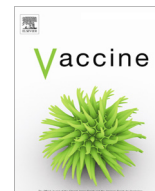




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## WHO Report

## Key criteria for the ethical acceptability of COVID-19 human challenge studies: Report of a WHO Working Group



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## ABSTRACT

This report of the WHO Working Group for Guidance on Human Challenge Studies in COVID-19 outlines ethical standards for COVID-19 challenge studies. It includes eight Key Criteria related to scientific justification, risk-benefit assessment, consultation and engagement, co-ordination of research, site selection, participant selection, expert review, and informed consent. The document aims to provide comprehensive guidance to scientists, research ethics committees, funders, policymakers, and regulators in deliberations regarding SARS-CoV-2 challenge studies by outlining criteria that would need to be satisfied in order for such studies to be ethically acceptable.

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## 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.<sup>1</sup> 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)<sup>2</sup> 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].<sup>3</sup> 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].<sup>4</sup> 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.

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].<sup>5</sup>

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 0.6–1% and fatal infection rates around 0.007%–0.031% [26,42].<sup>6</sup> 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 incompletely understood, no specific highly effective treatments are available (though recent trials have shown beneficial effects of dexamethasone and mixed results for other treatments), and severe disease or death can occur in young adults [17,18,28,29].<sup>7</sup> 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.

<sup>4</sup> Although animal models of COVID-19 could theoretically replace human challenge studies in many respects, it is currently not clear whether a reliable animal model will be developed, or how long this would take, and such models ultimately require validation with human data from epidemiological or clinical studies.

<sup>5</sup> 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.

<sup>6</sup> In early data from China, 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 26–30 face significantly higher risks than those aged 18–25 is currently unclear).

<sup>7</sup> Note, however, that 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].

<sup>1</sup> 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.

<sup>2</sup> 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 some degree of uncertainty remains.

<sup>3</sup> See also the WHO list in “Draft landscape of COVID-19 candidate vaccines”: <https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus-landscape-ncov.pdf> (accessed 4 May 2020).

**Table 1**

Eight criteria for SARS-CoV-2 challenge studies.

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

## 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.

### 4.1. Scientific Justification

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].<sup>8</sup> 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)<sup>9</sup> from among multiple candidates<sup>10</sup> 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 research<sup>11</sup> and public health measures aiming to protect higher-risk groups (including, for example, how vaccination of young healthy adults may provide indirect protection to higher-risk groups) [9,34].<sup>12</sup>

<sup>9</sup> 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, for example, drugs given to prevent infection.

<sup>10</sup> Given that multiple candidate vaccines will ultimately go through efficacy testing in humans, 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 that become available later (e.g., to determine the efficacy of second generation vaccines).

<sup>11</sup> For example, vaccine efficacy data in high-risk groups could be obtained subsequently with other research designs – for example, immune bridging studies (once correlates of protection are established), field trials and post-licensure observational studies.

<sup>12</sup> 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 may provide indirect protection to high-risk individuals (compare rubella vaccination of whole populations so as to protect unborn children); see also [Criterion 6](#).

<sup>8</sup> 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].

**Table 2**  
Examples of potential benefits, risks and risk minimization strategies (by group).

Group	Potential benefits	Risks	Risk minimization strategies
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 <sup>a</sup>	Risks of experimental infection, including serious illness and death Risks related to experimental vaccines (including the potential for vaccine-enhanced disease) Risks of inpatient isolation (e.g. mental health)	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 <sup>b</sup>	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 (i) infection leads to protective immunity; (ii) participants face a background risk of infection in the community; and (iii) 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.

#### 4.2. Assessment of risks and potential benefits

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.<sup>13</sup> 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);<sup>14</sup> (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<sup>15</sup> (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 discussion of risk minimization) to the extent possible without compromising the scientific value of a study.<sup>16</sup>

##### 4.2.1. 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

<sup>14</sup> 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.

<sup>15</sup> Marginal risk of participation may be very low, or possibly even negative, during a pandemic.

<sup>16</sup> 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.

<sup>13</sup> Similar considerations arguably apply in other situations of higher risk, greater uncertainty, and significant potential benefits (for example, some other first-in-human trials).



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.<sup>17</sup> 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;<sup>18</sup> 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,<sup>19</sup> 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.

### 4.3. Consultation and engagement

#### 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

<sup>17</sup> 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.

<sup>18</sup> 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.

<sup>19</sup> 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].

engagement at the local, national and international levels should begin immediately, since such studies are already being considered [7–9];<sup>20</sup> 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 as incorporating the views of challenge study participants or those who have expressed interest in participating [35,36].<sup>21</sup>

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](#)).

### 4.4. Coordination of research

#### 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

<sup>20</sup> Public engagement activities by groups interested in SARS-CoV-2 challenge studies have recently commenced (see <https://1daysooner.org/>, accessed 4 May 2020).

<sup>21</sup> Many people have already expressed interest in volunteering for SARS-CoV-2 human challenge studies (see, for example, <https://1daysooner.org/>, accessed 4 May 2020).

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.<sup>22</sup>

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<sup>23</sup> and more effective candidates by providing standardized safety data and directly comparable estimates of vaccine efficacy that would otherwise be difficult to obtain [23].<sup>24</sup>

#### 4.5. Site Selection

##### 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.<sup>25</sup>

<sup>22</sup> The “Solidarity” trial of COVID-19 therapeutics may provide a benchmark for cooperation between SARS-CoV-2 challenge study research groups.

<sup>23</sup> Challenge studies involving relatively few participants have low statistical power to detect rare vaccine safety issues – though standard field trials are also not usually powered to detect rare events such as Guillain-Barré syndrome. However, any safety signals (including, for example, regarding evidence of vaccine-enhanced disease) must be rapidly reported.

<sup>24</sup> Multi-arm trials (such as Solidarity) of vaccines can be particularly complex and demanding to conduct, and challenge studies could be used to prioritize experimental vaccines for inclusion therein (thereby reducing the total number of comparators and overall study complexity).

<sup>25</sup> 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](#)).

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 if the latter would divert scarce resources (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.

#### 4.6. Participant selection

##### 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, e.g., aged 18–30 years.<sup>26</sup> 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].<sup>27</sup> 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 (i.e., taking advantage of those who have already been wrongly disadvantaged). Any prospective participants who could reasonably be perceived 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

<sup>26</sup> 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).

<sup>27</sup> 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.

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.<sup>28</sup>

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].<sup>29</sup>

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].

#### 4.7. Expert review

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).

<sup>28</sup> 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).

<sup>29</sup> 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 may provide significant indirect protection to others at higher risk [34].

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 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.

#### 4.8. Informed consent

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.

#### Data statement

N/A.

#### Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [EJ] has received consulting fees from WHO and funding from The Wellcome Trust for research on the ethics of human challenge studies. CW receives consulting income from Cardialen, Eli Lilly & Company, and Research Triangle Institute International. MJS is he has received funding from The Wellcome Trust for previous research on the ethics of human challenge studies. No competing interests: SB,CE,GK,MK,KL,ER,CS,PGS, SS, RU].

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