are responsive to specific research questions, and range from studies of the carriage of microbes and immune responses in subclinical infection, through to the efficacy of therapeutic interventions for clinical disease. CHIS have used a range of microorganism strains, including those with a similarity to wild-type pathogens causing infections in the general community, and those which have been selected, adapted, attenuated and/or genetically modified to have specific characteristics such as lower levels of virulence, and/or greater susceptibility to curative treatments (see Box 3. Strain selection). Models of infection may also need to be appropriately responsive to population characteristics, including for example, prior exposure, co-infections and gut microbiomes. For example, CHIS in high-income countries (HICs) and low- and middle-income countries (LMICs) may use the same strains but differing dosing schedules and endpoints in response to host factors (see Annex 10. Malaria case study). In CHIS research, the rationale for choosing a specific model of infection must be clearly explained and justified.

4.1 DIAGNOSIS AND TREATMENT

During the design of CHIS, researchers may need to address potentially competing considerations relating to reducing risks, minimizing burdens and generating important scientific information. Research ethics guidance about minimizing potential risks and burdens of research gives rise to a presumption of early diagnosis and treatment of infection and disease where feasible. At times, CHIS researchers may propose to delay treatment and allow an infection to develop into disease, in order to enable additional sample and data collection to better answer a specific research question. In situations where researchers propose not to undertake the best or most rapid approach to diagnosis, and/or provide the best treatment as early as possible, a clear justification of any additional risks and burdens is required to inform evaluations of their acceptability.

The risks of serious and irreversible harm associated with some infections are such that treatment should generally be provided as soon as participants test positive and any proposals to delay treatment beyond this point require detailed justification and rigorous review. Proposed strategies for risk management and minimization should be especially carefully evaluated when there is greater uncertainty associated with the diagnosis of early infection (for example, due to the sensitivity of standard diagnostic methods), when diagnosis may be delayed in CHIS conducted on an outpatient basis, or when the best diagnostic methods are not available within the research context (for example, due to local laboratory constraints or clinical guidelines).

Approaches to treating induced infections should be evaluated within research ethics guidance addressing appropriate standards of care in research. It is important to consider obligations to provide the highest standard of diagnosis, supportive and curative care in the context of deliberate infection, and to justify how such obligations have been met in proposed CHIS. Where possible, approaches should draw on validated guidance for the treatment and management of the infection. Generally, it would be expected that the standards of care in CHIS are likely to be higher than those routinely available within local health systems.

Research designs in which participants are restricted to a specific location (such as a hospital ward, research clinic or hotel room) are commonly perceived to be more burdensome for participants than outpatient designs. Such designs may, however, be required in CHIS in order to enable risks and burdens to be appropriately managed and minimized. Specific characteristics which may prompt residential designs include the frequency of sample and data collection, the need to monitor participants’ symptoms to aid diagnosis and ensure timely and ef-
fective treatment, and the need to minimize risks of uncontrolled transmission to third parties. Close monitoring is also particularly important in CHIS associated with higher levels of uncertainty about clinical risk, such as when novel infection models are being tested, or when established models are used in novel contexts where participants may have differing contexts where participants may have differing immune responses to the model of infection.

4.2 INFECTION CONTROL

During the design and conduct of CHIS, careful consideration must be given to how any risks of unintended transmission will be managed and minimized, taking account of the microorganism being studied, the research population, and the local context – including local capacities for infection control (see section 5.1.2 Third-party and environmental risks and impacts and 6.1 Site selection). Residential CHIS designs may be proposed to enable effective infection control measures. Requirements to minimize risks of transmission to third parties may also influence inclusion criteria, for example, depending on the infectious agent under study, healthcare workers, food handlers, and people living with family members who may be particularly vulnerable to infection, may need to be excluded from specific CHIS. Specific attention must also be paid to the measures that research participants need to commit to (such as restrictions on travel), in order to minimize transmission risks, and to ensuring that these are explained clearly, and agreed to, during enrolment. Where relevant, participants' abilities to comply, and likelihood of complying, with infection control measures, should also be carefully considered and, where appropriate, monitored.

Box 3. Strain selection

The choice of microorganism strains to be used in CHIS is affected by multiple considerations, including availability, compliance with regulatory or manufacturing requirements, risk-burden profiles, strain characterization, associated disease/infection clinical characteristics, relevance to the interventions being tested, similarity to wild-type infection, and/or relevance to populations in the study setting. In tuberculosis (TB) CHIS, for example, the risks associated with a wild-type strain of TB would be unacceptably high. Instead, a current TB vaccine (bacillus Calmette-Guérin – BCG is used as the model of infection (see Annex 7. Tuberculosis case study).

It may also be necessary to use strains which are known to be susceptible to curative treatments in order to ensure the risks of research are appropriately managed and minimized (see Annex 10. Malaria case study). Researchers may also seek to select more or less virulent strains of a specific pathogen to replicate the symptoms and clinical profile of the infection under study (19). Some CHIS in vaccine development pathways may need to match the characteristics of the microorganism strain to those of the vaccine being tested, and in some cases the relevant microorganism strains of potential value in CHIS are produced as a by-product of vaccine manufacturing processes. For other diseases, well-established and validated laboratory strains of a pathogen differ from currently circulating wildtype strains but may nonetheless have the capacity to provide valuable insights into addressing the burdens of disease associated with current strains (see case studies in Annexes 4, 8 and 10).
4.3 WITHDRAWAL

Research ethics guidelines generally recognize participants’ rights to withdraw from research at any time, and for any reason (and without the need to provide a reason). In CHIS, as in some other infectious disease research addressing pathogens subject to public health measures, careful consideration is needed of how withdrawals may need to be managed to limit risks to participants, and risks of unintended transmission to third parties. In some CHIS, participants may be able to withdraw from research procedures and data collection, but researchers may be required to report the withdrawal of infectious patients, and local public health regulations may require them to take part in ongoing monitoring, treatment or infection control measures. These measures may be administered by researchers or public health agencies, and in some circumstances may include confinement in a clinical facility or isolation at their place of residence. Proposals to implement such measures and the capacities to enforce them must be evaluated and agreed with public health authorities and other relevant stakeholders during research design. The conditions justifying such requirements and means of minimizing associated burdens require careful consideration and justification, alongside proposed approaches for explaining them to participants during recruitment processes. CHIS participants should be made aware of and agree to such procedures as a condition of participation in a CHIS (see section 7.2 Understanding infection control and risks of transmission).
5. RISKS, BURDENS AND BENEFITS

CHIS are associated with a range of benefits, burdens and risks which require rigorous, holistic and systematic evaluation with reference to current guidance and consensus standards. As with all forms of healthcare research, in CHIS the anticipated burdens and risks of physical, psychological or social harms must be justified in terms of the scientific and social value of the research, within acceptable thresholds, and effectively managed and minimized (see section 3. Justification). In addition to consultation with relevant experts, engagement with communities and potential participants may play a valuable role in identifying and minimizing risks (see section 9. Engagement and 12. Social science research).

5.1 RISKS

Potential research risks must be assessed both individually and collectively to evaluate their acceptability (see Table 2). Risk assessments in CHIS must incorporate the capacity to effectively evaluate specific risks associated with the use of infection models which may arise both during and after research, in addition to proposed approaches to risk management and minimization. In CHIS conducted in epidemic or endemic settings, evaluations of the acceptability of risks to participants and third parties may be informed by comparisons to background risks of infection (that is, participants facing higher background risks of infection may face less marginal risk from being infected during CHIS). However, as with other forms of research, comparisons to background risks cannot justify participants being exposed to unacceptably high absolute research risks, nor limit researchers' responsibilities to minimize research risks (14,16).

TABLE 2. Potential risks of CHIS

<table>
<thead>
<tr>
<th><strong>Risks to participants:</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Risks of exposure to challenge agent (such as developing the disease being studied).</td>
<td></td>
</tr>
<tr>
<td>Risks associated with experimental vaccines / treatments being evaluated in CHIS (such as adverse reactions or vaccine enhanced disease).</td>
<td></td>
</tr>
<tr>
<td>Risks associated with study procedures (such as frequent blood draws or more invasive procedures such as bronchoscopy or lumbar puncture).</td>
<td></td>
</tr>
<tr>
<td>Risks associated with treatment of the challenge infection (such as the use of antibiotics) or treatment failure.</td>
<td></td>
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<tr>
<td>Risks of psychological harm (such as adverse effects of isolation on mental health).</td>
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<tr>
<td>Risks of social harm (such as stigmatization).</td>
<td></td>
</tr>
<tr>
<td>Post-trial risks (such as post-infection syndromes).</td>
<td></td>
</tr>
<tr>
<td><strong>Risks to third parties and communities:</strong></td>
<td></td>
</tr>
<tr>
<td>Risks of transmission to other individuals (such as research staff or household members) or to communities (for example, bystanders on public transport and/or the wider community).</td>
<td></td>
</tr>
<tr>
<td>Environmental risks (such as the contamination of local groundwater systems).</td>
<td></td>
</tr>
<tr>
<td>Erosion of public trust in research, the use of CHIS, and vaccines.</td>
<td></td>
</tr>
</tbody>
</table>
5.1.1 RISKS TO PARTICIPANTS

In practice, risk profiles for CHIS vary significantly, ranging from studies which carry minimal risk, or a minor increase over minimal risk, to those which are associated with higher risk. Current research ethics guidance and regulations address the amounts of risk that may be justified in research with competent healthy volunteers. However, they vary in their approaches to upper risk thresholds, and differing thresholds for CHIS have been proposed (29,30). Some diseases, in the absence of effective therapies to prevent or ameliorate disease, may be associated with such high risks of serious or irreversible harm that they should not be studied using CHIS, irrespective of the potential value of such research (14,31).

As with any first-in-human research, particular care is needed during the development of new infection models associated with increased uncertainty about potential risks to participants. Careful review is also required where infection models are used for the first time in new settings or populations where risk profiles may differ from those in previous studies. For example, for some pathogens the risks of exposure to a controlled infection are likely to be reduced in those with prior immunity (see Annex 10. Malaria case study), while for other pathogens they may be exacerbated (see Annex 4. Dengue case study).

Even infection models that have received regulatory approval and have well-characterized risk-benefit profiles (including those using live-attenuated vaccines) may still be associated with some risk of adverse outcomes (see Annex 7. Tuberculosis case study). In contexts where research-related harms may occur after completion of research procedures, mechanisms for the monitoring and management of such risks will also require careful consideration. As with all forms of clinical research, it is particularly important that risk minimization strategies effectively reduce the likelihood of serious or irreversible harms to participants (see Box 4. Risk minimization strategies: COVID-19 examples).

Assessments of the potential risks of research should also include consideration of how any social harms associated with research participation, including family discord or stigmatization, may need to be anticipated and ameliorated. Risks of psychological harm, such as adverse responses to infection control measures, also require assessment.

5.1.2 THIRD-PARTY AND ENVIRONMENTAL RISKS AND IMPACTS

In CHIS, as in other forms of research with infectious disease agents, systematic risk evaluations must encompass potential risks to third parties and to the environment of unintended transmission or contamination by microorganisms. Evaluations must be specific to the study and research context, and informed by consultation with relevant experts, to enable effective assessment of the nature, magnitude and longevity of transmission risks, and to determine how these should be managed and minimized. This will include consideration of the ways in which microorganisms being studied could potentially be transmitted by human interaction or vectors (such as mosquitoes), and/or could establish reservoirs in humans and animals, or in environments such as water supplies.

Risk minimization strategies for third parties focus on effective infection control and have implications for research design, site and participant selection, consent and engagement, as addressed elsewhere in this guidance (see sections 4, 6, 7 and 9 respectively). For example, when CHIS are proposed in contexts where transmission risks may be heightened by fragile local infrastructures for health and sanitation, it is important to assess the additional measures required to ensure that risks of transmission are appropriately managed and minimized, in consultation with relevant public health agencies (34).

In comparison with risks to research participants, risks to third parties have received relatively limited attention in research ethics guidance and regulation to date (35). Third party risks associated with CHIS should be carefully evaluated, monitored, and minimized, in consultation with relevant experts. Community engagement strategies should, where relevant, include activities to inform the identification, minimization and evaluation of the acceptability of such risks (36).

Abilities to effectively identify and inform third parties about specific transmission risks and minimization strategies will differ according to the nature and type of such risks in specific CHIS, and require careful consideration. Approaches to identifying and communicating with third parties are particularly important to evaluate where third party risks are potentially more than minimal, where risk minimization strategies require the cooperation of third parties, and/or if the local population perceives there to be significant potential risk even where these have been assessed as minimal. Responsibilities to inform identifiable third parties about research risks are discussed further in section 7.3.
Box 4. Risk minimization strategies: COVID-19 examples

In the context of potential COVID-19 CHIS, multiple complementary strategies to minimize research risks have been proposed (16,32,33). The implications of each of these for effective risk management require careful consideration on a case-by-case basis.

- Conducting research only in appropriate facilities with expert, experienced and appropriately resourced staff, high-level containment facilities and stringent infection control measures
- Participant selection criteria (low risk volunteers: healthy young adults)
- Minimizing numbers of participants, consistent with research goals
- Careful strain selection
- Careful choice of vaccines to be tested (where relevant)
- Exposing initial participants in novel designs to infection one-by-one with careful evaluation and titration of viral dose and stepwise dose-escalation
- Residential research designs incorporating close monitoring of participants, early diagnosis of infection, and supportive care (including critical care if required)
- Provision of proven specific treatments
- Long-term follow up of participants to identify any late effects of infection
- Plans to manage any long-term health consequences of participation
- Compensation for any research-related harms.

5.1.3 TREATMENT AND COMPENSATION FOR RESEARCH-RELATED HARMs

International research ethics guidance recognizes that participants who suffer research-related harms should receive prompt and appropriate treatment at no cost, and compensation to minimize the impact of such harms (14,16). In CHIS, it is important to recognize, justify and evaluate proposed provisions for compensation and treatment of research-related injuries in research participants and, if relevant, third parties. Proposals for effectively determining which injuries are research-related and appropriate mechanisms for their compensation and treatment may need to be developed in consultation with multiple stakeholders, including research sponsors, health authorities and insurers. Where relevant, such proposals may need to address mechanisms for third-party compensation and treatment, recognizing that in some contexts there are currently no established models for such provision.

5.2 BURDENS AND INCONVENIENCES

In addition to research risks, it is important to recognize that CHIS are associated with a range of research burdens and inconveniences, which require individual and collective consideration in conjunction with research risks. Some CHIS designs may pose minimal risks, but nonetheless involve significant burdens, including residential stays, substantial study procedures, and/or a disease model associated with burdensome symptoms (see Annex 4. Dengue case study). As with research risks, care is needed to characterize and evaluate both the nature and magnitude of the expected burdens of research participation, and the extent to which these can be managed, minimized and justified. As discussed in sections 9 and 12 below, the views of community members and experiences of researchers and research participants can play a key role in effectively identifying which aspects of research are likely to be experienced as burdensome, and means of minimizing burdens, and clearly communicating them to volunteers upon enrolment. Careful case-by-case consideration is needed of how best to address tensions between ensuring effective infection control and minimizing the burdens of research (for example, by enabling visits to, or outings from, residential research facilities during CHIS). In CHIS associated with higher levels of risk and/or burdens, careful evaluation is needed of whether cumulative risks and burdens remain within acceptable limits.
5.3 BENEFITS

As with all healthcare-related research, justifications for undertaking CHIS centre on their anticipated scientific and social value in terms of generating knowledge and interventions to promote human health and minimize suffering (see section 3. Justification). In some CHIS there may also be the potential of individual benefits to participants as a result of research participation. Such benefits include, for example, participants developing immunity to the pathogen being studied as a result of exposure to the infectious agent during research and/or receiving an effective experimental vaccine. Potential individual research benefits should be systematically identified and assessed during evaluations of the acceptability of proposed CHIS.

The aggregate risks and burdens associated with CHIS must be considered acceptable in light of the potential benefits to participants and the anticipated social and scientific value of the research. The fair distribution of risks, burdens and benefits of research amongst stakeholders, including research participants and communities, additionally requires careful consideration during reviews of the acceptability of proposed CHIS.
Many infectious diseases of global health importance are endemic in LMICs, and pathogens with a global distribution cause a higher burden of disease in such settings. CHIS are being conducted in a growing number of HIC and LMIC settings, and increasingly being recognized as an important component in research pathways addressing substantial inequitable burdens of infectious disease (2). To date, the vast majority of CHIS have been conducted in HICs, at times addressing pathogens associated with negligible local disease burden (see case studies in Annexes 4 and 8). While the results of CHIS conducted in HIC have often been generalizable to LMIC (see Annex 8. Typhoid case study), this is not always the case, owing to differences in environmental and population characteristics, including disease distributions, and host-pathogen and host-vaccine profiles (see Annex 10. Malaria case study). Consequently, there has been increased recognition of the potential value of supporting the development of infrastructure and research capacity to enable CHIS to be conducted in disease-relevant local populations in LMIC, where this meets local disease/research priorities and where such resources may not already exist.

**6.1 SITE SELECTION**

CHIS should only be conducted in sites that have the infrastructure, facilities, personnel and processes required to rigorously and safely conduct such research. It is important to evaluate how CHIS should be managed in populations with differing levels of prior, ongoing, or potential future exposure to relevant infectious pathogens (see section 5.1.1 Risks to participants). Site-specific consideration is needed of how risks to third parties may be exacerbated (for example, by background levels of vectors enabling transmission), the consequent infection control mechanisms required, and responsibilities to implement them (see typhoid and malaria case studies in Annex 8 and 10 respectively). The review of any additional resources and capacity-building required for the safe and effective conduct of CHIS should be undertaken in consultation with key stakeholders, potentially including public health officials, regulators, research sponsors, research ethics committees (RECs) and insurers (see sections 4.2 Infection control, 5.1.2 Third-party and environmental risks and impacts, and 9.1.2 Key stakeholders, as well as Annex 6. Schistosomiasis case study).

**6.2 PARTICIPANT SELECTION**

Participant selection criteria have a key role to play in ensuring that CHIS are scientifically valid, and that risks to participants and third parties are effectively managed and minimized (see sections 4 Research design and 5.1 Risks, and Annexes 3, 4, 5 and 9). Current standards in research ethics highlight the need for fair and inclusive approaches to the selection of research participants, recognizing both the importance of generating relevant evidence to inform approaches to addressing their health needs, as well as the need to ensure appropriate protections are in place (37). Within this context, a categor-
ical approach to characterizing specific populations as vulnerable, with a presumption of their exclusion from biomedical research, is increasingly perceived to be inadequate. Vulnerability has been characterized as ‘an increased likelihood of being wronged or incurring additional harm’, requiring especially careful evaluation of the probability and magnitude of additional physical, psychological or social harm during recruitment and research participation (14). Increasing support for presumptions of inclusion in global research ethics frameworks require researchers to justify both inclusion and exclusion criteria, and to determine which potential dimensions of vulnerability, such as limited literacy, should be ameliorated in the design and conduct of research, and how best to do so (38).

While some CHIS designs are anticipated to have minimal risk, other potential designs approach upper permissible limits of risk for research with healthy volunteers (see section 5.1 Risks). As with other forms of healthcare research, tensions may arise between ensuring the conduct of research which is responsive to the specific health needs of populations, while ensuring that such populations do not disproportionately bear research risks and burdens (see Annex 9. Zika case study). Careful deliberation and comprehensive and rigorous justification is required when CHIS are proposed in populations with relevant vulnerabilities. Vulnerability due to diminished cognitive or decision-making capacity requires particularly careful consideration in CHIS, given the need for participants to understand key aspects of the research associated with the implications of controlled infection, to minimize the risks of research for themselves and third parties (see section 7. Consent).

6.2.1 PAEDIATRIC CHIS
Children suffer from a significant burden of infectious disease. It is increasingly recognized that the inclusion of children in healthcare research is important to ensure that evidence can be generated about how best to address their health needs. Given the importance of rigorous and robust consent processes during the enrolment of healthy volunteers in CHIS, and concerns about the risks and burdens associated with such research, questions have arisen about whether it is ever acceptable to conduct CHIS with children in order to address population-specific health priorities (31,39).

International research ethics standards generally permit paediatric research which may not have the potential to benefit individual participants, provided there is compelling justification to conduct the research and that the risks are minimal or no more than a minor increase above minimal risk (14, 39). CHIS are associated with a range of risk-benefit profiles, including research where risks fall within such thresholds (see section 5.1 Risks). In paediatric populations, CHIS risk levels may lie within such thresholds when live-attenuated vaccines – which have been extensively studied and licensed for use in paediatric populations – are used as challenge agents (40,41).

Paediatric CHIS may be permissible where they comply with research ethics standards that characterize the additional protections required when enrolling participants who may lack appropriate decision-making capacity. These include restrictions on acceptable risk and burden profiles, and requirements for assent (in keeping with the child’s capacity) and parental or guardian permission. Proposals to conduct CHIS in children may raise significant concerns among stakeholders, and require substantial engagement with communities, experts, regulators and policy-makers to inform the appropriate design and conduct of such research, and to determine its acceptability (see section 9. Engagement).

The design of paediatric CHIS must be informed by relevant previous research in adult populations and, where available, relevant clinical trials in paediatric populations. In CHIS which are considered potentially justifiable in paediatric populations, careful attention must be paid not just to the management and minimization of risks, but also to how anticipated burdens of research may impact on paediatric participants, and whether and how such burdens can be minimized to acceptable levels.
7. CONSENT

The importance of seeking valid consent to research, using well-designed and contextually appropriate consent processes, is comprehensively addressed in current research ethics guidance and regulation. Consent processes for CHIS must be rigorous and robust, incorporating approaches to ensure that participants have understood key aspects of the research. Key elements of CHIS that participants must understand include that the study involves controlled infection, the potential risks and anticipated burdens of participation, and the measures that will be necessary to manage such risk and burdens. Where relevant, participants must also understand, and agree to comply with, the infection control measures required to minimize risks to third parties. Engagement activities and social science research may play an important role in informing the design and conduct of consent processes (see sections 9. Engagement and 12. Social science research). As with all healthcare research, it is important to evaluate potential influences on voluntary consent and ensure that these are not undue.

A commitment to fair participant selection requires that barriers to achieving valid consent must be addressed and ameliorated, wherever possible (see section 6.2 Participant selection). In relation to CHIS, questions have arisen about how rigorous requirements for understanding key aspects of research should influence inclusion and exclusion criteria. The requirements for understanding that are set out in this section should not be regarded as insurmountable barriers to supporting understanding amongst relevant populations; any proposed exclusion criteria based on such considerations must be justified (see Box 5. Understanding research). During the conduct of CHIS in paediatric populations with the capacity to assent to research, care is needed to develop robust assent processes, which appropriately support understanding and decision making, in addition to appropriate permission processes for parents and guardians.

7.1 UNDERSTANDING POTENTIAL RISKS AND BURDENS OF RESEARCH

Within the context of CHIS, consent processes may play an important role in the management and minimization of research risks, in addition to respecting participants’ autonomy. For example, in CHIS causing clinical symptoms of disease it is important for participants to understand how the disease manifests and the expected symptoms, not just to ensure that their consent is appropriately informed, but also to complement researcher’s abilities to undertake early diagnosis, appropriate symptom management and timely treatment. In some CHIS participants will need to understand how controlled infection may alter their immunity to specific pathogens, and the risks associated with subsequent natural infections with such pathogens (see Annex 4. Dengue case study).

Box 5. Understanding research

In some CHIS, recruitment has been restricted to participants with higher levels of education and familiarity with relevant topics to promote understanding and recruitment, particularly during CHIS using novel models of infection or conducted in novel research contexts (42–44). Research into those participants’ experiences of CHIS consent processes and research have informed subsequent consent processes for CHIS with broader inclusion criteria (45,46). In other contexts, RECs have prioritized generalizability and inclusivity, requiring that even CHIS with novel models of infection avoid exclusion criteria relating to education and relevant experience.
7.2 UNDERSTANDING INFECTION CONTROL AND RISKS OF TRANSMISSION

Where CHIS carry a risk of third-party infection, it is important for consent processes to detail the nature and likelihood of such risks, so that participants can evaluate the acceptability of potentially imposing risks of transmission on others. Consent processes should also comprehensively address proposed infection control measures, to enable participants to reflect on how acceptable and burdensome any constraints on their activities will be. Such understandings and evaluations are necessary to minimize the possibility that participants will find infection control measures unbearable, and/or become non-compliant (see Box 6. Explaining burdens of residential designs). If participants who withdraw from research will remain subject to public health authorities’ infection control measures, any ongoing restrictions on their activities will need to be comprehensively discussed and agreed, including the actions participants can take if they would like to dispute such measures (see section 4.2 Infection control).

Box 6. Explaining burdens of residential designs

In CHIS involving residential stays, information should be provided about provisions for participants’ safety, privacy, comfort, entertainment, and communication with family and friends, in addition to whether, and under what conditions, participants can receive visitors or leave study facilities for short periods. In some contexts, trial visits or stays in residential accommodation have been offered, and/or the experiences of participants previously undertaking such research have been shared to promote participants’ considerations of whether they would be willing to take part in research (46).

7.3 NOTIFICATION OF THIRD PARTIES

As discussed in section 5, some CHIS may pose potential risks to third parties. Where the levels of such risks are potentially acceptable, it is important to evaluate the extent to which the third parties can be identified prior to the conduct of research. Careful consideration is needed of whether and how to provide identifiable third parties with information about research risks, and their potential roles in participants’ decision making about research. Communication strategies about transmission risks should be developed in consultation with local infection control agencies and public health agencies, and may be valuably informed by social science research. Materials should be framed in a manner that is proportionate to the nature and magnitude of transmission risks, as well as responsive to third parties’ perceptions of risk. For example, it is important to ensure that communications do not raise undue concern about the risks of research within communities, and to minimize the likelihood of natural wild-type infections in third parties being perceived as being caused by controlled infection in participants.
In CHIS, as in other forms of biomedical research with healthy volunteers, frameworks for payments and non-financial compensation should ensure that participants receive fair and appropriate compensation for taking part in research while avoiding undue inducement. CHIS protocols should include a clear breakdown and justification of proposed approaches to reimbursement and compensation and, where relevant, additional incentives offered to research participants (47). In CHIS associated with greater burdens and inconveniences, or where additional incentives are proposed, ethics committees should carefully address any tensions arising between providing proportionate compensation and avoiding undue inducement.

Compensation rates for burdens and inconveniences should be consistent with local benchmarks for fair payment. Community engagement and social science research can play an important role in informing the development of locally appropriate compensation rates for burdens and inconveniences associated with CHIS models, where these are not already available (see sections 9. Engagement and 12. Social science research). The implications of proposed timings and structures of reimbursement and compensation also require careful consideration. For example, during lengthier studies, regular pro-rated payments throughout research participation may be more appropriate than lump sums being paid on completion or withdrawal from research.

In addition to fair and proportionate compensation, some CHIS protocols may include proposals to offer additional incentives to research participants, to promote recruitment and retention. Proposals for incentives require review within relevant national and international guidance frameworks for research, which have differing criteria for acceptability. Although views differ about the acceptability of offering compensation for the potential risks of research, there is consensus that participants must be compensated for any serious research-related harms which ultimately arise in practice, as discussed in section 5.1.3.
9. ENGAGEMENT

Meaningful engagement with communities and participants is increasingly recognized as a core element of respectful research practices (14). Consultative processes are intrinsically important as a means of demonstrating respect for the views and values of relevant stakeholders. Participatory processes may also play an important instrumental role in informing the design and conduct of appropriate research processes, and in building trust and confidence in research. At the inception of CHIS design, the potential value of consultation and engagement with communities, publics and key stakeholders should be carefully considered.

9.1 TAILORING ENGAGEMENT

As in other forms of healthcare research, participatory processes for CHIS may take a range of forms, in response to the aims of the engagement, the research context and the specific study design. In some contexts engagement may be minimal, such as when relatively routine CHIS (in which the risks and burdens of research are low and well characterized) are developed within longstanding CHIS research programmes. In contrast, more comprehensive participatory processes are appropriate when conducting CHIS involving factors such as novel models of infection, novel study populations, higher levels of risk and/or burdens, risks to third parties, and outbreaks, amongst others. For example, consultation and engagement was identified as a key criterion for ethical acceptability for the development of COVID-19 CHIS protocols (see Annex 3). Consideration should also be given to communication strategies for appropriate and timely engagement with relevant stakeholders throughout research, particularly when there is the potential for CHIS to receive attention in national and local media, and/or it is anticipated that concerns and misinformation may circulate in communities and social media.

9.1.1 COMMUNITIES

Community engagement strategies may be developed for a range of purposes, including exploring community acceptance of CHIS, and raising awareness about specific CHIS (see Annex 12). Focused and sustained participatory processes may additionally inform multiple aspects of research design, including the design of consent processes, evaluations of risks and burdens and associated minimization strategies, inclusion and exclusion criteria, and research processes and procedures. As with other forms of research, it is important to be clear about the respective responsibilities of researchers and communities during participatory processes. Respectful approaches to resolving differences of opinion are required, such as when recommendations from local communities cannot be adopted because they threaten the scientific validity of the research, or conflict with research ethics guidance. It is also important to recognize that there may be a range of potential outputs of participatory processes, including a decision not to conduct the research in the proposed population. Funding for engagement strategies may consequently be required in advance of, and independently from, funding for conduct of CHIS.

In addition to engagement prior to research, engagement may play an important role throughout and on completion of CHIS to ensure that issues are identified and addressed in a timely and appropriate fashion. Ongoing engagement may be particularly important where, for example, infection control measures limit participants’ social interaction during research, concerns are raised about specific CHIS in communities and social media, and CHIS research programmes are being established. Community engagement may also play a role in minimizing social harms of CHIS, such as when novel natural infections are perceived as arising from inadequate infection control during research. As with all healthcare research, when implementing strategies which promote community interest in discussing and engaging with CHIS, it is also important to consider how best to promote participants’ abilities to keep their involvement in research confidential.
9.1.2 KEY STAKEHOLDERS
In addition to engaging with communities and public, consultation with expert groups, including research regulators, ethics review committees, and public health officials, may be required, particularly when introducing CHIS into a novel research context. Additional potential stakeholders include relevant members of national science and technology councils, insurers, religious leaders and community gatekeepers.

It can be challenging for researchers to provide information and expertise about ethical and scientific issues raised by CHIS, while additionally facilitating stakeholders’ independence and ability to critique what is being presented. Consequently, it is important to evaluate whether independent expert advice and resources should be provided to inform consultations, and if so, what form it should take and who has the responsibility to provide it.

9.1.3 RESEARCH PATHWAYS
Consultation and coordination between researcher sponsors and researchers may also be important when CHIS are conducted to inform research and product development pathways. As discussed in sections 3 and 4, CHIS may play a range of roles in vaccine development pathways, including seeking preliminary estimates of vaccine efficacy to inform prioritisation of vaccine candidates. Coordination is particularly important where multiple vaccines are being simultaneously tested, to promote the collection of standardized safety data and enable direct comparative estimates of efficacy to facilitate the prioritization of vaccine candidates in product development pathways (See Annex 3).
10. FAIR COLLABORATIONS AND SHARING

The sharing of CHIS data, materials and infection models must take place in a fair, safe and transparent manner, which is appropriately responsive to the interests of multiple stakeholders, including study participants and their communities, and researchers sharing, and accessing, research outputs. In CHIS, as in other research involving pathogens of public health importance, the sharing of research materials, including pathogen strains must comply with frameworks for safe and secure transfer, storage and use, to minimize risks of misuse or inadvertent infection.

10.1 COLLABORATION

CHIS may involve multi-national research collaborations, particularly when conducted in LMIC. Increasing attention is being paid to ensuring that international health research collaborations are conducted fairly. As discussed in section 6, the global burden of infectious disease disproportionately affects LMIC. To date, however, limitations in research infrastructure and capacity have resulted in the majority of microorganism strains used in CHIS being developed in HIC, and the vast majority of CHIS being conducted in HIC.

CHIS should be conducted within relevant frameworks for fair collaborative research practices, including fair distribution of the benefits and burdens of research. In CHIS it is important to address how differing stakeholders’ interests should be recognized and respected. For example, multiple stakeholders may have interests in pathogen strains which have been isolated from patients in LMIC, developed into infection models in HIC, and used in CHIS in both HIC and LMIC. Stakeholders in global health research should also address the infrastructure, resources and capacity strengthening required to enable LMIC research institutions to initiate CHIS, where such studies are considered to place a critical role in addressing local infectious disease priorities.

10.2 SHARING

Recognition of the need for collective action to address health priorities is leading to increased emphasis on the importance of open research, including a rapid expansion of data sharing. Normative justifications for increasing mandates to share health research datasets include the importance of maximizing the utility of research data to advance science and healthcare, and to respect the contributions of research participants. The importance of sharing data equitably is also acknowledged: research datasets should not be shared in ways that exacerbate existing inequalities, but are instead appropriately responsive to the interests and concerns of relevant stakeholders in HIC and LMIC.

In CHIS, the importance has also been recognized of harmonizing research methodologies and sharing materials and/or infection strains, where feasible (34). Such sharing can promote comparison of study findings, inform research design, and strengthen capacity to conduct CHIS addressing specific health priorities. The use of harmonized methodologies and/or common materials also eases the regulatory process towards approval for the clinical studies as well as strengthening the supporting data used for submissions towards product licensure. As in other research involving pathogens of public health importance, their physical transfer may be limited due to logistical or regulatory restrictions. Under such circumstances, the sharing of methods, genetic sequences, or other reagents necessary for their production elsewhere is encouraged. However, regardless of the origin of the pathogen, it is always important to ensure that their use complies with appropriate practices for their safe and secure transfer, storage, containment and administration.
CHIS must be conducted with appropriate oversight and governance, in compliance with relevant ethics standards for research with human participants, guidelines for good clinical practice, and any other regulations applicable within the country in which the studies are conducted. The guidelines on good clinical practice require that clinical trials should only be conducted after the protocols have received a favourable opinion from the institutional review board or ethics committee. The implementation of a data and safety monitoring board (DSMB) or other independent data-monitoring committee is also suggested to monitor the progress of the CHIS and to recommend whether to continue, modify, or stop a trial. At present there is significant variation between national regulatory authorities regarding whether and how CHIS microorganism strains are reviewed and regulated, and the roles CHIS data may play in product development pathways. To enable effective, transparent and accountable governance of CHIS, further evaluation is recommended of regulations, policies, oversight models, and the extent to which these can, and should, be compatible internationally.

11.1 ETHICAL REVIEW

As with all other forms of health-related research involving human participants, CHIS must be reviewed by RECs which have the relevant training, expertise, and resources to conduct rigorous and effective review. At present, many CHIS are reviewed within existing national models for the ethical review of healthcare research. Where CHIS involving novel models of infection or research contexts are proposed, capacity-strengthening and consultation with ethics committees and relevant stakeholders may be particularly important to enable effective review (see section 9.1.2 Key stakeholders). Supplementary review procedures, including independent expert review at the national or international level, may be required when proposed CHIS have significant and contentious risk profiles, involve new models of infection, or are conducted within novel research contexts (see Box 7 and Annex 3).

Box 7. Ethical review of COVID-19 CHIS

WHO recommended that potential SARS-CoV-2 CHIS receive independent national review at the national or international level in addition to, or in conjunction with, local ethics review because such studies had the potential to be particularly controversial and their conduct had implications beyond the local setting (see Annex 3). Within the United Kingdom, the first country within which protocols for SARS-CoV-2 CHIS were submitted for review, the National Health Services Health Research Authority established a special REC with relevant expertise and a balance of expert and lay members. Specific training was provided to committee members to inform their consideration of the purpose of the study, the research team’s experience, how patient and participant views were included in research design, risk-benefit profiles, participant selection, consent processes and fair compensation (48). In addition, in April 2020, the WHO Blueprint programme established an international expert advisory group to develop a preparatory strategy so that if conditions were deemed appropriate, there would be a technically valid roadmap of what needed to be done to initiate a closely monitored challenge model of SARS-CoV-2 infection (32, 49).
11.2 REGULATION

In addition to complying with research ethics standards, CHIS must be conducted in compliance with good clinical practice as well as any relevant national and international regulations or guidelines for the development of microorganism strains and their use in CHIS. In some settings current legislation and regulation prohibiting intentional infection requires careful evaluation to determine if, and under what conditions, CHIS may be permitted. CHIS must also be compliant with any public health, environmental, and agricultural regulations regarding notification and control of potentially infectious pathogens.

11.2.1 MODELS OF INFECTION

At present there is significant variation within and between regulatory environments governing the development and administration of CHIS microorganism strains. In countries where CHIS are permitted, the manufacture of the infecting microorganism and its administration to humans may be subject to the same regulations on quality control and efficacy as vaccines or other therapeutic products. In contrast, in some settings the challenge agents are not considered to be medicinal products within national regulatory authorities' remits for review and authorization, leading to a lack of clarity about regulatory expectations and oversight of their quality control expectations (35). The applicability of regulations may also differ according to the type of challenge agent being used; challenge agents which have been genetically modified are typically subject to additional scrutiny and review (see Box 8. Examples of regulatory approaches to CHIS strains). An understanding of applicable regulations is necessary to enable researchers to identify processes and quality requirements that need to be met during the development, management, sharing and use of infectious agents. In demonstrating the safety and quality of the inoculum used in infection models, it is important to show the degree to which processes are compliant with good manufacturing practice principles, even if a full good manufacturing practice process/product is not required or cannot be implemented (for example, due to the type of microorganism being studied).

11.2.2 PRODUCT DEVELOPMENT AND LICENSURE

As discussed above (see sections 3. Justification and 4. Research design), CHIS may play a range of roles in vaccine development pathways, such as providing a better understanding of the immunological response to the infection, seeking preliminary estimates of vaccine efficacy, and informing prioritization of vaccine candidates to be entered into further efficacy trials. In exceptional circumstances, CHIS studies may provide sufficient evidence in support of a conditional vaccine approval, such as when pivotal efficacy trials may not be feasible or practicable to conduct. Where CHIS are conducted to inform vaccine development pathways, early discussions between researchers and regulators is important to clarify the limitations and roles that CHIS data may have in supporting the regulatory decisions about vaccine candidates.
11. GOVERNANCE, REVIEW AND OVERSIGHT

11.3 TRANSPARENCY AND OVERSIGHT

The increasing interest in conducting CHIS in a range of LMICs and HICs highlights the need for increased international transparency to inform the design and review of research, and effective governance. At present, the variation in regulatory approaches and reporting requirements for CHIS make it more challenging to identify consistently where and when CHIS have been conducted, the numbers of participants involved, the outcomes of research, risk benefit profiles and the nature and effectiveness of strategies to minimize risks and burdens. Consistent reporting requirements are needed, including preregistration on appropriate trial registries, publication of CHIS protocols, and rapid and comprehensive reporting of research harms, serious adverse events and sentinel events. As in all healthcare research, it is additionally important to address publication biases and promote the publication of negative results, such as those relating to ineffectiveness of models of infection or interventions being tested. An international model of CHIS oversight could draw on existing networks for research oversight, such as those developed by WHO, and the expertise and experience of regulatory agencies.

Box 8. Examples of regulatory approaches to CHIS strains

At present, the majority of microorganism strains used in CHIS have been partially or completely developed in HICs, which have differing regulatory approaches to their development and use (31). When exported, microorganism strains may then undergo additional national regulatory review in the recipient country.

<table>
<thead>
<tr>
<th>Regulatory agency</th>
<th>Relevant guidance</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>International</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WHO</td>
<td>Human challenge trials for vaccine development: regulatory considerations (31)</td>
<td>General guidance document, recommends that CHIS strains are manufactured to the same good manufacturing practices level as the vaccine under study. Recommended for implementation in WHO member states.</td>
</tr>
<tr>
<td><strong>Regional</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe – European Medicines Agency (EMA)</td>
<td>Auxiliary medicinal products in clinical trials (50)</td>
<td>Regulations do not include detailed specific guidance about CHIS strains. European Medicines Agency guidance is non-binding and requires member state ratification.</td>
</tr>
<tr>
<td><strong>National</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>United Kingdom Medicines and Healthcare products Regulatory Agency (MHRA)</td>
<td>No specific regulation for microorganism strains</td>
<td>The Advisory Committee on Releases to the Environment (ACRE) and the Department for Environment, Food, and Rural Affairs (DEFRA) have responsibilities for genetically modified strains.</td>
</tr>
<tr>
<td>United States Food and Drug Administration (FDA)</td>
<td>Current Good Manufacturing Practice, both for microorganism strains and for other investigational products (such as vaccines)</td>
<td>Institutional Biosafety Committee and/or the Recombinant DNA Advisory Committee review is required for genetically modified strains</td>
</tr>
</tbody>
</table>

Adapted from (2)
Consultative and participatory engagement with relevant stakeholders is increasingly recognized as a core element of respectful research practices, and can play an important role in informing the design and conduct of CHIS (see 9. Engagement). In addition to participatory processes, consideration should be given to the role that social science research may have in identifying and informing appropriate responses to ethical issues arising during the design and conduct of CHIS.

Embedding social science research within CHIS has provided valuable insights into stakeholders’ views about, and experiences of, research participation. Findings from embedded social science research may valuably inform multiple aspects of the design and conduct of CHIS, including: research design, the development and conduct of participatory processes, consent processes, risk and burden management and minimization, withdrawal policies and procedures, appropriate compensation for research participation, and ethical and regulatory oversight (see Annex 13). Conducting social science research may be particularly important during the implementation of CHIS involving novel models of infection and/or novel study populations or sites, in order to identify priorities for the development of appropriate responses to ethical issues arising in practice.

It may be valuable to conduct social science research prior to the conduct of CHIS to explore stakeholder perspectives about the acceptability of proposed studies. Findings from such studies may inform decisions not to conduct research; consequently, funding for such research is required in advance of, and independently from, funding to conduct CHIS.
REFERENCES


ANNEX 1. CONSENT: ESSENTIAL INFORMATION

Before requesting consent to participate in controlled human infection studies (CHIS), information addressing the following aspects of the study should be provided to potential participants in clear, concise and accessible language, and opportunities to discuss specific aspects and address queries must be provided. Individual jurisdictions may have additional specific informational requirements.1

1. WHY THE RESEARCH IS BEING DONE:
   • Pathogen and associated health burdens (locally and globally)
   • Research questions
   • Anticipated social and scientific value

2. ELIGIBILITY CRITERIA

3. EXCLUSION CRITERIA

4. NUMBER OF PARTICIPANTS IN THE STUDY

5. WHAT WILL HAPPEN DURING THE STUDY (PROCEDURE, TIME(S)/FREQUENCY, DURATION, LOCATION)
   • Screening process
     - Feedback of results
     - Potential public health reporting requirements [where relevant]
   • Research procedures
     - Infection or disease model
     - Exposure to infection
       ■ Mode and dosage
       ■ Differing research arms/groups [where relevant]
     - Experimental treatments/vaccines
       ■ Differing research arms/groups [where relevant]
     - Monitoring and diagnosis
     - Treatment [where relevant]
   • Infection control measures and compliance requirements [where relevant]
   • Post-trial monitoring [where relevant]

6. ADDITIONAL BURDENS:
   • Time commitments
   • Symptoms of infection/disease [where relevant]

7. RISKS (COMMON AND RARE, DURING AND SUBSEQUENT TO RESEARCH):
   • Risks of exposure to the micro-organism strain
   • Risks of exposure to experimental vaccines and/or treatments [where relevant]

• Risks associated with diagnostic measures (for example, frequent blood draws)
• Risks of psychological and/or social harm
• Potential for additional unknown risks

8. POTENTIAL PERSONAL BENEFITS, IF ANY

9. PROPOSED FEEDBACK OF INDIVIDUAL RESULTS FROM SCREENING AND DIAGNOSTIC TESTS

10. VOLUNTARINESS OF PARTICIPATION

11. OPTION TO WITHDRAW
• Nature of ongoing obligations to comply with measures for participant safety and/or infection control measures following withdrawal and avenues for appeal [where relevant]

12. REASONS PARTICIPANTS MAY NEED TO BE WITHDRAWN FROM THE STUDY BY RESEARCHERS

13. ALTERNATIVES TO PARTICIPATION [IF RELEVANT]

14. PARTICIPANT RESPONSIBILITIES
• Disclosure of relevant information prior to research
• Avoidance of actions which may adversely affect participants or study results
• Feedback to research team needed to enable effecting monitoring and risk/burden minimization (reporting onset of disease symptoms, for example) [where relevant]
• Infection control [where relevant]
  – Compliance
  – Discussion about infection control measures with relevant third parties

15. PERSONAL PRIVACY
• Protection of privacy during research
• Protection of identifiable private information
  – Limits (public health reporting requirements, for example) [where relevant]

16. SAMPLES AND DATA
• Data confidentiality and protections
  – Limits (public health reporting requirements, for example) [where relevant]
• Uses in current study
• Potential storage and future uses
• Sharing
• Genetic testing / sequencing [where relevant]

17. REQUEST TO ACCESS PARTICIPANTS’ HEALTH RECORDS [WHERE RELEVANT]
• Which information
• Proposed uses
• Who will have access

18. REIMBURSEMENT FOR OUT-OF-POCKET COSTS

19. COMPENSATION FOR PARTICIPATION (FINANCIAL AND NON-FINANCIAL)
• Itemized by study process/stage
• Incentive/bonus [where relevant]
• Timing and methods of compensation
20. TREATMENT AND COMPENSATION FOR RESEARCH-RELATED HARMs

21. ETHICAL REVIEW AND APPROVAL, CONTACT DETAILS

22. OPPORTUNITY TO DISCUSS QUERIES WITH THE RESEARCH TEAM
   • Prior to consent
   • During research

23. CONTACT FOR CONCERNS OR RESEARCH-RELATED HARMs

24. RESEARCHERS’ RESPONSIBILITY TO INFORM PARTICIPANTS ABOUT:
   • Novel research findings which may influence study design or participants’ decisions to take part in research, and the potential to seek revised consent [where relevant]
   • Protocol violations and implications

25. PROPOSALS TO ASSESS PARTICIPANT UNDERSTANDING [WHERE RELEVANT].
ANNEX 2. CHECKLIST FOR ETHICS COMMITTEES

Issues to address during the ethical review of CHIS include:

1. JUSTIFICATION – DOES THE STUDY HAVE APPROPRIATE, SUFFICIENT AND SCIENTIFIC VALUE?
   - What is the research question?
     - Is the research question important?
     - Does the study have the capacity to provide valuable new information to address the research question?
   - Will the results of the study contribute to:
     - understanding the infection and/or prevention and/or treatment or the infection and/or a programme of research focused on understanding the infection and contributing to its prevention and/or treatment?
   - Are the results of the study anticipated to be generalizable to the relevant population?
     - If not, is the use of a model of infection that will not produce generalizable results justified?
   - If a placebo arm is planned:
     - is there scientific confirmation that a placebo arm is needed?
     - what are the consequences of being on the placebo arm and how will these be appropriately managed?
     - Has post-trial access to treatment for the placebo group been considered?
   - Will conducting the study detract from clinical care/public health responses to the infection?
   - Are there equally feasible alternative research methods which are likely to provide similarly meaningful answers equally rapidly?

2. RESEARCH DESIGN
   - What has informed the study design?
   - Has there been consideration of the role of consultation and engagement with expert stakeholders, communities and publics to inform the design and conduct of the research?
   - Has there been independent expert scientific peer review of the proposal?
   - Has there been a systematic review of relevant literature?
     - Will relevant literature be monitored throughout the research, and amendments to the protocol proposed where appropriate?
   - Has the choice of the micro-organism strain and model of infection been explained and justified?
   - Are researchers proposing to use the best approach to diagnose the infection and/or provide the best treatment as early as possible?
     - If not, what additional risks and burdens are associated with the proposed approach?
     - Are any additional risks and burdens justified?
   - Does the research design effectively address infection control requirements?
   - Will infection control measures have implications for participants who wish to withdraw from the research?
3. **RISKS, BURDENS AND BENEFITS**
   - Have the physical, psychological and social risks and burdens been identified, minimized, and assessed accurately enough to be evaluated?
   - What uncertainties are associated with research risks?
   - Will the potential benefits of the proposed study outweigh the risks and burdens?
   - Are the risks and burdens individually and cumulatively acceptable?
   - Are there any potential benefits associated with research participation?
   - How will participant risks and burdens be managed and minimized during and following the research?
   - How will treatment and compensation be provided for any research-related injuries sustained during or subsequent to the research?
   - How will risks to third parties be managed and minimized?
   - Is the quality of the micro-organism strain assured?
     - What manufacturing standards have been used?
     - Has evidence of quality control been provided?
   - How will micro-organism strains be safely and securely transferred, stored, used and disposed of?

4. **SITE SELECTION**
   - Does the research address health priorities in the target population?
   - Does the research team have appropriate relevant expertise to conduct the research and is there appropriate clinical expertise to treat any resulting infection/disease?
   - Does the research site have the appropriate infrastructure, facilities, personnel and processes to effectively and safely conduct the research?
   - Has there been consultation with local key stakeholders about the safe and effective conduct of the research and whether it is acceptable?

5. **PARTICIPANT SELECTION**
   - What are the proposed inclusion and exclusion criteria and what considerations (including risk minimization for participants and third parties) have informed their development?
   - Will participants with diminished capacity to consent, or incompetent participants, be eligible to participate?
     - If so, what additional processes and protections will be implemented?
   - How will potential participants be approached?
   - What screening processes will be implemented for potential participants:
     - to promote scientific validity and/or
     - to minimize potential risks and burdens?

6. **CONSENT AND NOTIFICATION**
   **6.a Consent**
   - Do the research staff involved in consent processes have the appropriate training, expertise, experience and accountability frameworks?
   - Is the design and development of consent processes and documentation informed by:
     - A review of literature including:
       - Relevant evidence-based approaches to the effective design and conduct of consent processes?
       - Relevant social science research into CHIS?
     - Consultation and engagement with
       - Communities and public?
       - Key stakeholders?
• Are the proposed consent process and associated materials appropriate?
• What opportunities will there be for participants to reflect, discuss with others, and ask questions?
• What key aspects of the research must the participants understand?
  – How will their understanding of these be promoted and evaluated?

6.b Notification

• Does the research pose acceptable risks to third parties which require notification?
  – If so, how will third parties be notified about potential risks?

7. REIMBURSEMENT, COMPENSATION AND INCENTIVES

• Has a schedule and breakdown of proposed approaches to reimbursement and compensation been provided? Is this appropriate?
• How will participants be reimbursed for out-of-pocket expenses?
• Will participants be compensated for research participation?
• Are there proposals to offer additional incentives to participate?

8. PRIVACY AND CONFIDENTIALITY

• How will participants’ privacy be protected?
  – Are there conditions under which identifiable details about participants may be shared with third parties, such as public health authorities?

9. DATA MANAGEMENT AND SHARING

• How will research data be curated, securely stored, and shared?
• How will research methods, materials and findings be shared?

10. REVIEW AND OVERSIGHT

• Is there a trial steering committee in place?
• Is a data safety and monitoring committee in place?
• Will the study protocol be registered and published?
• How will safety reports of adverse events and serious adverse events be shared?

Substantially adapted from: The United Kingdom Health Research Authority’s specialist ad hoc Research Ethics Committee, Research Ethics Committee’s review of the global first SARS-CoV-2 Human Infection Challenge studies, unpublished review, 2021.
ANNEX 3. KEY CRITERIA FOR THE ETHICAL ACCEPTABILITY OF COVID-19 HUMAN CHALLENGE STUDIES

WHO WORKING GROUP FOR GUIDANCE ON HUMAN CHALLENGE STUDIES IN COVID-19

1. PREAMBLE

The pandemic of coronavirus disease 2019 (COVID-19), caused by SARS-CoV-2, poses an extraordinary threat to global public health, socioeconomic stability, food security and other social goods (1, 2). Left unchecked, COVID-19 would probably claim millions of lives and place extreme strain on health care systems worldwide. While control measures such as physical distancing can help to reduce the spread of COVID-19, these measures come at enormous social and economic costs that may be disproportionately borne by underprivileged groups. Major challenges for the current public health response include (a) a lack of safe, effective vaccines and treatments; and (b) gaps in scientific knowledge regarding pathogenesis, immunity and transmission (3, 4).

Controlled human infection studies (or “human challenge studies”) involve the deliberate infection of healthy volunteers. Such studies can be particularly valuable for testing vaccines (5, 6). They can be substantially faster to conduct than vaccine field trials, in part because far fewer participants need to be exposed to experimental vaccines in order to provide (preliminary) estimates of efficacy and safety. Such studies can be used to compare the efficacy of multiple vaccine candidates and thus select the most promising vaccines for larger studies. Well-designed challenge studies might thus not only accelerate COVID-19 vaccine development (7–9), but also make it more likely that the vaccines ultimately deployed are more effective.

Challenge studies are also used to study processes of infection and immunity from their inception (5). They could thus be used to (a) validate tests for immunity to SARS-CoV-2, (b) identify correlates of immune protection, and (c) investigate the risks of transmission posed by infected individuals (4, 10). Such findings could significantly improve the overall public health response to the pandemic.

This document aims to provide guidance to scientists, research ethics committees, funders, policy-makers, and regulators in deliberations regarding SARS-CoV-2 challenge studies by outlining key criteria that would need to be satisfied in order for such studies to be ethically acceptable.

2. ETHICS OF HUMAN INFECTION CHALLENGE STUDIES

Challenge studies have a long history, including early research with smallpox, yellow fever and malaria that changed the course of global public health (5). In the last 50 years, challenge studies have been performed safely in tens of thousands of consenting adult volunteers under the oversight of research ethics committees (5, 11, 12). These studies have recently helped, for example, to accelerate the development of vaccines against typhoid (13) and cholera (14), and to determine correlates of immune protection against influenza (10).

Research involving the deliberate infection of healthy volunteers may seem intuitively unethical, and there are numerous prominent historical examples of unethical research involving deliberate infection of research subjects (5). However, there is a consensus among ethicists who have reflected upon human challenge studies that the intentional infection of research participants can be ethically acceptable under certain conditions, such as those in which modern challenge studies are conducted (5, 15–20).

Challenge studies are nonetheless ethically sensitive and must be carefully designed and conducted in order to minimize harm to volunteers and preserve public trust in research. In particular, investigators must adhere to standard research ethics requirements. Furthermore, research should be conducted to especially high standards where (a) studies involve exposing healthy participants to relatively high risks; (b) studies involve first-in-human interventions (including challenge) or high levels of uncertainty (for example, about infection, disease and sequelae); or (c) public trust in research is particularly crucial, such as during public health emergencies (5, 15, 17–19, 21).

3. WHY SARS-COV-2 CHALLENGE STUDIES ARE BEING CONSIDERED

The global public health response to COVID-19 could be significantly enhanced by safe, effective vaccines and treatments, reliable measures of correlates of immune protection, and improved scientific knowledge of the disease and its transmission (3, 4). It is widely agreed that vaccines would be particularly important, and over 100 candidate vaccines are currently being developed (22). Well-designed human challenge studies provide one of the most efficient and scientifically powerful means for testing vaccines, especially because animal models are not adequately generalizable to humans (11–13, 24). Challenge studies could thus be associated with substantial public health benefit in so far as they (a) accelerate vaccine development, (b) increase the likelihood that the most effective (candidate) vaccines will ultimately become available, (c) validate tests of immunity, and (d) improve knowledge regarding SARS-CoV-2 infection and transmission.

3. Among other requirements highlighted in this document, preserving public trust in research requires minimizing harm not only to volunteers but also to research staff and third parties.
4. First-in-human challenge studies may nevertheless involve less uncertainty than, for example, first-in-human drug trials, because many more human data regarding pathogenesis are already available; although millions have been infected with SARS-CoV-2, these data are still emerging, so significant uncertainty remains.
6. Determination of experimental vaccine efficacy requires that a sufficient number of research subjects in both vaccinated and control arms are actually exposed to – that is, “challenged” by – the pathogen in question. To the extent that transmission of SARS-CoV-2 is low, vaccine field trials take more time and require larger numbers of participants to produce clear results. In a human challenge study, by comparison, all participants are exposed, which is a major reason why they involve smaller numbers of participants and can be completed quickly.
Challenge studies might be particularly likely to accelerate the availability of vaccines where there is appropriate coordination between researchers, manufacturers and regulators (18, 21). In any case, such studies should be incorporated into wider research programmes involving larger studies to provide more precise estimates of safety and efficacy (potentially including adaptive trial designs if appropriate) (5, 9, 24). SARS-CoV-2 challenge studies could add value to other types of vaccine research by enabling (a) accurate assessment of asymptomatic infection, (b) more rapid and standardized testing of multiple vaccine candidates, and (c) testing vaccines in contexts where there is little continuing transmission (for example, due to public health measures or during inter-epidemic periods) (5, 18, 25).

Although more data will help to clarify relevant risks, current estimates suggest that participation in SARS-CoV-2 challenge studies would be least risky for young healthy adults. In those aged 18-30 years (whether healthy or not), hospitalization rates for COVID-19 are currently estimated to be around 1% and fatal infection rates around 0.03% (26). As required by the criteria below, SARS-CoV-2 challenge studies should be conducted in specialized facilities, with especially close monitoring and ready access to early supportive treatment for participants, including critical care if required (27). However, SARS-CoV-2 challenge studies may (at present) be thought to involve higher levels of risk and uncertainty than other commonly accepted human challenge studies because the pathogenesis of COVID-19 is currently poorly understood, (with the recent exception of remdesivir) there is no specific treatment available, and severe disease or death can occur in young adults (17, 18, 28, 29).

Global public trust in research and vaccines depends on there being heightened vigilance to ensure that, if they proceed, SARS-CoV-2 challenge studies are conducted to the highest scientific and ethical standards. Eight ethical criteria for conducting SARS-CoV-2 challenge studies are set out in Table 1.

**TABLE A3.1** Eight criteria for SARS-CoV-2 challenge studies

<table>
<thead>
<tr>
<th>Scientific and ethical assessments</th>
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<tbody>
<tr>
<td>Criterion 1: Scientific justification</td>
<td>SARS-CoV-2 challenge studies must have strong scientific justification</td>
</tr>
<tr>
<td>Criterion 2: Assessment of risks and potential benefits</td>
<td>It must be reasonable to expect that the potential benefits of SARS-CoV-2 challenge studies outweigh risks</td>
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<tr>
<th>Consultation and coordination</th>
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<tbody>
<tr>
<td>Criterion 3: Consultation and engagement</td>
<td>SARS-CoV-2 challenge research programmes should be informed by consultation and engagement with the public as well as relevant experts and policy-makers</td>
</tr>
<tr>
<td>Criterion 4: Coordination</td>
<td>SARS-CoV-2 challenge study research programmes should involve close coordination between researchers, funders, policy-makers and regulators</td>
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<tr>
<th>Selection criteria</th>
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<tbody>
<tr>
<td>Criterion 5: Site selection</td>
<td>SARS-CoV-2 challenge studies should be situated where the research can be conducted to the highest scientific, clinical and ethical standards</td>
</tr>
<tr>
<td>Criterion 6: Participant selection</td>
<td>SARS-CoV-2 challenge study researchers should ensure that participant selection criteria limit and minimize risk</td>
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<tr>
<th>Review and consent</th>
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<tbody>
<tr>
<td>Criterion 7: Expert review</td>
<td>SARS-CoV-2 challenge studies should be reviewed by a specialized independent committee</td>
</tr>
<tr>
<td>Criterion 8: Informed consent</td>
<td>SARS-CoV-2 challenge studies must involve rigorous informed consent</td>
</tr>
</tbody>
</table>

7. In the cited paper, estimated infection fatality risks for individuals aged 20–29 years and for those 10–19 years were 0.03% and 0.007% respectively. Specific data were not reported for 18–20 year olds, but the range here includes this group in light of the aim to restrict participation in challenge studies to adults (those aged 18 years and older); other ranges have been proposed (see, for example, Eyal, Lipsitch and Smith (9)). Given the acknowledged relationships between age and probability of severe disease, investigators may consider conducting initial challenge in younger adults (e.g. age 18–25 years) before consideration of inclusion of older individuals (although whether, or the extent to which slightly older individuals, for example, those aged 25–30 face significantly higher risks than those aged 18–25 is currently unclear).

8. On the other hand, widely accepted challenge studies, for example with malaria and influenza, have led to unexpected rare but severe outcomes in healthy participants (that is, they also involved significant uncertainty); see Nieman et al. (28) and Sherman et al. (29).

9. On the other hand, widely accepted challenge studies, for example with malaria and influenza, have led to unexpected rare but severe outcomes in healthy participants (that is, they also involved significant uncertainty); see Nieman et al. (28) and Sherman et al. (29).
**4. ETHICAL CRITERIA**

The following list of criteria for the ethical acceptability of SARS-CoV-2 challenge studies is not exhaustive, and other usual research ethics criteria and local requirements should be met. This document has been informed by emerging literature regarding the ethics of challenge studies, including other frameworks (19, 30). The criteria are not mutually exclusive: they are interconnected in numerous important ways. For SARS-CoV-2 challenge studies to proceed, it should be demonstrated that all eight criteria have been satisfied.

**CRITERION 1: SCIENTIFIC JUSTIFICATION**

**SARS-COV-2 CHALLENGE STUDIES MUST HAVE STRONG SCIENTIFIC JUSTIFICATION**

In the context of the current pandemic, there may be several justifications for conducting SARS-CoV-2 challenge studies, which may offer a range of potential public health benefits of varying magnitudes (see Criterion 2). Scientific justification would be strongest where studies aim to produce results of public health importance, especially to the extent that similar results could not feasibly be obtained as efficiently or expediently in other study designs involving less risk to human participants (9, 31). The justification of challenge studies should situate them in a coherent overall strategy involving the coordination of research and other activities that ultimately aim to improve the public health response to COVID-19 (see Criteria 2, 3 and 4) (32, 33).

Particularly important results would include those that would be expected to lead to large public health benefits being achieved sooner than would otherwise be possible. This could occur, for example, where studies (a) inform the selection of the safest and most effective vaccines (or treatments)10 from among multiple candidates12 for further study or (potentially) conditional licensure; and (b) inform other important clinical and public health measures (for example, by generating knowledge regarding correlates of immune protection, asymptomatic infection and transmission).

Potential public health benefits are greatest where there is a clear plan for relevant knowledge, tests, vaccines or other interventions to be made widely available to the global population.

Investigators should aim to obtain the maximum amount of scientific knowledge per individual participant challenged while not undermining the primary aims of the study or exposing participants to undue risk (see Criterion 2). This could include, for example, collecting additional samples during challenge trials for secondary analyses of host–pathogen interactions.

The justification of challenge studies should include specification of their role in vaccine development pathways, broader research programmes, and planning of public health responses (18, 32, 33). For example, the justification should describe how the results of challenge studies involving only young healthy adults (see Criterion 6) would inform further research13 and public health measures aiming to protect higher-risk groups (including, for example, the vaccination of young healthy adults to provide indirect protection to higher-risk groups) (9, 34).

10. Although challenge studies involve the additional risk associated with being infected with a challenge strain (compared to vaccine field trials, which do not increase the probability of infection), it is ethically salient to assessments of risk that challenge studies involve fewer participants, who are more closely monitored and provided with immediate treatment (see Criterion 2). This may be particularly salient, for example, if there are concerns regarding potential vaccine-enhanced disease (9, 31).

11. In the context of high incidence of COVID-19 in the community, it will probably be more ethically acceptable to conduct treatment trials primarily in infected patients (and/or contacts of patients). However, there may nevertheless be circumstances in which it is justified to test treatments in challenge studies.

12. Where it is reasonable to expect that multiple candidate vaccines will ultimately go through efficacy testing in humans (as appears to be the case for SARS-CoV-2), challenge studies can be an efficient way to provide direct comparisons of efficacy (which are otherwise often difficult to obtain) – thus informing evidence-based decisions about which interventions to use (see Criterion 4). It may therefore be justifiable (in line with the goal of situating particular studies in overall research strategies) to perform challenge studies with the first available vaccines (even if they will simultaneously be tested in field trials) in order to provide comparisons with other vaccines in future.

13. For example, vaccine efficacy data in high-risk groups could be obtained subsequently with other research designs – for example, immune bridging studies (once useful correlates of protection are established), field trials and post-licensure observational studies.

14. The (scientific and social) value and ethical acceptability of vaccine research is not contingent on (early) demonstration of efficacy in high-risk groups, in part because vaccination of (large numbers of) low-risk individuals provides indirect protection to high-risk individuals (compare rubella vaccination of whole populations so as to protect unborn children); see also Criterion 6.
**CRITERION 2: ASSESSMENT OF RISKS AND POTENTIAL BENEFITS**

**IT MUST BE REASONABLE TO EXPECT THAT THE POTENTIAL BENEFITS OF SARS-COV-2 CHALLENGE STUDIES OUTWEIGH RISKS**

- There should be systematic assessment of potential benefits and risks
- To the extent possible, these potential benefits and risks should be quantified
- Potential benefits and risks should be compared with other feasible study designs
- Expected benefits should be maximized
- Risks should be minimized.

It is a standard research ethics requirement that, on balance, benefits should outweigh risks. Given the ethically sensitive nature of SARS-CoV-2 challenge studies, assessment of their potential benefits and risks should be especially rigorous.\(^{15}\) Potential benefits and risks should be evaluated for each of three key groups: (a) participants; (b) society (in general); and (c) third-party contacts of participants.

To the extent possible, the potential benefits and risks of SARS-CoV-2 challenge studies should be quantified (and, if necessary, modelled) and compared with those of other relevant study designs. For example, quantification of benefits should include estimates of (a) when, and how much faster, vaccines might realistically be expected to become available for use as a result of challenge studies being performed (for example, prior to, or potentially instead of, larger field trials);\(^{16}\) (b) how many lives might thereby be saved; and (c) other public health benefits of improved scientific knowledge (for example, regarding correlates of protection). Quantification of risks should include estimates of (a) the number of participants exposed to risk; (b) absolute risk to participants (in light of the latest data); and (c) marginal risk to participants\(^{17}\) (that is, the additional risk of participation compared to background risk of infection) (5, 21).

Above and beyond the systematic assessment of potential benefits and risks, and judgement that the former outweigh the latter, expected benefits should be maximized and risks should be minimized, other things being equal. For example, benefits should be maximized to the extent possible without increasing risks to participants, and risks should be minimized (see Table 2 and following subsection) to the extent possible without compromising the scientific value of a study.\(^{18}\)

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15. Similar considerations arguably apply in other situations of higher risk, greater uncertainty, and significant potential benefits (for example, some other first-in-human trials).

16. In light of consultation – for example, with regulators – regarding the possibility of authorizing emergency use of a vaccine on the basis of challenge study data alone; see Criterion 4.

17. Marginal risk of participation may be very low, or possibly even negative, during a pandemic.

18. If the same information can be gained using a research method or trial design that exposes participants to less risk, the lower-risk option should be adopted.
ANNEX 3. KEY CRITERIA FOR THE ETHICAL ACCEPTABILITY OF COVID-19 HUMAN CHALLENGE STUDIES

### ANNEX 3. KEY CRITERIA FOR THE ETHICAL ACCEPTABILITY OF COVID-19 HUMAN CHALLENGE STUDIES

a. Participants might benefit in this way if (a) infection leads to protective immunity; (b) participants face a background risk of infection in the community; and (c) challenge infection confers an equal or lower likelihood of severe disease (for example, in light of methods of challenge as well as early diagnosis and treatment during participation) as compared to infection in the community.

b. Participants who become immune as a result of challenge infection (or an experimental vaccine) would be less likely to be a source of transmission in the community after completion of the study.

### TABLE A3.2 Examples of potential benefits, risks and risk minimization strategies (by group)

<table>
<thead>
<tr>
<th>Group</th>
<th>Potential benefits</th>
<th>Risks</th>
<th>Risk minimization strategies</th>
</tr>
</thead>
</table>
| Society     | • Number of lives saved and cases of disease averted by earlier availability of a (safer or more effective) vaccine.  
              • Earlier return to normal global social functioning and associated economic and public health benefits | • Erosion of trust in challenge studies, research in general, or vaccines because of perceptions of challenge studies in this context or harms that arise for participants or third parties | • Public engagement regarding research design                    |
| Participants| • Immunity induced by experimental vaccines (if effective)  
              • Immunity from experimental infection
d| • It must be reasonable to expect that the potential benefits of SARS-CoV-2 challenge studies outweigh risks | • Selection of low-risk participants  
              • Reducing numbers of participants where feasible  
              • Initial challenges conducted one by one, with careful titration of viral dose  
              • Close monitoring, early diagnosis and supportive care, including critical care if required  
              • Specific treatments if proven effective  
              • Careful challenge strain selection  
              • Testing of vaccines with lower likelihood of causing vaccine-enhanced disease  
              • Selection of sites where there is background risk of infection  
              • (reduced marginal risk of participation)  
              • Long-term follow-up  
              • Compensation for any study-related harms |                                                                                  |
| Third parties | • Indirect benefits of participants becoming immune | • Risk of infection of research staff  
              • Risk of transmission of infection to third parties in the community | • Selection of sites with stringent infection control processes, including protective equipment for staff |

a. Participants might benefit in this way if (a) infection leads to protective immunity; (b) participants face a background risk of infection in the community; and (c) challenge infection confers an equal or lower likelihood of severe disease (for example, in light of methods of challenge as well as early diagnosis and treatment during participation) as compared to infection in the community.

b. Participants who become immune as a result of challenge infection (or an experimental vaccine) would be less likely to be a source of transmission in the community after completion of the study.
RISK MINIMIZATION
The design of initial SARS-CoV-2 challenge studies, if such studies proceed, should involve a range of risk minimization strategies (see Table 2). Third-party risks should be minimized by the use of protective equipment for trial staff and the conduct of studies on an inpatient basis (until participants are no longer infectious) in facilities that permit stringent infection control.

Risks to participants should also be carefully controlled and minimized. For example, participants in initial studies should first be challenged one by one, with meticulous titration of viral dose.\textsuperscript{19} Challenge studies involving previously infected individuals could also aim to determine correlates of protection and generate additional knowledge regarding immunity. More generally, a key risk minimization strategy should involve limiting participation to adults (that is, those able to provide informed consent) estimated, based on the best available data, to be at lowest risk – for example, healthy adults aged 18–30 years (see Criterion 6). Despite efforts to minimize risks, severe harms may still occur, and there is currently significant uncertainty regarding the pathogenesis of COVID-19. There are thus strong reasons to conduct such studies especially carefully and to provide participants with high-quality supportive care (including intensive care if required), long-term follow-up (for any lasting harms), and full compensation for any harms that occur. Participant selection criteria should be revised in accordance with evolving evidence.

Investigators should revise challenge study designs with further risk minimization strategies, including provision of specific, curative treatment or use of attenuated challenge strains if or when these become available. Although treatment is one important way of reducing risk, the existence of specific, curative treatments is not a necessary condition for the ethical acceptability of challenge studies;\textsuperscript{20} however, if or when proven specific treatments are developed, these should be administered to participants as required. The use of wild-type challenge strains may be ethically permissible,\textsuperscript{21} although challenge strains (whether wild-type or attenuated) should be as well characterized as possible in order to minimize risks. If an attenuated challenge strain that would be expected to produce results generalizable to wild-type infection is developed by the time studies are ready to commence, this would permit further minimization of risks.

CRITERION 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

Consultation and engagement activities should ideally be rapid, rigorous, and mutually informative, such that the views of the public and expert groups are updated in light of each other. Public engagement at the local, national and international levels should begin immediately, since such studies are already being considered (7–9);\textsuperscript{22} and they should continue throughout the research programme and afterwards. Such consultations should seek considered public views on proposed research plans with engagement techniques that enable genuine dialogue in advance, and hence without unduly delaying potentially beneficial research. There should be a focus on transparently presenting relevant risks and potential benefits (see Criterion 2) as well

\textsuperscript{19}. Conducting initial challenge infections one by one is similar to practice in first-in-human phase I drug trials (especially since the TGN1412 trial, where simultaneous administration of an experimental agent to multiple participants led to significant harm) (5). Conducting SARS-CoV-2 challenge one by one might involve, for example, especially close monitoring of viral load and symptoms in the very first participant(s), and proceeding with subsequent participants only when there is confidence that the infection in the prior participant is beginning to resolve (without unexpected or unacceptable adverse events). As more becomes known about the pathophysiology of SARS-CoV-2 infection and COVID-19 (including among challenge study participants), it may be appropriate to proceed more rapidly (for example, by challenging participants in groups after initial challenges prove safe) in order to avoid undue delay.

\textsuperscript{20}. For example, challenge studies are approved and performed for pathogens with no specific treatment (for example, rhinovirus, rotavirus and dengue) as well as for influenza (for which existing antivirals may not always prevent complications of disease, for example myocarditis). Supportive care is provided in all cases.

\textsuperscript{21}. There is a lack of coherent regulation regarding challenge strains, and wild-type or near-wild-type strains have been used for a range of pathogens (5).

\textsuperscript{22}. Public engagement activities by groups interested in SARS-CoV-2 challenge studies have recently commenced (see https://1daysooner.org/, accessed 4 May 2020).
as incorporating the views of challenge study participants or those who have expressed interest in participating (35, 36).

Goals of public engagement should include assessing local acceptability of SARS-CoV-2 challenge studies, responding to community concerns, maximizing transparency, and understanding the potential impact of research on the community (especially in light of other social and public health disruptions related to the pandemic) (37). Methods should be appropriate to the pandemic context and could include online engagement techniques conducted by groups with relevant expertise. To maximize the benefits of these activities, they should be regularly updated in light of emerging data and ideally involve experienced social scientists working within the overall research programme and public health response (35, 36).

There should also be simultaneous local and international consultation and coordination (see Criterion 4) between researchers, ethics committee members, policy-makers, and other relevant experts in the science and ethics of challenge studies. This should help to ensure that the other criteria in this document are satisfied and that research designs are optimized, taking into account expert consensus and input from public engagement. As part of consultation with relevant experts, SARS-CoV-2 challenge study designs should be the subject of independent scientific review (see Criterion 7). Consultation with local policy-makers (for example within departments of health) should aim to coordinate any proposed research with local public health policy and the pandemic response (see Criterion 4).

**CRITERION 4: COORDINATION OF RESEARCH**

**SARS-COV-2 CHALLENGE STUDY RESEARCH PROGRAMMES SHOULD INVOLVE CLOSE COORDINATION BETWEEN RESEARCHERS, FUNDERS, POLICY-MAKERS AND REGULATORS**

Coordination activities should situate SARS-CoV-2 within a coherent set of international programmes of research and aim to ensure that the potential public health benefits of relevant research can be realized with maximum safety and efficiency (33). Research should thus be coordinated with public health agencies in order to avoid unduly compromising the local public health response to COVID-19, for example during peak transmission periods (33). Studies should have adequate oversight from other relevant authorities (including WHO where appropriate).

All SARS-CoV-2 challenge studies must be pre-registered in appropriate repositories, and there should be a comprehensive list of all such studies maintained at the international level. Study data should be shared rapidly and ideally made publicly available (with appropriate protections). Especially important data include those regarding measures of vaccine safety and efficacy, as well as any harm to participants. If multiple research groups conduct SARS-CoV-2 challenge studies, these programmes should, as far as possible, be (a) standardized (in order to maximize benefits by obtaining comparable results in larger numbers of participants), including by sharing of challenge strains and vaccine candidates, and (b) designed so as to avoid unnecessary duplication.

There should be coordination between researchers, policy-makers and regulators regarding vaccine development. Early coordination with regulators should focus in particular on how data from challenge studies would be used (for example, in the context of decisions to initiate field trials with promising vaccine candidates, and what role, if any, challenge study data would have in decisions regarding pre-approval, licensure, or emergency use of experimental vaccines) (18). Coordination is thus especially important where multiple vaccines are to be tested, as this may facilitate the selection of safer and more effective candidates by providing standardized safety data and directly comparable estimates of vaccine efficacy that would otherwise be difficult to obtain (23).
CRITERION 5: SITE SELECTION

SARS-COV-2 CHALLENGE STUDIES SHOULD BE SITUATED WHERE THE RESEARCH CAN BE CONDUCTED TO THE HIGHEST SCIENTIFIC AND ETHICAL STANDARDS

Given the urgency, risk and uncertainty involved, initial SARS-CoV-2 challenge studies should only be conducted in centres with significant experience in designing, reviewing and conducting human challenge studies. These centres should also have access to appropriate facilities in which to prepare challenge strains, and safe, comfortable isolation for participants. Centres should also ideally have experience with community engagement (see Criterion 3). There should be provision for high-quality care (including intensive care if required), long-term follow-up of participants, and full compensation for any research-related harm (see Table 2 and Criterion 2).

Background risk of infection is an important consideration in site selection. On the one hand, when local background probability of infection is high (for example, during or soon before peak transmission of SARS-CoV-2 in the local community), participants face less marginal risk from being infected during study participation. Nevertheless, the absolute risk participants face within a study remains a consideration in study design, and care should be taken to minimize absolute risks of participation even where marginal risks are low (because background probability of infection is high) (see Criteria 2 and 6). On the other hand, peak periods of local transmission might be inappropriate times to conduct challenge studies, as they could divert scarce resources (such as staff, protective equipment, health care) away from (other) public health response activities that should be prioritized during such periods.

Decision-makers will thus need to balance competing considerations, for example reduction of marginal risk for participants versus the coordination of research with the public health response (33). It might be appropriate to conduct SARS-CoV-2 challenge studies even where background risks are (currently) low, so long as the absolute risk to participants remains acceptable in light of relevant assessments (see Criterion 2), especially if conducting such studies in high-incidence settings is infeasible or would undermine the local public health response.

CRITERION 6: PARTICIPANT SELECTION

SARS-COV-2 CHALLENGE STUDY RESEARCHERS SHOULD ENSURE THAT PARTICIPANT SELECTION CRITERIA LIMIT AND MINIMIZE RISK

The safety of participants is a key necessary condition for the ethical acceptability of challenge studies. Participant selection criteria must be designed so that there is a high level of confidence that participation is as safe as possible. Initial studies should thus be limited to young healthy adults, for example, aged 18–30 years. Within these groups, selection criteria might prioritize those who face high background probability of infection (to the extent that this does not reflect background social injustice) because such participants would face less marginal risk and a potential for direct benefit (for example, if participation results in some degree of immunity to SARS-CoV-2, and participants are exposed to infection after completion of the study) (5, 21). Those whose background risk is high as a result of social injustice should be excluded from participation because their inclusion could be considered unethical exploitation (that is, taking advantage of those who have already been wrongly disadvantaged). Any prospective participants who could reasonably be perceived

27. Background risk of infection is a function of the probability of infection and the magnitude of harm related to infection or disease. Here, the key consideration is the background probability of infection. Higher background probability of infection reduces the marginal probability of infection accrued due to study participation (during which the proportion of participants infected is typically 90–100%). The magnitude of harm depends primarily on facts about the participant’s risk of severe disease - and participants who face a higher expected magnitude of harm should be excluded, especially in initial studies (see Criteria 2 and 6).

28. This age range has been selected based on recent estimates (cited here), which were stratified by decade (see section 3 above). It might be appropriate, if or when the safety of challenge in this group has been demonstrated, to consider sequentially broadening selection criteria, including with regard to age ranges (see note below).

29. Such immunity might result from the challenge infection or an experimental vaccine (if the latter turns out to be effective). However, (a) more data are needed to clarify the degree and duration of immunity to SARS-CoV-2 resulting from infection; and (b) the efficacy of an experimental vaccine will be uncertain at the time of study commencement. Thus, such benefits are merely potential, rather than expected, benefits.
to be vulnerable in other ways that would undermine their consent or put them at greater risk (for example, as a result of the mental health strain of inpatient isolation during the study) should also be excluded.

Even with such criteria in place, participants may still face absolute risks or levels of uncertainty related to SARS-CoV-2 infection that might be higher than some other ethically acceptable “non-therapeutic” studies involving risk to healthy volunteers (for example, some phase I drug trials and many well established challenge studies), although still within acceptable upper limits to research risk (see Criterion 2) (5, 17, 18). In addition to other risk minimization strategies, selection criteria should thus be updated promptly in light of emerging evidence that would help to stratify prospective participants further and thus enable selection of those at (even) lower risk. If such data justify confidence or reasonable suspicion that any particular (sub)groups are at significantly heightened risk of serious illness (or death) resulting from infection, then they should be excluded from participation in initial studies.30

Selecting participants who are low risk (for severe disease following infection) prioritizes the safety of participants over the generalizability of results to higher-risk participants (for example, older individuals and those with comorbidities; see Criterion 1). Prioritizing the safety of participants is standard in modern challenge studies and acceptable in so far as studies with low-risk participants nevertheless produce useful results (for example, that would help to identify the most promising vaccine candidates or validate correlates of protection) (5, 38).

Challenge studies have sometimes involved health care workers or self-experimentation by researchers (5, 39), and it has been suggested that participation of such groups would be appropriate for SARS-CoV-2 challenge studies in particular. On the one hand, such individuals (assuming they are young healthy adults) may be appropriate candidates for inclusion, as they already face higher probability of infection or are particularly well informed about the risks of infection (31). On the other hand, (a) such individuals could feel pressured to participate (thereby undermining the voluntariness of informed consent); (b) other potential participants may be just as able to provide informed consent (5, 35, 36, 40); and (c) in some cases, their higher prior probability of infection may not be an ethical reason in favour of inclusion if the additional probability is due to injustice (for example, a lack of reasonable provision of protective equipment). Furthermore, essential workers should not be recruited to challenge studies where this would unduly compromise the pandemic public health response (see Criteria 4 and 5) (33).

CRITERION 7: EXPERT REVIEW

SARS-COV-2 CHALLENGE STUDIES SHOULD BE REVIEWED BY A SPECIALIZED INDEPENDENT COMMITTEE

SARS-CoV-2 challenge studies should be the subject of specialized independent review in addition to or in conjunction with a standard local ethics review, as is the case for some other types of research that may be controversial or involve higher levels of risk and uncertainty (5, 41). In all cases, review procedures should involve high levels of expertise and be conducted rapidly (potentially in parallel) without compromising the stringency of review. There should be regular consultation between investigators and (at a minimum) the local ethics committee, including immediately before and during the conduct of the study, especially in light of new data (for example, regarding risks).

A specialized review committee should include members with relevant scientific expertise and members with research ethics expertise specific to challenge studies. Given the urgency of the current global pandemic, committees with experience in conducting rigorous emergency review

30. Under certain conditions, it may be appropriate to include some groups at higher risk (such as older individuals) in later studies where this would be important to permit the development of interventions for these groups and where similarly useful data regarding higher-risk groups could not be obtained in a lower-risk study population (or other lower-risk study design). Similar approaches have been used in a challenge study for respiratory syncytial virus that has recently been safely conducted with older adults (who face higher risks than younger adults) after initial studies in younger adult participants (see https://clinicaltrials.gov/ct2/show/NCT03919591, accessed 4 May 2020).

31. It is thus fair to select young healthy adults even though they do not represent groups at highest risk of severe disease (see footnote 13). Furthermore, the use of effective vaccines in (large numbers of) low-risk individuals would provide significant indirect protection to others at higher risk (34).
may be well placed to conduct (local or independent) review. In order to improve pandemic preparedness, greater capacity should be built and maintained to permit such review in more locations in future.

Even where a local (that is, institutional) ethics committee has relevant specialized expertise, there should be independent review of initial SARS-CoV-2 challenge studies, as such studies may be particularly controversial and their conduct may have implications beyond the local setting (for example, regarding coordination of research efforts, and global public trust in research; see Criteria 3 and 4). Independent review should ideally be conducted at the national or international level (for example by WHO or another appropriate international agency), in part to reduce the effects of any potential conflicts of interest on the review process.

**CRITERION 8: INFORMED CONSENT**

**SARS-COV-2 CHALLENGE STUDIES MUST INVOLVE RIGOROUS INFORMED CONSENT**

Informed consent processes should be particularly rigorous in SARS-CoV-2 challenge studies because of the heightened potential risks and uncertainties involved (5, 7). Challenge studies routinely incorporate tests of participant understanding during the informed consent process (5). Such tests are particularly important in SARS-CoV-2 challenge studies, and should be based on the best available data regarding risks (and uncertainties) as well as relevant evidence regarding how important and complex information should be conveyed to participants to maximize understanding.

Consent should be revisited throughout the study, as is often the case for other challenge studies. This should occur, for example, when new relevant data (for example, regarding risks) become available after the study has commenced, and immediately prior to challenge with SARS-CoV-2. Consent processes and participant selection criteria (see Criterion 6) should be such that there is virtually no doubt that participants comprehensively understand the potential risks of participation and that consent is voluntary.
REFERENCES


ANNEX 4. DENGUE CASE STUDY

1. BACKGROUND

Dengue is a vector-borne disease caused by four closely related arboviruses. Many dengue infections cause few or no symptoms (the latter are referred to as asymptomatic). However, when a person has been infected with a strain of dengue before, the second infection is more likely to be serious, and severe dengue can be fatal (1). There are no specific effective treatments for dengue, although supportive medical care is effective in reducing the fatality risk of severe dengue.

Only one dengue vaccine has been licensed to date; this vaccine is effective in terms of preventing dengue among people who have been exposed to dengue at least once before (seropositive individuals). However, the vaccination of individuals who haven’t previously been exposed to dengue (seronegative individuals) results in an increased the risk of hospitalization and severe dengue in those who get infected after being vaccinated, which limits its public health applications (2). Dengue controlled human infection studies (CHIS) have been conducted since 1902, and were initially concentrated primarily in endemic areas (3). More recently, two different types of dengue CHIS have been developed in North America, as illustrated below.

2. CASE STUDIES

2.1 CASE STUDY 1: DENGUE INFECTION MODEL

One type of dengue CHIS, an infection model, aims to infect participants without causing significant symptoms of disease (4). For this purpose, US investigators used a genetically modified strain of Dengue virus that had been initially isolated in 1974 (5) and was previously developed as a vaccine (like many other live attenuated vaccines, which involve giving people weakened living pathogens in order to produce immunity but not clinically significant infection). This viral strain consistently produced measurable viral loads in blood, but also commonly caused fatigue, rash, headache, and muscle and joint aches. These effects made it inappropriate to use as a vaccine, but potentially appropriate as a challenge strain. When given to dengue seronegative young healthy adults in the United States, it consistently produced, on average, overall mild dengue infection, enabling the development of a model against which (other) experimental vaccines could be tested for their efficacy at reducing infection by this strain (6). Participants in these studies were closely monitored during their infection and followed up for approximately six months after the study. Although it is referred to as an infection model, this type of CHIS does cause some disease symptoms, though less than the model discussed below.

2.2 CASE STUDY 2: DENGUE DISEASE MODEL

At another research centre in the United States, dengue CHIS have been conducted as a disease model – that is, with the aim of producing (more) symptoms among participants while still ensuring that risks are minimized to acceptable levels (4). One role of such a model is to produce reliable clinical endpoints (such as disease or symptomatic infection) in order to determine vaccine efficacy against such endpoints, rather than against measurements of viral load alone. Dengue fever was the chosen clinical endpoint of the study and was defined as fever for at least 48 hours accompanied by symptoms (headaches, muscle and joint pain, rash) and detection of the virus in blood. This research programme used different strains of dengue virus to the infection model discussed above. Some strains reliably produced dengue disease in participants as defined by the clinical endpoint above. Several participants developed serositis, that is inflammation and fluid in the abdomen or around the heart and lungs, a sign which is associated with more severe dengue infections, but did not develop other symptoms of severe disease related to these abnormalities and recovered without specific treatment.
3. EXAMPLES OF KEY ETHICAL CONSIDERATIONS

3.1 BENEFITS
The currently licensed dengue vaccine has significant limitations, and thus one potential public health benefit of continued dengue CHIS is the testing of second-generation vaccines (7). Both the dengue models above also have the potential to provide important information about aspects of dengue infection, disease, and immunity. Some scientifically useful results regarding dengue disease have been unexpected (for example, the finding of asymptomatic serositis in several participants), reflecting prior uncertainty about the pathogenesis of dengue (8).

Recent dengue CHIS have enrolled only seronegative individuals, because experiencing a first infection during CHIS participation carries relatively low risks. However, this might limit the generalizability of findings from dengue CHIS (for example, regarding vaccine efficacy) to second infections, which are the most likely to be severe and therefore the largest contributors to the burden of dengue disease. Under certain conditions, exposing seropositive individuals in a dengue CHIS might be associated with relevant public health benefits, however as discussed below, risks would need to be rigorously minimized – especially as there are no specific treatments for dengue.

3.2 RISKS TO PARTICIPANTS AND THIRD PARTIES
A relatively unique risk of dengue CHIS participation is the risk of second dengue infection. If participants are infected with dengue for the first time during the study, they may face higher risks of dengue infection if they are subsequently exposed in an endemic area (9). Participants are counselled about this risk during the consent process. Moreover, as discussed above, the currently licensed dengue vaccine, if given to seronegative individuals who are subsequently infected, is associated with vaccine-enhanced disease – that is, a higher risk of severe disease when infected after vaccination (10,11). This could occur with future vaccines for dengue and/or other pathogens and represents an important risk (or uncertainty) regarding vaccine trials in general. On the one hand, vaccine-related disease enhancement could lead to unexpectedly greater harms in a vaccine CHIS. This suggests that other risk minimization strategies, including close monitoring of participants, must be especially comprehensive where there is any likelihood of this occurring. On the other hand, vaccine-enhanced disease could be even more problematic in vaccine field trials than in challenge studies, because field trials typically involve tens of thousands more participants than challenge studies, and so it is not possible to monitor participants as closely as in CHIS.
REFERENCES


1. BACKGROUND

Influenza is a globally pervasive, seasonally epidemic disease caused by influenza viruses A and B, and influenza pandemics are key threats to global public health. Although influenza primarily affects the respiratory tract, causing fever and coughs among other symptoms, influenza disease can also damage a range of organ systems. Current pharmaceutical interventions include moderately effective vaccines and antiviral treatments, although these may be less effective in some higher risk groups, including older adults (1). Influenza controlled human infection studies (CHIS) have been conducted since 1937 (2), and have been used to investigate vaccines since the 1940s (3), and antiviral treatments since the 1960s (4). These studies have also been used to determine immune correlates of protection (5, 6) – that is, blood tests measuring immune responses (to previous infection or to vaccination) that predict whether a person will be protected from future infection.

Influenza CHIS are generally safe and rarely cause severe symptoms, although controlled influenza infection does commonly lead to temporary reduced lung function, changes on lung imaging suggestive of chest infection, liver test derangement, and moderate clinical symptoms (7,8). In a review of CHIS enrolling around 2500 people, one participant developed a serious heart condition which later resolved; this participant had a prior history of cardiac disease and greater care is now taken to exclude such patients from influenza CHIS (7). Given the potential for participants to transmit infection to other people in the community, influenza CHIS are generally conducted as inpatient studies in facilities with appropriate infection control and biosafety measures.

2. CASE STUDY

A 2018 influenza CHIS in the United States recruited 74 healthy young adult volunteers to investigate immune correlates of protection (5). Prospective participants were carefully screened over three months prior to study participation and tested for any respiratory virus infection just before beginning the study (because the presence of more than one infection during the CHIS could increase risks to participants and/or undermine the validity of results). The participants were isolated for the duration of their infection during the study to reduce the risk of transmitting the infection to others and followed up for at least two months after the end of the research.

This study sought to validate data from the 1970s regarding one type of immune correlate of protection: hemagglutinin inhibition (HAI) titres. The HAI levels defined in older CHIS have since been widely used in public health practice and vaccine research worldwide. The 2018 study confirmed previous data regarding HAI titres being correlated with a reduced probability of detecting influenza virus in volunteers (an indicator of the likelihood of potential transmission to others), but not with a reduced risk of developing symptoms. The study also produced novel results regarding a different correlate of protection, neuraminidase inhibition (NAI) titres; the findings suggested that NAI titres might be an even better correlate of protection than HAI titres across a range of measures of influenza disease.
3. EXAMPLES OF KEY ETHICAL CONSIDERATIONS

3.1 BENEFITS
Influenza CHIS have been used to develop several vaccines and therapeutics, and there has recently been greater interest in conducting such studies with multiple potential aims relevant to public health (7, 9). Identifying immune correlates of protection can be important for public health responses to influenza and other infectious diseases because these measures can be used to determine, for example, whether a vaccine is likely to be effective in a given person (or population) and how likely it is that a person who has previously been infected or vaccinated is likely to be (re)infected with a given strain of influenza in the future. Identifying more accurate correlates of protection can therefore be associated with large potential public health benefits, for example by informing policies about the conditions under which people should be (re)vaccinated against influenza.

3.2 RISKS TO PARTICIPANTS
Influenza often causes relatively mild disease, but both influenza A and B viruses are in rare cases associated with serious disease even in apparently healthy young adults, as well as with rare lasting harms post-infection, including Guillain-Barré syndrome (10). Key CHIS risk minimization strategies include careful selection of participants, as well as close monitoring and – if necessary – treatment during a study; however, current influenza antivirals provide imperfect protection against severe disease.

3.3 PARTICIPANT AND STRAIN SELECTION
One limitation of influenza vaccines is that they are less effective in older adults, in whom a large proportion of the burden of influenza disease occurs. This might also be a limitation of the generalizability of current influenza CHIS designs, which do not include older adults – in part because including such participants would involve higher risks. However, a recent CHIS with respiratory syncytial virus (RSV) – which, like influenza, causes more severe disease in older adults (as well as in young children) – has been conducted safely in adults aged 60–75 years (11).

The selection of an appropriate strain to use in an influenza vaccine CHIS may also have implications regarding risks to participants as well as the generalizability of results to influenza epidemics – in part because circulating strains of influenza change from year to year.


1. BACKGROUND

Schistosomiasis is a parasitic neglected tropical disease caused by flatworms called schistosomes, that are transmitted to humans via freshwater snails. The disease affects over 200 million people worldwide, from Latin America, to Northern and sub-Saharan Africa, the Eastern Mediterranean, and parts of Asia. The majority of disease burden occurs in sub-Saharan Africa, and the epidemiology of schistosomiasis is expected to evolve with climate change (1). Short term schistosomiasis infection can cause significant acute symptoms (such as fever, headache, rash, and itch) but usually results in no direct lasting harm. In contrast, longer term infection causes significant morbidity and, in some cases, permanently affects the functions of multiple vital organs, which is the result of deposition of schistosome eggs in tissues. Highly effective anti-parasitic treatments are available for schistosomiasis, and symptoms of the infection can also be treated with anti-inflammatory medications. As for many neglected tropical diseases, there is no vaccine for schistosomiasis. Until recently, controlled human intervention studies (CHIS) had never been performed for this pathogen.

2. CASE STUDY

A research group in the Netherlands recently completed the first schistosomiasis CHIS, involving 17 young healthy volunteers in a dose escalation study to determine a tolerable dose of challenge infection that would also produce reliable results (2). The challenge parasites were only of the male sex, and thus could not produce any eggs. They were introduced via the skin, where they caused a local rash, and several volunteers experienced potential symptoms of clinical acute schistosomiasis disease. In five volunteers, the symptoms were classed as severe, and in one case exposed to the highest dose tested, significant symptoms persisted for six weeks (2). The more severe symptoms were concentrated among the volunteers who received the highest dose of parasites; the authors thus concluded that a lower dose (which still produced reliable results) would be more appropriate to use for future studies (2). No serious adverse events occurred, and all challenge infections were successfully treated as per the study protocol. With this first in-human dose escalation study completed in a non-endemic area, researchers are considering conducting further schistosomiasis CHIS in endemic areas, such as in Uganda, where stakeholder engagement and local risk assessments have recently commenced (3, 4).
3. EXAMPLES OF KEY ETHICAL CONSIDERATIONS

3.1 THIRD-PARTY RISK
Schistosomiasis CHIS to date have been carefully designed to minimize third-party risks of transmission, which may be even more important where such studies are conducted in endemic or potentially endemic areas (3). In particular, because the transmission of schistosomiasis requires the production of eggs as part of the reproductive cycle involving both female and male mature parasites, researchers have taken care to challenge volunteers only with male parasites (5). This risk reduction approach requires careful production of the challenge strain and volunteers who are not likely to be infected with female parasites from another source. Using only male parasites results in no reproduction of parasites in the volunteer (reducing the risk of chronic infection) as well as no eggs being produced, thus preventing transmission of the challenge strain to third parties.

3.2 UNCERTAINTY
Schistosomiasis has been recognized as a distinct cause of disease for over 100 years. Despite being a neglected tropical disease, the pathogenesis and transmission of schistosomiasis are considered to be relatively well understood. However, CHIS research has produced unexpected findings regarding acute schistosomiasis symptoms. It was previously thought that acute schistosomiasis syndrome was primarily caused by an immune reaction to certain phases of the schistosome parasite life-cycle, especially egg production. However, several healthy European volunteers in the schistosomiasis CHIS experienced potential symptoms of acute schistosomiasis, including one case of prolonged fever and headaches (2, 6). Further testing demonstrated that the (male only) challenge strain of schistosomes had not reproduced and eggs were not detected (6). This study therefore resulted in improved scientific knowledge regarding the pathophysiology of acute schistosomiasis. Such outcomes also reflect uncertainty regarding the frequency of adverse events in novel CHIS models, and the case illustrates that such uncertainties are not unique to novel pathogens, which may have implication for CHIS consent processes more generally.
REFERENCES


1. BACKGROUND

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, is currently associated with the largest mortality burden of any infectious disease, with well over one million global deaths per year and around 10 million active infections. Furthermore, approximately one quarter of the global population is thought to be asymptptomatically infected with latent (inactive) TB. TB is a highly transmissible infection; it has been estimated that each active person with active lung infection might generate, on average, around 14–45 secondary cases (1). The current TB vaccine, known as BCG for bacillus Calmette-Guérin, is 100 years old, and is derived from a related organism, *Mycobacterium bovis*. The BCG vaccine is protective against extrapulmonary forms of TB in children but is less effective when administered to adults.

Although treatments are highly effective against sensitive strains of tuberculosis, treatment requires four to six months of multi-drug therapy, which involves significant risks of side effects as well as the risk of drug-resistant TB strains emerging if therapy is incomplete. Drug-resistant TB is a key global health threat. Although newer drugs have recently become available for resistant strains, multidrug-resistant and extensively drug-resistant TB is difficult and expensive to treat, and sometimes impossible to cure. To date, there have been no controlled human infection studies (CHIS) involving *M. tuberculosis*; however, CHIS are conducted with BCG, which is part of the *M. tuberculosis* complex (a genetically related group of mycobacterium species that can cause TB in humans) (2, 3).

2. CASE STUDY

In 2019, 106 healthy young adults were recruited for a CHIS with BCG in South Africa. BCG is usually given as a vaccine for public health purposes via injection into the skin, and previous CHIS have administered BCG via the skin to test other (experimental) vaccines (4). This study instead administered BCG directly to the lungs of volunteers, via a bronchoscopy; participants in the control arm had a bronchoscopy without BCG. This was an early trial to assess the safety and feasibility of such an approach, but also involved measuring immune responses to BCG. Study participants included people who had been exposed to a case of TB in their household, as well as people who had previously been treated for TB. In people infected with TB, BCG vaccination (of the skin) can, rarely, cause a severe local reaction (Koch’s phenomenon), so there was a risk that giving BCG via the lungs to such individuals might cause a similar reaction. The first five participants were therefore monitored particularly closely; no such reactions occurred. Overall, the rate of adverse events was no higher among people receiving BCG lung challenge than those undergoing placebo bronchoscopy (although given the relatively small sample size, this would not rule out rare adverse events) (5, 6).
3. EXAMPLES OF KEY ETHICAL CONSIDERATIONS

3.1 BENEFITS
Despite centuries of clinical experience and research, many key aspects of TB infection, disease, and immunity, remain poorly understood. Moreover, the one available vaccine is only partially effective, and increasing rates of drug-resistant TB make developing new interventions particularly important. It is therefore conceivable that CHIS, whether with BCG or another strain of mycobacteria, could play an important role in improving scientific knowledge regarding TB, investigating the immunological effects of BCG lung challenge, and ultimately testing novel interventions. Field efficacy studies of TB vaccines generally have to be very large and conducted over many years, so using CHIS to select the most promising vaccines to test in such studies has been advocated. Given the very substantial annual global burden of disease and death attributable to tuberculosis, accelerating the development of effective new vaccines, for example, might result in large global health benefits. Challenge with BCG (whether via skin or lung) faces limitations regarding generalizability, but currently represent the only human CHIS strain relevant to TB.

3.2 RISKS TO PARTICIPANTS AND THIRD PARTIES
Exposure to BCG carries few risks apart from scarring (if given via the skin) and Koch’s phenomenon (see above). It may also be associated with benefits, because the challenge strain is also a licensed vaccine, although its benefits in adults are lower than those in children (7). In rare cases, people exposed to BCG can develop disseminated disease from the vaccine strain, which requires significant antibiotic treatment (8, 9). This risk can be reduced by excluding participants with immune system deficiencies, although it cannot be ruled out altogether.

There have been no proposed CHIS with wild-type tuberculosis (M. tuberculosis) in the modern era, as this would involve significant risks to participants and third parties. Although such risks could be controlled to a large degree if it could be ensured that participants completed treatment and were isolated until testing demonstrated resolution of any acute infection, the required multi-drug therapy itself also carries risks. Therefore, despite the substantial benefits that TB CHIS could plausibly be associated with, it is currently unclear whether the risks could ever be justifiable. If relevant attenuated strains, or safe and simpler curative treatments of TB were to be developed in future, such risks could potentially be reduced.
REFERENCES


1. BACKGROUND

Typhoid is a bacterial infection and the major cause of enteric fever, which is associated with a significant global burden of disease, particularly in low- and middle-income countries (LMIC). Deliberate human infection with *Salmonella Typhi* to cause typhoid has been conducted for over 100 years (1–4). *Salmonella Typhi* is on the WHO priority list of antibiotic-resistant pathogens due to its increasing resistance to available antibiotic treatments. Recent controlled human infection studies (CHIS) performed in the United Kingdom have included pivotal research resulting in the pre-qualification of a new typhoid vaccine candidate by WHO, which was subsequently shown to be efficacious in field trials performed in endemic populations (5, 6). As the burden of typhoid infection is concentrated in LMIC, it has also been suggested that typhoid CHIS could be performed in endemic settings to produce data more useful and relevant to those populations (7, 8). The advances made with the typhoid CHIS model have led to the development of CHIS with related pathogens, including *Salmonella Paratyphi* A, the predominant cause of paratyphoid infection, and mixed infection models (9, 10).

2. CASE STUDY

The typhoid CHIS research programme in the United Kingdom started 10 years ago (11). Multiple studies have been conducted using a well-characterized strain of *Salmonella Typhi* bacteria originally obtained from a patient in 1958 (12). In the studies, participants are followed up as outpatients, with close monitoring of those who develop symptoms. In addition to recruiting healthy adults, participant selection criteria exclude those with gallbladder disease (which is a risk factor for chronic carriage of typhoid) and/or those who work in occupations that could increase third-party risk (food handling, healthcare, etc.). Participants are also requested to inform close contacts of their involvement in the study. All participants are provided with curative treatment if they develop symptoms or at the end of the study. Proof of cure is obtained on at least two occasions after treatment, in accordance with national guidance in the United Kingdom (12). Participants are paid for taking part based on the burdens of participation, including large time commitments, and in line with research ethics norms.
3. EXAMPLES OF KEY ETHICAL CONSIDERATIONS

3.1 BENEFITS
Among other scientific benefits, typhoid CHIS have played a key role in the development of vaccine candidates that will likely produce substantial public health benefits, and helped to rule out less promising candidates (13). Although the United Kingdom CHIS were conducted in a non-endemic population, results regarding vaccine efficacy were shown to be generalizable to endemic populations, in Nepal for example. The programme has resulted in significant advances in understanding about the biology, transmission, treatment and prevention of typhoid infection, in addition to the development of accurate tools to measure immune responses and characterize and diagnose infection (9, 10).

3.2 RISKS TO PARTICIPANTS AND THIRD PARTIES
Although typhoid CHIS use only treatment-sensitive strains, participants still face some risks, and so multiple risk minimization strategies are in place. On the one hand, outpatient study designs make participation less burdensome for volunteers insofar as they are not required to be isolated at the study facility and can largely continue their normal daily activities. On the other hand, this necessitates vigilant monitoring of participants when symptoms develop or laboratory tests confirm the presence of typhoid infection. Typhoid infection is also in rare cases associated with lasting effects, including post-infectious irritable bowel syndrome and post-infectious arthritis, and some participants may therefore require longer-term follow-up (14). The most severe complications of typhoid infection include perforation of the bowel and internal bleeding. However, these complications occur following several weeks of illness, and so in the CHIS the risk is mitigated by the close monitoring performed (including daily symptom and temperature measurement) and treatment of all participants by 14 days after challenge.

Risks to third parties are low where participants have access to adequate sanitation, as is the case with United Kingdom typhoid CHIS. Specific additional measures include the provision of hand-washing instruction and assessment, soap, disposable gloves and paper towels. These risks are reduced still further by close monitoring and treatment of participants, as well as via the exclusion criteria described above. Further, the studies are coordinated with local and national public health agencies, including sharing the genetic sequences of challenge strains (15). In the unlikely event of a local typhoid outbreak, this would enable testing to determine whether any community infections were caused by spread of the challenge strain from study participants to others. Third-party risks of typhoid CHIS might be higher in settings with less access to sanitation. However, CHIS with other enteric pathogens such as cholera and Shigella (which, like typhoid, spread via the faecal-oral route) have been conducted on an inpatient basis in a specialized facility in Thailand which involves special treatment of sewage to reduce such risks; such an approach could potentially be replicated in other settings (16, 17).
1. BACKGROUND

Zika virus is a mosquito-borne flavivirus, first identified in humans in 1952 (1). The vast majority of Zika infections in adults and children are asymptomatic or associated with mild symptoms of short duration. From the 1960s to 1980s, Zika infections in humans were only identified sporadically in Africa and Asia, with the first recorded large outbreak reported in the Federated States of Micronesia in 2007. In 2015, Brazil reported a major outbreak of Zika, associated with severe neurological birth defects (collectively termed congenital Zika syndrome (CZS)) and complications during pregnancy, including miscarriage and preterm birth. Additional associations between Zika infection and severe neurological complications in adults and children were identified, including Guillain-Barré syndrome. Outbreaks and evidence of transmission soon appeared throughout the Americas, Africa, and other regions of the world. In January 2016 WHO declared that the rapid geographic spread of Zika and its recent association with clusters of neurological disorders, constituted a Public Health Emergency of International Concern (2).

The association of Zika infection with clusters of neurological disorders prompted a dramatic expansion of research into what had previously been an under-researched virus. Vaccine development was identified as a priority, and by 2017 over 40 vaccine candidates were being evaluated in pre-clinical studies, with several progressing to Phase I and II trials (3). However, by mid-2017, Zika incidence levels had dropped to such low levels that field trials of vaccine efficacy were infeasible (4, 5). Despite this decline in incidence, the development of effective Zika vaccines has been identified as a critical global health need, given the potential for future outbreaks and the lack of effective treatments (4). However, forecasting the location, size and duration of future Zika outbreaks remains very complex and challenging, hampering the capacity to effectively conduct field trials of vaccine efficacy (6).

2. CASE STUDY

In 2016, a proposal to conduct a controlled human infection study (CHIS) to investigate a Zika virus vaccine was developed and submitted to the United States National Institute of Allergy and Infectious Diseases. The proposal sought to gain understanding of early stages of Zika infection and provide preliminary evidence about the protective efficacy of experimental Zika vaccines in order to inform vaccine development pathways and accelerate licensure. The trial was to be conducted in the United States, with healthy volunteers, and would administer low doses of Zika virus and be conducted on an inpatient basis during the 10- to 14-day period it typically takes to clear Zika infection.

To complement ethical review of the protocol, the United States National Institute of Allergy and Infectious Diseases and the Walter Reed Army Institute of Research established an independent interdisciplinary expert panel to address the question of whether a Zika CHIS could be ethically justified and if so, under what conditions. In February 2017, the panel's report was released and concluded that although Zika CHIS could be ethically conducted, it would be premature to conduct them at that time (7).
3. EXAMPLES OF KEY ETHICAL CONSIDERATIONS

3.1 SOCIAL AND SCIENTIFIC VALUE
One of two key considerations informing the expert panel’s conclusion that a Zika CHIS would be premature at the beginning of 2017 was the perceived lack of evidence that a CHIS was needed in order to accelerate vaccine development pathways. During the deliberations of the panel there was unprecedented and substantial research interest in Zika, including multiple clinical trials conducted with vaccine candidates. During the course of 2017, however, Zika transmission levels dropped significantly, rendering field trials of Zika vaccine efficacy no longer feasible and leading to some vaccine developers halting research (4, 5).

Low levels of ongoing disease transmission are not the only challenge for traditional field trials of Zika vaccine efficacy. Current evidence suggests that even asymptomatic maternal infections can cause CSZ, requiring vaccines to not just prevent Zika disease, but also prevent infection with Zika (sterilizing immunity) if they are to effectively prevent vertical transmission of Zika during pregnancy (4, 8). Large-scale efficacy trials of Zika vaccine candidates are consequently made more complex by the need to detect all Zika infections, of which the vast majority are asymptomatic (6). These and other challenges in Zika vaccine development pathways have led to increased recognition of the social and scientific value of Zika CHIS following the epidemic. In particular, Zika CHIS have been recognized as potentially offering the only currently feasible opportunity to evaluate and demonstrate the efficacy of Zika vaccine candidates and support licensure applications (4, 9).

3.2 RISKS TO THIRD PARTIES
A second key consideration informing the expert panel’s conclusion that a Zika controlled human infection study would be premature in 2017 was the concern that the risks of research for third parties could not be adequately identified, managed and minimized (7). In addition to being transmitted by mosquitoes, Zika virus can also be sexually transmitted and vertically transmitted during pregnancy. Effective infection control is consequently critical to ensure that third parties do not face the risk of infection – some degree of CSZ, for example, is estimated to occur in approximately one in seven infants born to mothers infected with Zika during pregnancy (4). At the time of the panel’s reflections, there were substantial uncertainties about the amount of time that patients infected with Zika could transmit that infection. Upper estimates of sexual transmission were six months (10, 11), raising questions about the feasibility of effectively implementing precautions to prevent transmission over that length of time.

Ongoing research into transmission of Zika has demonstrated that in patients with low viral loads there is very limited evidence of infectious virus persisting in semen for more than 30 days, and that transmission from infected males is much more common than from infected females (12). Such findings have informed the development of risk management strategies for third parties in a novel Zika CHIS protocol, which would restrict enrolment to healthy female volunteers. To be eligible volunteers would need to be under the age of 55 years, not pregnant, and committed to using highly reliable birth control for at least eight weeks post inoculation.
REFERENCES


1. BACKGROUND

Malaria is a parasitic infection associated with an enormous global burden of disease, particularly in low- and middle-income countries (LMIC), and infection studies with malaria have been conducted for over 100 years (1, 2). Among other public health benefits, early studies were able to prove that malaria was transmitted by mosquitoes, as a consequence of which vector control methods have played an important role in reducing the malaria disease burden. Malaria controlled human infection studies (CHIS) have been used to investigate vaccines and treatments, as well as to learn about the pathophysiology of human malaria infection and immune responses to malaria parasites (1). Such studies have recently been conducted in a range of settings, including multiple research centres in sub-Saharan Africa and one in Colombia (1). These research programmes are increasingly coordinated, and standardized methods have been adopted across multiple centres where feasible (3, 4). Recent controlled human malaria infection studies, as they are often called, have tested multiple vaccines (including the RTS,S vaccine) (5) and treatments (6, 7); studies in endemic areas also generate unique additional scientific knowledge – for example regarding naturally-acquired immunity (8).

2. CASE STUDIES

2.1 CASE STUDY 1: FALCIPARUM MALARIA STUDIES IN KENYA

Falciparum malaria CHIS have been conducted in Kenya since 2014 (9, 10), along with several other African centres in United Republic of Tanzania, Gabon, and Equatorial Guinea (11–13). In collaboration with these and other international partners, the Kenyan group uses a well-characterized laboratory strain of falciparum malaria, believed to be of African origin, which was obtained from a patient in the Netherlands in 1978 (14). Participants are injected with parasites and generally isolated while actively infected with malaria. Initial Kenyan CHIS were primarily focused on model development but other potential endpoints include generating knowledge regarding naturally-acquired immunity and/or testing vaccine efficacy (8, 5). Severe symptoms were unusually common in the first study (16), but are generally rare in challenges studies conducted with participants previously exposed to malaria (17). Participants receive payment for participation in light of the burdens of participation, including the amount of time needed to participate in the study, and in line with local wages and research ethics norms. The Kenyan research programme is closely linked with longstanding local institutional community engagement activities, and study designs have been revised in light of feedback from the community and volunteers (9, 18).

2.2 CASE STUDY 2: VIVAX MALARIA STUDIES IN COLOMBIA

A research group in Cali, Colombia, has been conducting a programme of vivax malaria CHIS since 2009 (19–22). The study centre is in a high-altitude location with no local mosquitoes, but malaria parasites are acquired from infected donors in endemic parts of the country. Participants are exposed to infection via standardized mosquito bite using wild-type parasites which are maintained in a laboratory setting. Participants are not isolated, but they are requested not to visit endemic areas during the study. The researchers frequently conduct multiple secondary scientific analyses on samples from these CHIS (23) and have also investigated vaccine efficacy (19). Severe symptoms are extremely rare. Participants receive reimbursement for costs but no significant payment for participation, in line with local research ethics and community norms (24). Examples of Key Ethical Considerations
3. EXAMPLES OF KEY ETHICAL CONSIDERATIONS

3.1 BENEFITS
Malaria CHIS have played a pivotal role in advancing scientific understanding of the disease and in testing vaccines and treatments. The above research programmes in endemic areas provide opportunities for additional scientific and public health benefits, including the testing of interventions in study populations that are similar to those most affected by malaria. It is hoped that studies of naturally acquired immunity may inform the design of future vaccines. These programmes have also helped to build and/or consolidate local and regional capacity for research and community engagement.

3.2 GENERALIZABILITY
As in many types of clinical research, there is an inherent trade-off between maximizing the generalizability of research findings and minimizing research risks (and/or other important study design considerations). The above case studies illustrate how research design can influence generalizability in several ways. Conducting malaria CHIS in endemic settings may help to improve the generalizability of results to similar populations. However, malaria CHIS have only been conducted in adults and results (such as those regarding vaccine efficacy) may not always be fully generalizable to children, who bear the majority of the global burden of malaria. With regards to the selection of a challenge strain, using a well-characterized laboratory strain can help to standardize research designs and potentially reduce certain risks; however, results from CHIS with local wild-type strains may be more generalizable to malaria infections occurring in the community (17).

3.3 RISKS TO PARTICIPANTS AND THIRD PARTIES.
Although malaria is a highly treatable infection, malaria challenge studies involve risks and require participants to be closely monitored to ensure that they do not develop serious clinical manifestations of disease. This sometimes requires participants to remain at the study centre for long periods of time, especially if they might have difficulty returning to the centre or accessing healthcare in a timely manner outside of the study. However, outpatient malaria challenge studies have been conducted safely in multiple countries, and the risks of severe disease are generally lower for vivax than for falciparum malaria, and also lower for participants from endemic settings than those from non-endemic settings.

In most malaria CHIS it is unlikely that malaria could be transmitted from participants to others in the community because of the short duration of infection and the fact that transmissible forms of malaria parasites take time to develop and are not present in the first few days of infection. Further measures to reduce third party risk include conducting studies in non-endemic settings where few or no mosquitoes are present (including the cities of Cali in Colombia and Nairobi in Kenya, for example), isolating participants for at least part of the duration of their infection, and treating all participants whether they develop symptoms or not.

3.4 COMMUNITY ENGAGEMENT
The Kenyan research programme has had a strong element of community engagement, and the group have published papers regarding lessons learned from conducting CHIS and associated community engagement activities (9, 18). This could be considered a model of best practice because the engagement activities informed research design, and the dissemination of lessons learned (along with scientific results) can help to standardize and improve research programmes at other centres (24).
REFERENCES

ANNEX 11. ROTAVIRUS CASE STUDY

1. BACKGROUND

Rotavirus infection is the leading global cause of diarrhoea-associated morbidity and mortality among children under the age of five years old (1). Live-attenuated rotavirus oral vaccines prequalified by WHO include Rotarix (GlaxoSmithKline), RotaTeq (Merck) and Rotavac (Bharat Biotech). Two of these (Rotarix and RotaTeq) have been evaluated in large trials and licensed in over 100 countries (2, 3). However, they are more effective in high-income settings, where they prevent over 80% of cases of severe rotavirus diarrhoea, than in low- and middle-income countries (LMIC), where they prevent 35–63% cases (3).

In 2012 Rotarix was incorporated into the Zambian expanded programme on immunization, where it has an effectiveness ranging from 26% to 56% (4). Research demonstrates that in Zambia, as in other LMICs, multiple contextual factors limit Rotarix efficacy (5). These include gastrointestinal factors that can interfere with vaccine uptake, including stomach acid, ingestion of breast milk containing high titres of maternal antibodies and a high prevalence of baseline gastrointestinal dysfunction. Immune responses to the vaccine can further be impaired by simultaneous infections, past exposure to disease, competing vaccines, malnutrition, and genetic predisposition. Research into the efficacy of rotavirus vaccines is additionally hampered by a lack of correlates of protection (measurable parameters to confirm that the immunization has provided effective protection against rotavirus disease).

In response to the lower efficacy of current rotavirus vaccines in LMICs, development of a novel trivalent rotavirus subunit vaccine (P2-VP8) is underway. This vaccine is currently being studied in Phase III efficacy trials in multiple LMICs, including Zambia (6). It is hoped that this vaccine, as it is administered by injection, will bypass the gastrointestinal factors limiting efficacy in oral vaccines. Initial results are expected to be available in 2025, six years after the trials started.

2. CASE STUDY

In 2020, Zambian researchers commenced a paediatric CHIS which aimed to evaluate the efficacy of vaccine protection against rotavirus infection, and investigate correlates of protection following vaccination (7). The design and review of the CHIS was informed by a two year programme of engagement with stakeholders about ethical and regulatory frameworks for undertaking CHIS in Zambia (8, 9).

To prepare for the CHIS, researchers undertook an exploratory open label study of infants receiving two standard doses of Rotarix at six and ten weeks of age as part of the national programme of immunization (10). As a live-attenuated vaccine, Rotarix typically causes mild symptoms of rotavirus disease while increasing the ability of paediatric immune systems to effectively identify and respond to future rotavirus infections. In the exploratory study the first vaccine dose was considered to be the primary vaccination, and the second dose was evaluated to determine its potential role as an infectious agent providing insights into correlates of protection and vaccine effectiveness. The study results supported the potential usefulness of Rotarix vaccine as a challenge agent in CHIS.
In the CHIS participants are recruited at six weeks of age and randomised into one of four study arms where the initial vaccines are administered with the aim of promoting immunity to rotavirus disease. In the control arm, participants receive two doses of Rotarix in accordance with the national programme of immunization. In the intervention arms participants receive doses of P2-VP8*, or a combination of both P2-VP8* and Rotarix (7). Following these immunizations, at 18 weeks of age, all study participants receive an additional standard dose of Rotarix (see Table 1). This final dose is given with the aim of enabling researchers to examine how effectively participants' immune systems respond to controlled exposure to a live-attenuated strain of rotavirus, given the immunizations received to date. An additional aim of the research is to explore the means of identifying and measuring correlates of protection against a live-attenuated strain of rotavirus from blood, saliva and stool samples.

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3. EXAMPLES OF KEY ETHICAL CONSIDERATIONS

3.1 JUSTIFICATION
The inclusion of children in healthcare research can be important to ensure that evidence can be generated about how best to address their health needs. A key ethical requirement in such research is that its anticipated value in terms of generating knowledge to address children's health needs provides a compelling justification for it to be undertaken. Given the very significant health burdens associated with rotavirus diarrhoea in LMICs, the development of novel vaccines with increased efficacy and exploring dosing schedules which may improve the performance of existing vaccines are paediatric research priorities. Conducting Phase III trials of novel rotavirus vaccines can be very expensive and time consuming, as very large samples sizes are needed to compare their efficacy against existing vaccines in national programmes of immunization (including Rotarix). In this context CHIS have the potential to address important research questions about correlates of protection that can be more difficult to study in Phase III trials. This CHIS additionally requires a significantly smaller sample size to address its research questions (hundreds of participants rather than the thousands needed in Phase III trials of comparative efficacy) and can be completed more rapidly. Results from the CHIS about the potential efficacy of the vaccination schedules in each of the study arms, as measured by the response to a dose of Rotarix at 18 weeks of age, may play a key role in the prioritisation of future research to inform rotavirus vaccination programmes. Defining correlates of protection can also facilitate studies to develop new vaccines in future.
3.2 RISKS AND BENEFITS
Research ethics norms and standards set out additional protections required when recruiting participants who lack decision-making capacity, including restrictions on acceptable risk and burden profiles. In this CHIS, researchers’ approaches to managing risks and ensuring that they are minimised within acceptable thresholds include the use of Rotarix, which has been extensively studied and licensed for use in paediatric populations, as the infectious agent. The safety and immunogenicity of the second vaccine in the study – P2-VP8 – have also been carefully evaluated prior to advancing it to efficacy testing in large-scale Phase III trials (11). With the aim of promoting immunity to rotavirus disease, all CHIS participants will receive either the two doses of Rotarix in the current national programme of immunization, or the schedule of three P2-VP8 vaccinations currently being evaluated in a Phase III efficacy trial (6), in addition to further study vaccinations (see Table 1). Additional measures to reduce risks include the close monitoring and follow up of research participants over five months by the expert research team.

An aim of this CHIS is to evaluate vaccine combinations and schedules which have the potential to improve the prevention of severe rotavirus diarrhoea in LMICs. Participants may potentially receive a direct benefit from taking part in the CHIS, by receiving a combination of vaccines that provides better protection from rotavirus than the current national immunization schedule.
REFERENCES


ANNEX 12. SCOPING REVIEW OF ENGAGEMENT ABOUT CONTROLLED HUMAN INFECTION STUDIES

1. ENGAGEMENT STUDIES IDENTIFIED, SETTINGS AND INFECTION MODELS

A scoping review of CHIS engagement activities was undertaken in July 2021 to complement the discussion about engagement in Section 9 of the guidance. In total, the search identified nine eligible studies that reported outcomes for workshops and engagement meetings (1–9), which are summarized in Table 1. The workshops and meetings took place across eight countries, Gabon (1), India (2), Kenya (3), Malawi (4), Uganda (5), United Kingdom (6, 7), Viet Nam (8), and Zambia (9). The main infection models that were addressed included malaria, schistosomiasis, typhoid, chikungunya, dengue, shigella, influenza, and hookworm.

2. STAKEHOLDERS

The engagement events targeted a wide range of stakeholders. The choice of stakeholders to engage was based on their roles or potential roles in the conduct of the study including potential volunteers and sites, reviewing and approving bodies, administrative and regulatory authorization, monitoring of study, previous experiences of CHIS, potential for third party infection. Stakeholders engaged included actual and potential study participants, researchers, ethics committees, national regulatory authorities, Community Advisory Board (CAB) members, administrative authorities, senior members of government, health professionals, journalists, lawyers and members of the public.

3. AIMS, CONTENT AND OUTCOME OF THE ENGAGEMENT ACTIVITIES

Table 1 summarizes the types of stakeholders who were engaged, and the aims and outcomes of the engagement activities reported across the eight studies. A common objective across the studies was the identification of potential barriers or challenges towards the establishment of future specific CHIS models and potential approaches to addressing them. One of the papers (3) was a case study of lessons learnt following the implementation of a CHIS in Kenya.

The United Kingdom meeting focused on five main areas, including regulatory and ethical implications, and methodological considerations of a controlled human influenza virus infection model (CHIVIM) (7, 8). The Indian meeting developed questions to capture the legal, social, and infrastructural issues specific to the three CHIS scenarios (malaria, typhoid and chikun-
The Zambian workshop established small specialized groups (consisting of regulators, ethicists, community engagement and scientists) to discuss questions around methodological issues, and multidisciplinary teams to discuss issues around risks and burdens for participants, benefits of CHIS and participant safety (9). Workshop attendees for the Viet Nam study deliberated on predefined questions around public engagement, reimbursement and consent; the possibility of implementing dengue/shigella CHIS and the main ethical issues to consider, including populations to include/exclude (8). For the Kenyan study (3), the main areas addressed in various consultation and sensitization were the role of the Kenya Medical Research Institute (the research institute and parastatal that undertook the study) and details about the proposed study. Additionally, feedback sessions with the volunteers and academics at the University of Nairobi (the site of the study) also included discussions on challenges that were encountered, lessons learnt and implications for future CHIS.

4. EXPERIENCE, SUCCESS AND LEARNINGS

All except one of the reviewed studies focused on implementation of potential CHIS, a single study reported on lessons learnt from implementing a malaria CHIS in Nairobi, Kenya (3). The Kenyan study reported that volunteer information sheets of future studies would be updated to address questions that were raised at community sensitization meetings. Additionally, early engagement with key stakeholders (four years before study commencement), including with medical students who have prior understanding of research concepts provided useful feedback in study design, facilitated acceptance and support of CHIS model in key national stakeholders, and acquisition of relevant approvals.

The key lessons learnt from the consultative processes for the Viet Nam study included the need to: adopt a stepwise approach to identify and address barriers and challenges to implementing CHIS research in Viet Nam; develop a regulatory framework relevant to the Vietnamese setting; and work with key partners to explore and where possible adapt current legislation (8). In the case of the Zambian study, the authors reported the main recommendations were to review the CHIS guidelines and legal frameworks to address local considerations and align with international ones; review of the good manufacturing practices and analogous requirements and propose what might be acceptable for Zambia; and develop an engagement strategy for conduct of CHIS in Zambia (9).

Following the workshop in Uganda, the authors outlined some key preparatory steps towards the establishment of a CHIS for schistosomiasis. These included the need to undertake risk assessments for importation of infected snails, develop local facilities and expertise for production of the challenge product, undertake community engagement and pilot studies to support a valid consent process, develop and review of protocol and product dossier in joint meetings that combine ethical, regulatory and environment management authorities (5). The authors of the Indian workshop paper acknowledged that valuable insights and recommendations were learnt from the deliberation on the three possible case scenarios of CHIS that highlighted potential issues around India’s (inadequate) readiness from a regulatory and ethical perspective (2).

An important learning from the Malawi meeting was the need to ensure that any potential CHIS addresses public health challenges and is aligned with the national research agenda, ensure capacity development in the country, and possess appropriate scientific and ethical rigour, including considerations for benefit and risk (4). Experts and local authorities at the Gabon meeting recommended that the successful implementation of a hookworm CHIS requires taking the local context into consideration, that public education intentionally targets communities and relevant authorities involved, and that the concerns of the community are adequately addressed (1). Panellists at the United Kingdom meeting agreed on specific recommendations to improve the standardization and usefulness of the CHIVIM for vaccine development, and on the creation of a research network of institutions working with a standardized CHIVIM that could contribute important data to support more rapid development and licensure of novel vaccines (6, 7).
5. CONCLUSION

Considering the novel nature of this research approach, especially in LMIC settings, lessons learnt from sites with experience of implementing CHIS can constitute a powerful resource for new settings exploring the possibility establishing a CHIS. Given that CHIS model is new in many settings, early engagement with a range of stakeholders, including communities where potential volunteers would be recruited from, seemed to be invaluable in gaining early feedback on whether a CHIS model would be acceptable or not, issues that need to be considered for the site/country/population and to inform on the CHIS model design. This highlights the importance of collaborating with stakeholders with relevant experience in establishing and implementing CHIS, including but not limited to experience in reviewing, approving, regulating, monitoring, implementing and participating in a CHIS.

### TABLE A12.1: Characteristics of included engagement activities

<table>
<thead>
<tr>
<th>Author/year (location)</th>
<th>Disease</th>
<th>Stakeholders</th>
<th>Aim</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alabi et al. 2021 (Gabon) (1)</td>
<td>Hookworm</td>
<td>Ministry of Health, the National Drug Authority, the National Ethics Committee, researchers and clinicians, sociologists, community representatives, and CHIS researchers from Uganda and The Netherlands</td>
<td>Held as a first step to the establishment of controlled hookworm human infection model in an endemic setting in order to identify key challenges and develop strategies to address them</td>
<td>The meeting’s discussion covered: the roles of the different regulatory institutions involved; the need to strengthen existing regulatory capacity and the role of legislation; ethical considerations; consideration of cultural and social peculiarities, need to have joint review meetings and engagement between researchers and regulatory bodies from inception to completion; need to consider the use of the local strain of hookworm for the challenge infections, capacity building for the local production of challenge material, and the establishment of adequate quality assurance procedures. Challenges discussed included positive donors without coinfection and potential for third party risks.</td>
</tr>
<tr>
<td>Elliott et al. 2018 (Uganda) (5)</td>
<td>Schistosomiasis</td>
<td>Researchers, community members and regulators in Uganda, CHIS researchers from Kenya, Malawi and The Netherlands</td>
<td>To explore the possibility of establishing a CHIS in Uganda by identifying key challenges and to develop strategies to address them</td>
<td>Recommended preparatory steps include: risk assessment for importation of infected snails; develop local infrastructure and technical capacity to produce challenge pathogen; community engagement from national to grass-roots level; pilot studies to establish approaches to ensure valid consent and voluntariness, and strategies to select volunteers who can avoid natural infection during the 12-week CHIS; build regulatory capacity; develop study protocols and product dossier in close consultation with ethical and regulatory partners; and plan for review of protocol and product dossier in a joint meeting combining ethical, regulatory and environment management authorities.</td>
</tr>
<tr>
<td>Author/year (location)</td>
<td>Disease</td>
<td>Stakeholders</td>
<td>Aim</td>
<td>Outcome</td>
</tr>
<tr>
<td>------------------------</td>
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<tr>
<td>Gordon et al. 2017 (Malawi) (4)</td>
<td>Non-specific</td>
<td>Researchers, national regulatory authorities and ministries of health (Malawi and Uganda) and funder</td>
<td>To discuss the scientific and public health value of conducting CHIS in Malawi, and the research governance issues that need to be addressed</td>
<td>Considerations for conducting CHIS in Malawi include: the CHIS should be aligned to the National Research Agenda; the study should be scientifically and ethically justified based on the local context; whether the CHIS model would increase the infrastructural and human resource capacity in the country; the proposed model should be of quality, backed by published data; have governance structures in place and safety should be demonstrated.</td>
</tr>
<tr>
<td>Hodgson et al. 2015 (Kenya) (3)</td>
<td>Malaria</td>
<td>Case study to document lessons learnt from the first malaria CHIS conducted in Nairobi, Kenya.</td>
<td>Researchers, research Institutes and Universities, Ministry of Health staff, Ethics committee members and regulators in Kenya</td>
<td>Detailed discussion with key stakeholders four years before the start of the study was an important two-way process that increased understanding and acceptance of the CHIS model among key national stakeholders and allowed important feedback to guide the study design and increase speed of future ethical and regulatory approvals. All bodies that were consulted were supportive of the study and recognized its importance. Meetings at the medical schools provided an excellent forum to explain the study to the target educated audience with a prior understanding of the concept of research.</td>
</tr>
<tr>
<td>Innis et al. 2019 (United Kingdom) (6,7)</td>
<td>Influenza</td>
<td>To assess the role of a standardized controlled human influenza virus infection model (CHIVIM) towards the development of novel influenza vaccine candidates.</td>
<td>Vaccine researchers, public health officials, regulatory experts, and representatives from the pharmaceutical industry</td>
<td>Limitations to implementation of CHIVIM included: limited access to challenge viruses and assays, lack of consensus regarding role of the CHIVIM in vaccine development pathway, need for increased standardization of CHIVIM trials in order to produce comparable results that can support universal vaccine licensure, and concerns regarding risk to study participants and community. To these, it was recommended that WHO and other key stakeholders provide guidance on standardization, challenge virus selection and risk management; that a common repository of well-characterized challenge viruses, harmonized protocols, and standardized assays be made available to researchers and a network of research institutions performing CHIVIM trials to be created, and to increase number of sites. Panellists also agreed on specific recommendations to improve the standardization and usefulness of the model for vaccine development.</td>
</tr>
<tr>
<td>Author/Year (Location)</td>
<td>Disease</td>
<td>Stakeholders</td>
<td>Aim</td>
<td>Outcome</td>
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<td>------------------------</td>
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<tr>
<td>Kestelyn et al. 2019 (Viet Nam) (8)</td>
<td>Shigella and Dengue</td>
<td>Participants at the 2017 Global Health Bioethics Network summer school, key individuals from Vietnamese government and research institutions, ethics committees, universities, major collaborating hospitals, and CHIS researchers in South East Asia</td>
<td>To explore initial perceptions and barriers to conducting CHIS in Viet Nam.</td>
<td>CHIS should be reviewed initially using current guidelines for medical research involving human subjects but additional regulatory and ethical guidelines specific to CHIS are required; tension between scientific progress and individual benefits/risks specific to CHIS needs to be addressed; ensure fair recruitment and inclusion of volunteers, achieve an acceptable level of informed consent, and deciding on appropriate compensation; have a strong social science component in parallel to the clinical studies; need to establish trust and equal partnerships; establishment of an effective communication strategy.</td>
</tr>
<tr>
<td>Kunda-Ng’an-du et al. 2021 (Zambia) (9)</td>
<td>Non-specific</td>
<td>Bioethicists, regulatory authority, and scientists from within Zambia and other African countries</td>
<td>To understand views, expectations, and experiences of ethical and regulatory bodies, and other stakeholders involved in CHIS in the region; identify core ethical issues for CHIS implementation in other LMICs and their implications for CHIS in Zambia; and develop modalities to address these issues from lessons learnt.</td>
<td>Key points considerations for CHIS implementation in Zambia: need for in-country legal framework and guidelines; need for adequate informed consent based on understanding of the concept of CHIS and study requirements; requirements for heightened vigilance to assure participant safety; need for rigorous health screening prior to enrolment; suitable infrastructure for containment; personnel to provide appropriate treatment including emergency resuscitation and evacuation if indicated. Recommendations for conducting CHIS in Zambia: compensation for burden of participation; access to care and provision for study related injury; withdrawal and exit procedures to preserve individual and community safety; and need for researchers to actively engage key gate keepers including civic leaders to avoid circulation of misinformation.</td>
</tr>
<tr>
<td>Vaz et al. 2019 (India) (2)</td>
<td>Malaria, typhoid and chikungunya</td>
<td>Epidemiologists, community/public health experts, microbiologists, infectious disease specialists, basic and translational scientists, ethicists, journalists and lawyers</td>
<td>To discuss three CHIS scenarios for diseases of public health importance in India and understand and deliberate on the relevant scientific, safety, ethical and regulatory considerations.</td>
<td>Conditions for implementation of CHIS include: a compelling scientific, legal, ethical and regulatory justification; the risks and processes must be supported with robust safeguards; regulatory framework for CHIS; long term health insurance cover; need for a multi-disciplinary ethics committee to review CHIS with specific domain expertise and training, an appropriate Government regulatory body; regulatory and ethical frameworks must be developed in consultation with the public and the various stakeholders, with transparency and due diligence.</td>
</tr>
</tbody>
</table>
REFERENCES


A scoping review of social science research into CHIS was undertaken in July 2021 to complement the discussion about social science in section 12 of the guidance. In total, 19 studies were identified; Table A13.1 summarizes the countries and CHIS models that are explored in the included studies. Nine of the 19 studies addressed CHIS that had been or were being implemented (1-9) and 10 focused on planned or hypothetical CHIS (10-19).

1. STUDY PARTICIPANTS

The choice of study participants was largely based on individuals and groups deemed to have a direct or indirect stake in an actual or hypothetical CHIS. In practice, studies included a broad range of participants, including former and current CHIS volunteers, potential CHIS volunteers, CHIS research teams and other health researchers, research ethics committee members, community representatives, administrative leaders, religious leaders, health professionals and members of the public (see Table 2). Where CHIS had been implemented, recruitment generally focused on former and current CHIS participants, (1, 2, 5–9) while studies of hypothetical or planned CHIS tended to include a broader range of the participants described above.

2. MAJOR THEMES EMERGING FROM FINDINGS ACROSS THE STUDIES

2.1 KEY CONSIDERATIONS FOR DECISION MAKING ABOUT PARTICIPATION

Key and interconnected considerations in making decisions about participation include the acceptability of the CHIS approach used, features of the research that supported or undermined motivation and decision-making processes.

2.1.1 Acceptability of CHIS

Findings on ‘acceptability’ were largely articulated as conditions to be met before a CHIS model could be considered acceptable in a specific setting (5, 9–11, 13, 14, 19). A key ‘condition’ for acceptability emerging across all the studies was the need to be certain about safety of the specific CHIS model, in some cases reflected by the perceived rigour of, and trust in, scientific and ethics review processes undertaken before studies could be implemented (7).

While it was not always possible to identify specific concerns underpinning acceptability, a general marker for ‘unacceptability’ seemed to come from potential or actual volunteers’ perceptions that ‘other people’ were more suitable CHIS volunteers than themselves (19). Similarly, ‘acceptability’ was potentially flagged through a lack of regret about participation, or a will-
ingness to participate in another similar study in future (1, 5–7). In this way, across implemented CHIS, volunteers were generally open and accommodating to CHIS, expressing no regrets and willing to participate in other similar studies in the future (1, 2, 5–9). At the same time, there was a general view from South India that CHIS (especially the deliberate infection aspect) were incompatible with a principle of ‘do no harm’ and should only be undertaken when other alternative research strategies have been considered (19).

In relation to COVID-19 studies, the decision on whether to conduct a CHIS was recognized as the role of scientists and relevant authorities (11). Two studies exploring public acceptability suggested broad support for this research strategy (10, 11); some participants argued that a carefully controlled infection through a CHIS would be safer and more acceptable than natural exposure to the wild pathogen (11). The specific details of how a COVID-19 CHIS would be run were seen core to its acceptability, including procedures for voluntary informed consent, inclusion criteria, medical care or support, compensation, regulation, and robust community engagement (13, 14).

2.1.2 Motivation
Eight studies (2, 5–9, 15, 18) specifically identified factors or motivations for volunteers to participate in a CHIS, in practice or hypothetically. The most common factors were: i) the level and form of remuneration or/and compensation involved; ii) the levels and forms of risk/safety involved; and iii) in balancing these, trust in the researchers and research institutions running the CHIS (5–8).

The topic of reimbursement and compensation was frequently discussed in the reviewed literature (1–7, 9, 12, 14–17, 19). Overall, there was broad agreement across the studies that, although an important incentive/motivation to participate in CHIS, compensation was not a major factor to drive participation (2, 6, 8). Compensation and payments were seen as a core benefit of participation (see also section 2 below on experiences of participation). Additional incentives to participate included a sense of altruism in relation to expected outcomes of CHIS, appreciation of an opportunity to assess personal health status, a demonstration of patriotism, the wish to contribute towards the development of a future vaccine (2, 5–9, 11, 15, 18) and valuing the opportunity for adventure or having a sense of curiosity (2, 6).

Across the studies (implemented and hypothetical/planned) there was broad agreement on the need for a fair/reasonable compensation for CHIS volunteers, with some specifically advocating for compensation for burdens and risks assumed (2, 12). However, the approach to achieving fairness around payments was recognized as challenging, especially in settings where incomes are typically uncertain and undocumented, and costs difficult to quantify.

Among former CHIS volunteers, there was generally a perception that the compensation was reasonable (1, 2, 5–9), although some felt it should be increased (1, 6, 9). The implemented and proposed models of payment varied across the studies, with some disbursing the compensation at specific points during the study (6, 8, 9), while others disbursed a lumpsum to volunteers after study completion (1, 5, 7). Across the sites where compensation payments were made as lumpsum at the end of the study, authors recommended future studies to disburse payments at regular intervals throughout the participation period (1). In one study, participants advocated for an hourly payment equivalent to unskilled labourer payment in the context where the CHIS is taking place (12). It was also recommended that mode of compensation for CHIS should be determined in consultation with study communities (1).

2.1.3 Decision making processes around participation
Ten studies discussed decision-making processes around participation. Across the implemented CHIS, volunteers described consulting others including family members (for example parents, spouses, siblings and grandparents), friends, and religious leaders (1, 2, 5–9). In some cases, consultation aimed to check general support and in others, more specific practical support needed to allow the individual to be away from family/domestic responsibilities (for example, childcare or existing jobs). In seeking advice, the response from those consulted varied from full support to discouragement and opposition.

From a hypothetical viewpoint, individuals within groups likely to be targeted for recruitment and members of the public similarly described a need for consultation (including teachers for a study that targeted university students as participants) in deciding whether to join a CHIS (11, 14, 15). The issues considered in decision-making are described under the sections on acceptability of CHIS, experiences of participation, understanding of key elements of the research and potential concerns and uncertainties (1, 2, 5–7, 9, 11).
2.2 EXPERIENCES OF PARTICIPATION
Emerging issues included in this theme were the positive (perceived benefits) and negative (perceived risks and burdens) experiences of participation in CHIS that were being or had been implemented (1, 2, 5–9); and the perceived balance between these.

2.2.1 Positive experiences
Across the six implemented studies, positive experiences included a range of tangible and intangible forms of physical, psychological, economic and social benefits. In addition to compensation, positive experiences by former volunteers included: access to medical health checks during eligibility assessment and while in residence; good residential living conditions; meeting new people and developing relationships with researchers and other volunteers; new learning opportunities (including increased knowledge about the conduct of clinical trials and disease under study); the opportunity to contribute towards important research and vaccine development; expressed appreciation of the ‘hardship’ that research participants undergo (for CHIS volunteers who work in research or medical fields); and fun and enjoyable experience of going through the study with other volunteers and study staff (1, 2, 5–7, 9).

2.2.2 Negative experiences
Negative participation experiences were also described, similarly generating physical, psychological, economic, and social forms of burdens. The three most commonly reported burdens across the implemented CHIS included experiencing unpleasant symptoms of the disease, uncomfortable study procedures (including regular and voluminous blood draws, nasal washes and throat swabs), and disruptions in work schedule (including change of work schedule or taking off time from work) (1–2, 5–7, 9). Other reported burdens included disruptions of private businesses while in residence, anxieties around health screening, limited right to movement after exposure to the infectious agent, discomfort with mandatory enrolment on an effective contraceptive by female volunteers, stress in meeting family needs before taking up residency at the in-patient facility, missing and being unable to support families during residency, interpersonal conflicts during residency, and cases of spousal conflicts (1, 5). Across some of the studies volunteers reported experiencing more burdens than anticipated and felt that the CHIS had higher burdens than risks (1, 5, 6). One study involving key stakeholders with expertise and experience relevant to CHIS in LMIC mentioned that there is a broad agreement among CHIS experts that the risks associated with a CHIS are lower when conducted in endemic settings compared to non-endemic settings (3, 4).

2.3 PARTICIPANTS’ UNDERSTANDING OF KEY ELEMENTS OF THE RESEARCH
This theme explored CHIS volunteers’ understanding of key elements of the specific CHIS, including the specific risks and burdens and the inclusion of ‘deliberate infection’ (1, 2, 5–7, 9). Most studies described a process of checking understanding (for example using a quiz) as a requirement of participation (1, 5–7). Across the studies, a broad understanding of the key elements of the CHIS, including risks and burdens, was reported. For example, volunteers in a malaria CHIS understood that they were going to be infected with malaria parasites and that they might get sick as a result but will be treated with antimalarials (5, 7). A CHIS in the USA reported that volunteers had high level of understanding of core features of a malaria CHIS, including the risks involved; in this study, volunteers reported that their understanding of risks did not change across the course of the study (6). Where levels of understanding were seen as high, volunteers and research teams generally attributed this to effective and successful engagement and consent processes, including researchers’ willingness to respond to questions from potential volunteers (5–7, 9). At the same time, some studies reported challenges around prior understanding amongst volunteers, for example, by showing that participation turned out to be more arduous than had been anticipated (1, 5, 6).

2.4 POTENTIAL CONCERNS AND UNCERTAINTIES
In relation to hypothetical and planned CHIS, a number of concerns and uncertainties were raised, which map to some degree on to those described by actual volunteers. The reported concerns and uncertainties related to the need for more precise information about the potential benefits and burdens of participation for a specific CHIS, including, the risks of death, severe disease or long-term injury or vaccine failure. A separate concern was raised about the need to have public support for CHIS, particularly to maintain trust in this research approach in the event of an unforeseen death or permanent disability of a volunteer (11, 14–17, 19). For any potential
COVID-19 CHIS, participants were keen that potential volunteers should be transparently and honestly informed about the uncertainties associated with study participation due to lack of precise information about the disease (11).

3. CONCLUSION

The studies in this review explored a range of perceptions and issues relating to concepts of acceptability, motivation and decision making for participation, perceived benefits, risks and burdens, and payments for study participation being the predominant themes. Many of the studies employed an embedded approach, exploring and interrogating critical issues during the implementation of CHIS as they emerge, with the potential to contribute towards practice in the short-, medium- and long-term. The use of embedded social science approaches in the early stages of the establishment and implementation of CHIS can make a critical contribution to identifying potential challenges, key priorities and perspectives about ethical issues to inform the appropriate design and conduct of such research. Social science research addressing ongoing, proposed and hypothetical studies moreover can identify and elucidate critical issues for consideration in the planning and implementation of successful engagement and consent processes; public perception or views about CHIS that feed into developing appropriate communication strategies; provide the basis for what is acceptable in CHIS and procedures and areas that need adjustment; and inform the development of ethics and regulatory guidelines and frameworks and useful case studies to accompany such guidelines and frameworks. Additionally, the findings can help optimize participants’ experience and improve the design of the CHIS by preparing the ground for implementation of CHIS that meets the expectations of volunteers without compromising ethical and scientific standards. This may involve identifying procedures and areas that can be adjusted to minimize the risks and burdens and maximize the anticipated benefits, while still maintaining scientific rigour. Social science research around CHIS also provides an opportunity to document grounded/context-specific perspectives that can feed into locally responsive policies around CHIS.

TABLE A13.1 Geographic sites and CHIS models

<table>
<thead>
<tr>
<th>Country site</th>
<th>CHIS models</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kenya</td>
<td>Malaria</td>
<td>(1, 5, 7)</td>
</tr>
<tr>
<td>Zambia</td>
<td>Typhoid</td>
<td>(15)</td>
</tr>
<tr>
<td>Malawi</td>
<td>Pneumococcal infection</td>
<td>(9, 14)</td>
</tr>
<tr>
<td>India</td>
<td>Non-specific</td>
<td>(19)</td>
</tr>
<tr>
<td>China</td>
<td>COVID-19</td>
<td>(16)</td>
</tr>
<tr>
<td>Thailand</td>
<td>Non-specific</td>
<td>(13)</td>
</tr>
<tr>
<td>The Netherlands</td>
<td>Malaria, hookworm and schistosomiasis</td>
<td>(2)</td>
</tr>
<tr>
<td>The USA</td>
<td>Malaria</td>
<td>(6)</td>
</tr>
<tr>
<td>United Kingdom</td>
<td>Typhoid, COVID-19, Leishmaniasis</td>
<td>(8, 11, 12, 17)</td>
</tr>
</tbody>
</table>

Multiple countries/territories

<table>
<thead>
<tr>
<th>Countries</th>
<th>CHIS models</th>
<th>Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australia, Canada, China, Hong Kong SAR, New Zealand, South Africa, Singapore, the USA and United Kingdom</td>
<td>COVID-19</td>
<td>(10)</td>
</tr>
<tr>
<td>Canada, Germany, the USA and United Kingdom</td>
<td>COVID-19</td>
<td>(18)</td>
</tr>
<tr>
<td>Countries across Africa, Asia, North America, South America, Europe</td>
<td>Non-specific</td>
<td>(3, 4)</td>
</tr>
</tbody>
</table>

ANNEX 13. SCOPING REVIEW OF SOCIAL SCIENCE STUDIES ON CONTROLLED HUMAN INFECTION STUDIES 82
TABLE A13.2 Characteristics of included studies

<table>
<thead>
<tr>
<th>Title/author/country/territory</th>
<th>Disease</th>
<th>Objective/issues explored</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Broockman et al 2020. Broad cross-national public support for accelerated COVID-19 vaccine trial designs (Worldwide - Australia, Canada, China, Hong Kong SAR, New Zealand, South Africa, Singapore, the USA and United Kingdom) (10)</td>
<td>COVID-19</td>
<td>To measure public opinion about the ethics of accelerated vaccine trial designs. Preferences, ethical acceptability and scientific validity of accelerated COVID-19 trials over conventional ones. Respondents' successful comprehension of the study designs and demographic questions.</td>
<td>Members of the public</td>
</tr>
<tr>
<td>Chi et al 2021. Understanding the benefits and burdens associated with a Malaria Human Infection Study in Kenya: Experiences of study volunteers and other stakeholders (Kenya) (1)</td>
<td>Malaria</td>
<td>To explore research participants and stakeholder’s experiences of burdens and benefits of the malaria CHIS and their implication</td>
<td>CHIS volunteers, study team, community representatives, CE staff and administrative leaders</td>
</tr>
<tr>
<td>Gbesemete et al 2020. Exploring the acceptability of controlled human infection with SARS-CoV-2-a public consultation (United Kingdom) (11)</td>
<td>COVID-19</td>
<td>To understand public attitudes to a CHIS for SARS-CoV-2, and pre-requisites for enrolment/ Acceptability, concerns, risks and how best to communicate them and acceptable compensation for CHIS as well as the concept of 'open science' in the context of CHIS</td>
<td>Potential CHIS volunteers/ members of the public</td>
</tr>
<tr>
<td>Grimwade et al 2020. Payment in challenge studies: Ethics, attitudes and a new payment for risk model (United Kingdom) (12)</td>
<td>Non-specific</td>
<td>To provide empirical data surrounding current payment practices in CHIS and the attitudes towards payment in CHIS; critically assess these data to determine whether current practices and attitudes are ethically justified; and propose a framework for ethically justifiable payment of CHIS participants</td>
<td>CHIS experts and members of the public</td>
</tr>
<tr>
<td>Hoogerwerf et al 2020. Money-oriented risk takers or deliberate decision makers? A cross sectional survey study of participants in controlled human infection trials (The Netherlands) (2)</td>
<td>Malaria, hookworm and schistosomiasis</td>
<td>To quantitatively investigate the motivation, decision-making process and risk propensity of participants in CHIS trials compared with a control group as well as participants' views on ethical questions in CHIS trials</td>
<td>Former CHIS volunteers and non-CHIS volunteers (control group)</td>
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</table>
To provide empirical data surrounding ethical questions in CHIS trials compared with a control and risk propensity of participants in motivated, decision-making process.

Methods

<table>
<thead>
<tr>
<th>Methods</th>
<th>Findings</th>
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<tbody>
<tr>
<td>Quantitative. Online survey</td>
<td>Broad cross-national support for both the CHIS and the integrated trial over standard vaccine trials. For study 1, participants saw the CHIS as slightly more likely to be ethical, scientifically valid, and that they would be more likely to take an approved vaccine if it had been tested using this design. In Study 2, (the integrated trial) participants were more likely to prefer that scientists conduct the integrated trial instead of the standard trial. The few who preferred the standard trial still considered the integrated trial to be ethical.</td>
</tr>
<tr>
<td>Qualitative. In depth interviews (IDIs), focus groups discussions (FGDs) and non-participant observations (NPOs) n = 100</td>
<td>Participants reported physical, psychological, social and economic burdens and benefits at various stages of participation in the malaria CHIS. Some of the key benefits included, the study compensation, good living conditions while in residence, access to health check-up among others. The burdens experienced by participants were discomfort as a result of experiencing malaria symptoms and some of the study procedures as well as fear and anxiety around deliberate infection and early exit from the study.</td>
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<tr>
<td>Qualitative. Online focus groups. n=57</td>
<td>Study participants were positive about the CHIS and would consider volunteering for altruistic reasons. However, they felt that the decision to allow such a CHIS should be made by the scientific community and ethics bodies, not the public. A major concern was about personal risks, hence these and levels of uncertainty should be expressed clearly. The public should be informed about the study and regular updates provided to ensure transparency and accountability.</td>
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<tr>
<td>Quantitative. Online surveys n = 300</td>
<td>Those surveyed supported the view that CHIS participants should be paid a substantial amount of money and the amount should even be higher for more risky CHIS. Members of the public thought CHIS participants should be paid approximately triple the United Kingdom’s minimum wage and should be paid for the risk they endure throughout participation. CHIS experts thought CHIS participants should be paid more than double the United Kingdom’s minimum wage but were divided on the payment for risk.</td>
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<tr>
<td>Quantitative. Survey n = 217</td>
<td>Motivations to participate were mostly altruistic. Trust in the study team was the most important factor considered in the decision to participate. Other factors considered were; time investment, severity of symptoms, chance of developing symptoms and financial compensation / an easy way to make money. Former CHIS participants considered the study to be of no or little risk, were proud of their participation and would consider participating in a similar study and advise others to participate. Opinions about ethical issues were as follows: participants found it acceptable to be deliberately infected with a pathogen and that it was understandable that immediate withdrawal from the study may not always be possible. Compensation was considered as an incentive to participate but was not a major factor to drive participation.</td>
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</table>
### Table: Scoping Review of Social Science Studies on Controlled Human Infection Studies

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<thead>
<tr>
<th>Title/author/country/territory</th>
<th>Disease</th>
<th>Objective/issues explored</th>
<th>Participants</th>
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</thead>
<tbody>
<tr>
<td>Jamrozik &amp; Selgelid 2020. Ethical issues surrounding controlled human infection challenge studies in endemic low-and middle-income countries (worldwide) (3)</td>
<td>Non-specific</td>
<td>To examine ethical implications of endemic LMIC CHIS regarding (a) potential direct benefits for participants, (b) risks to participants, (c) third-party risks, (d) informed consent, payment of participants, and (f) community engagement</td>
<td>Key stakeholders with expertise and experience relevant to LMIC CHIS (expertise in research ethics, and/or involvement in the regulation and/or funding of CHIS research)</td>
</tr>
<tr>
<td>Jamrozik &amp; Selgelid 2021. Human challenge studies in endemic settings: Ethical and regulatory issues (worldwide) (4)</td>
<td>Non-specific</td>
<td>To fill a gap in the current literature by focusing particularly on ethical and regulatory issues that are specific and/or highly salient to CHIS conducted in LMICs/ Areas of consensus regarding ethical issues and regulation in the context of LMIC CHIS, as well as unresolved issues that require further study/analysis</td>
<td>Key stakeholders with expertise and experience relevant to LMIC CHIS (expertise in research ethics, and/or involvement in the regulation and/or funding of CHIS research)</td>
</tr>
<tr>
<td>Jao et al 2020. Deliberately infecting healthy volunteers with malaria parasites: Perceptions and experiences of participants and other stakeholders in a Kenyan-based malaria infection study (Kenya) (5)</td>
<td>Malaria</td>
<td>To explore stakeholders’ perceptions and experiences of deliberate infection and the moral implications of the same/ understanding and acceptability of deliberate infection and reasons for participation</td>
<td>CHIS volunteers, CHIS research staff and community representatives</td>
</tr>
<tr>
<td>Kaewkungwal et al 2019. Conducting human challenge studies in LMICs – A survey of researchers and ethics committee members in Thailand (Thailand) (13)</td>
<td>Non-specific</td>
<td>To examine the views of researchers and REC members in Thailand about CHIS. Whether they believe that conducting CHIS in Thailand would be appropriate and what they regard as the most important concerns raised by such studies</td>
<td>REC members and researchers who had experience with health-related research at universities, non-university hospitals, and research institutes</td>
</tr>
<tr>
<td>Kapumba et al 2020. Stakeholder views on the acceptability of Human infection studies in Malawi (Malawi) (14)</td>
<td>Non-specific</td>
<td>To examine stakeholder perceptions about the acceptability and ethics of CHIS in Malawi, to inform decisions about a planned pneumococcal challenge research and wider understanding of CHIS ethics in LMICs.</td>
<td>Frontline research staff, medical students, community representatives, religious leaders, members of MLW’s Community Advisory Group, REC members, senior clinicians and district health management officials.</td>
</tr>
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</table>
### Methods

**Qualitative. Interviews n = 45**

- **Findings**: i) Potential individual benefits for participants in endemic settings – participants may receive direct benefits such as enhanced immunity that can reduce severity of future infections. ii) Risks to participants: participants in endemic settings are more likely to experience less risk as compared to those from non-endemic settings especially if the risks are minimized. iii) Third party risks – since these kinds of risks might undermine public/community trust in research, it is important to have robust community engagement and carefully designed research procedures. iv) Consent – recruiting educated/tertiary educated individuals may not be ethically justified compared to those from the endemic areas who may be more familiar with the pathogens under investigations. v) Payment: participants should be compensated for burdens experienced and the level of payments should be informed by community consultations. vi) Community engagement and public acceptability – community acceptance should be formally assessed and be an essential part in setting up and maintaining CHIS capacity in LMIC.

**Qualitative. Interviews n = 45**

- **Findings**: Areas of consensus: CHIS in LMIC can be acceptable where i) there is sound scientific rationale and strong scientific and ethical standards; ii) they are necessary to produce results that are relevant to the eventual target population for interventions under development; iii) they have the potential to accelerate development of interventions that can significantly reduce disease burden in endemic settings; iv) there is a need to build regulatory and ethics capacity in CHIS in LMIC; v) risks, harms and burdens are minimized; vi) high quality informed consent is ensured; vii) public engagement etc. is conducted. Unresolved issues: i) how the scientific aim to produce generalizable results should be weighed against the protection of participants; ii) burdens and benefits (appropriate benefit sharing, acceptable limits of burdens, managing risks in case of withdrawal after challenge etc.); iii) selection and payment of participants; iv) governance (need for CHIS specific ethical guidelines, special review for CHIS, regulation of challenge strains).

**Qualitative. In-depth interviews (IDI), focus group discussions (FGDs) Non-participatory observations (NPOs) n = 69**

- **Findings**: The concept of deliberate infection was considered unusual in all categories of participants interviewed. Factors influencing decisions to participate were: study incentives, trust in the research institution, assessment of associated burdens and motivation to support malaria vaccine development. Burdens experienced were greater than had been anticipated initially, fluctuated over time and were related to specific procedures and events.

**Quantitative Survey n = 240**

- **Findings**: Considerations rated as important for the conduct of CHIS were scientific rationale, safety, appropriate risks, robust informed consent process, governance and balance of risk-benefit ratio. Those rated as having lower importance yet have been described as important for CHIS in LMICs were a publicly available rationale, national priority, and community engagement.

**Qualitative. Deliberative FGDs, follow-up interviews and key informant interviews n = 69**

- **Findings**: A pneumococcal CHIS research in Malawi was considered to have potential benefit to the population however acceptability of the study would be dependent on voluntary and informed consent (with clear and open explanations), fair selection of participants, adequate medical care, compensation and reimbursement, regulation (careful review and approval) and adequate community engagement. Key concerns raised were participant safety and negative community reactions. Beyond pneumococcal studies, participants also expressed their perceptions about acceptability of other types of CHIS. For other types of CHIS (e.g. malaria and typhoid) there were mixed views especially around developing symptoms and long residential stays with majority suggesting starting with pneumococcal CHIS then expanding to the rest.
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<tr>
<th>Title/author/country/territory</th>
<th>Disease</th>
<th>Objective/issues explored</th>
<th>Participants</th>
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<tbody>
<tr>
<td>Kraft et al 2019. Exploring Ethical Concerns about Human Challenge Studies: A Qualitative Study of controlled human malaria infection study Participants’ Motivation and Attitudes (the USA) (6)</td>
<td>Malaria</td>
<td>To understand CHIS participants’ motivations for joining CHIS and their attitudes about risk, payment, and the possibility of undue inducement/burdens, deception by participants</td>
<td>Former CHIS volunteers</td>
</tr>
<tr>
<td>Kunda-Ng’andu et al 2021. Exploring willingness to participate in future Human Infection Studies in Lusaka, Zambia: A nested qualitative exploratory study (Zambia) (15)</td>
<td>Typhoid</td>
<td>To understand potential participants’ willingness to participate in a CHIS using the example of typhoid, knowledge regarding typhoid and perceived risk; knowledge of CHIS and reactions when introduced to the concept behind CHIS/ motivations, perceived risks and burdens</td>
<td>Students from higher learning institutions</td>
</tr>
<tr>
<td>Njue et al 2018. Ethical considerations in Controlled Human Malaria Infection studies in low resource settings: Experiences and perceptions of study participants in a malaria Challenge study in Kenya (Kenya) (7)</td>
<td>Malaria</td>
<td>To explore the experiences and perceptions of participants in a malaria CHIS/ perceptions about the informed consent process, the study and concept of deliberate infection, motivation to participate, decision making process and experiences of being in the study</td>
<td>CHIS Volunteers and study team</td>
</tr>
<tr>
<td>Oguti et al 2020. Factors influencing participation in controlled human infection models: A pooled analysis from six enteric fever studies (United Kingdom) (8)</td>
<td>Typhoid</td>
<td>To explore the experiences and perceptions of participants in a malaria CHIS/ Motivations, attitudes and factors influencing participation</td>
<td>Former CHIS volunteers</td>
</tr>
<tr>
<td>Pan et al 2021. Perspectives of research ethics committee members on human challenge studies in the development of vaccines against COVID-19: a mixed methods study (China) (16)</td>
<td>COVID-19</td>
<td>To investigate attitudes, views, and suggestions on human challenge studies from the perspective of a local Chinese REC</td>
<td>REC members</td>
</tr>
<tr>
<td>Parkash et al 2021. Assessing public perception of a sand fly biting study on the pathway to a controlled human infection model for cutaneous leishmaniasis (United Kingdom) (17)</td>
<td>Leishmaniasis</td>
<td>To inform development of a study to test the safety and effectiveness of a sand fly biting protocol using uninfected sand flies and a CHIS using Leishmania major-infected sand flies/ draft study volunteer-facing materials (including issues around study design, recruitment, feasibility, inclusion criteria, ethical issues, and the plain English summary)</td>
<td>Students and staff from the University of York, former CHIS volunteer, former vaccine study volunteer, patient research ambassador, and lay volunteers from the local community</td>
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<tr>
<td>Methods</td>
<td>Findings</td>
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<tr>
<td>Qualitative Interviews (baseline and exit)</td>
<td>Most participants reportedly consulted with others about research participation, with the reactions from others ranging from full support to scepticism. Three main motivations for participating were expressed (altruistic, experiential, and financial), with nearly all participants expressing some degree of altruistic motivation. Overall, most participants felt the study had more burdens but less risk.</td>
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<td>(n = 16)</td>
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<tr>
<td>Qualitative Interviews and focus groups</td>
<td>Typhoid was considered a serious disease with potential for life-long consequences and death. Some of the participants expressed unrestricted willingness to participate, others said that they needed to consult parents and professors while some expressed fear of death and illness. Those who were willing to participate gave the following reasons as motivating factors to participate in CHIS: monetary compensation, altruism and being part of a team that comes up with a vaccine. Concerns highlighted by participants included separation from family and duties, having insufficient information to decide, inadequate access to care, severe disease, life-long injury or side-effects, death and vaccine failure.</td>
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<td>(n = 66)</td>
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<tr>
<td>Qualitative IDIs, FGDs and observations</td>
<td>The main motivations to participate were compensation, health care benefits, and wanting to contribute to the health of communities. Participants also demonstrated an understanding of the key elements of the study and were not worried about being challenged with malaria given that the CHIS strain is curable, and they live in a malaria endemic setting. They also had seen former participants not having any issues and got assurances from the study team that the study was safe. Participants were generally positive about how the study was conducted and the care provided while they were in the study. Concerns which were raised in regard to participation were about the frequency and volume of the blood draws as well as the associated discomfort.</td>
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<td>(n = 36)</td>
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<td>Quantitative Survey</td>
<td>The most cited motivations for participation were a desire to contribute to the progression of medicine, financial reimbursement and curiosity about clinical trials. Most participants were satisfied with the information provided before participation while few were concerned about study-related risks. The majority of participants also consulted other people before deciding to participate and most of them were advised against joining the study. Most of the participants were satisfied with the care they received from the staff, would consider participating again in such a study and probably recommend the study to a friend or relative.</td>
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<td>(n = 201)</td>
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<td>Qualitative and quantitative Online survey</td>
<td>The core ethical issue identified was the risk of harm to the participants. It was also highlighted that CHIS should observe uniform principles of ethics in medical research regardless of circumstances. All participants were of the opinion that human challenge studies should provide compensation to its participants and that sufficiently informed consent is necessary. Some of participants were against CHIS and the key concerns they raised were around representativeness and fairness of participant selection, benefit, and risk, vulnerable groups, compensation to participants, informed consent as well as the ethics of CHIS in general.</td>
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<tr>
<td>and IDIs</td>
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<td>(n = 36)</td>
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<tr>
<td>Qualitative study</td>
<td>Issues that emerged from the consultation were around i) quality of volunteer-facing written information (need for clarity, consideration of the visual material used and consideration of written consent); ii) improving study design (alternative suggestions for volunteer engagement e.g. use of grouped study inductions, volunteer experience videos, websites and blogs; ways to improve recruitment e.g. use of internet technologies, word of mouth and radio methods; etc.); iii) factors to motivate involvement in the research e.g. remuneration, altruism and both remuneration and altruism. Generally, the group engaged responded positively to the study aims.</td>
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<td>Public involvement consultation, involving</td>
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<td>presentations and Q&amp;As</td>
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<td>(n = 10)</td>
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ANNEX 13. SCOPING REVIEW OF SOCIAL SCIENCE STUDIES ON CONTROLLED HUMAN INFECTION STUDIES 89
<table>
<thead>
<tr>
<th>Title/author/country/territory</th>
<th>Disease</th>
<th>Objective/issues explored</th>
<th>Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rose et al 2021. Characterizing altruistic motivation in potential volunteers for SARS-CoV-2 challenge trials (worldwide – the USA, Canada, United Kingdom and Germany) (18)</td>
<td>COVID-19</td>
<td>To assess whether the goals and values of a group of individuals who proactively declared their intent to volunteer to participate in a COVID-19 challenge trial are compatible with ethical participation and why they consent to research with net risks and burdens to themselves/ Sociodemographic factors, Altruistic motivation, values, and behaviour as well as risk preferences and behaviours</td>
<td>Potential volunteers COVID-19 CHIS</td>
</tr>
<tr>
<td>Toto et al 2021. “At first, I was very afraid”—a qualitative description of participants’ views and experiences in the first Human Infection Study in Malawi (Malawi) (9)</td>
<td>Pneumococcal infection</td>
<td>To assess acceptability among the healthy adult volunteers who had completed a feasibility study, including their opinions on study recruitment and consent procedures, medical care and support, compensation, and community engagement</td>
<td>CHIS volunteers</td>
</tr>
<tr>
<td>Vaz et al 2020. Public perceptions on Controlled Human Infection Model (CHIM) studies—a qualitative pilot study from South India (India) (19)</td>
<td>Non-specific</td>
<td>To engage with the public and local stakeholders on their perceptions of acceptability, concerns and participation in CHIS studies, in the Indian context, and thereby influence guidelines to be more people-centred</td>
<td>Members of the general public and key informants (microbiologists, clinicians, public health workers, social workers, REC members, media representatives, lawyers, and human rights activists)</td>
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<tr>
<td>Methods</td>
<td>Findings</td>
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<tr>
<td>Quantitative n = 2910</td>
<td>The majority of participants were willing to volunteer in COVID-19 CHIS because of altruistic motivation and behaviour. There was no evidence that CHIS volunteerism is disproportionately associated with psychological or demographic factors that might raise ethical concerns. There was also no evidence that volunteerism is associated with high levels of socioeconomic vulnerability that might make volunteers subject to exploitation.</td>
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<td>Qualitative Exit interviews n = 16</td>
<td>CHIS were found to be acceptable in Malawi. Participation was dependent on three conditions namely: motivation, compensation and advocacy. Motivating factors included perceived individual benefits, societal value, wanting to know one's general health status, compensation, altruism and patriotism. Participants described both positive and negative experiences in regard to compensation. Positive aspects of participation included staff attitudes/friendly nature, safety monitoring and support for health care. Negative aspects included getting sick, uncomfortable study procedure and fear of receiving the inoculum.</td>
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<td>Qualitative FGDs and IDIs n = 110</td>
<td>The lay public considered safety as a key concern in CHIS studies and this was expressed in terms of fear of death. Participants also felt that people other than themselves may be ideally suited as participants, including risk takers, those without dependents, the more health and research literate, financially sound and those altruistic in nature. Suggestions were also made to first explore other alternative research strategies to CHIS, despite acknowledging the potential benefits of conducting CHIS. If CHIS were conducted, they should lead to public good.</td>
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</table>


9. Toto NM et al. “At first, I was very afraid”—a qualitative description of participants’ views and experiences in the first Human Infection Study in Malawi. Wellcome Open Research. 2021, 6(89): 89.


