World Health Organization

# Key criteria for the ethical acceptability of COVID-19 human challenge studies

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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.[1] 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)[2] 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)*.[3] Well designed human challenge studies provide one of the most efficient and scientifically powerful means for testing vaccines, especially because animal

[1] 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.

[2] 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.

[3] 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).

models are not adequately generalizable to humans *(11–13, 24)*.[4] 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)*.[5]

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)*.[6] 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

[4] 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.

[5] 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.

[6] 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).

treatment available, and severe disease or death can occur in young adults *(17, 18, 28, 29)*.[7] 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 1. Eight criteria for SARS-CoV-2 challenge studies**

| | | |
|---|---|---|
| **Scientific and ethical assessments** | | |
| Criterion 1 | Scientific justification | SARS-CoV-2 challenge studies must have strong scientific justification |
| 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 |
| **Consultation and coordination** | | |
| 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 |
| Criterion 4 | Coordination | SARS-CoV-2 challenge study research programmes should involve close coordination between researchers, funders, policy-makers and regulators |
| **Selection criteria** | | |
| Criterion 5 | Site selection | SARS-CoV-2 challenge studies should be situated where the research can be conducted to the highest scientific, clinical and ethical standards |
| Criterion 6 | Participant selection | SARS-CoV-2 challenge study researchers should ensure that participant selection criteria limit and minimize risk |
| **Review and consent** | | |

[7] 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)*.

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|---|---|---|
| Criterion 7 | Expert review | SARS-CoV-2 challenge studies should be reviewed by a specialized independent committee |
| Criterion 8 | 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.

### *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)*.[8] 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)[9] from among multiple candidates[10] 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

[8] 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)*.

[9] 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.

[10] 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.

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[11] 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)*.[12]

### *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.[13] 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.

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[11] 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.

[12] 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.

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

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);[14] (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[15] (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.[16]

**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<br>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)<br>Immunity from experimental | Risks of experimental infection, including serious illness and death<br>Risks related to experimental | Selection of low-risk participants<br>Reducing numbers of participants where feasible |