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Human Challenge Studies for The Early Development of Vaccines: Evolution to Ethics

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ABSTRACT

Human challenge trials are studies in which participants are deliberately exposed to a particular infection-causing organism (whether or not they have been vaccinated). Human challenge studies are an important part of a lot of current research, particularly when it comes to vaccine development. While human challenge trials aren't new, but they're typically used in the development of treatments for diseases that are considered less lethal and that scientists have gained a better understanding over time, such as malaria. The method, which involves intentionally infecting volunteers with the novel Coronavirus, is being promoted to "speed up" the availability of new vaccines. This challenging organism could also be pathogenic, adapted, and/or attenuated from wild-type or genetically modified in a suitable manner. This article mainly involves outlining key criteria which may need to be satisfied so as for such studies to be ethically acceptable. However, scientists, research ethics committees, funders, policy-makers, and regulators close for the early rollout of the vaccines in deliberations regarding SARS-CoV-2 challenge studies.

INTRODUCTION

The worldwide public health, socioeconomic stability, food security, and other social goods are all at risk from the Coronavirus Disease 2019 (COVID-19) pandemic, which is caused by SARS-CoV-2. COVID-19 would very certainly kill millions of people and put enormous strain on the world's healthcare systems. Physical separation and other control measures can assist to slow the spread of COVID-19, but they aren't foolproof. These policies come with a high social and economic cost, which may be borne disproportionately by the poor. (a) A lack of safe, effective vaccinations and adequate treatments are major problems for the present public health response. (b) Unsolved scientific questions about infection, immunity, and transmission. [1, 16]

Healthy volunteers are deliberately infected in controlled human infection research (also known as "human challenge studies"). Such research is more useful in the development of vaccinations. Because fewer people need to be exposed to experimental vaccines to give (preliminary) safety and efficacy estimates, they can be much faster to undertake than vaccine field trials. These studies can be used to compare the efficacy of different vaccination candidates and so identify the most promising vaccines for further research.[2] Well-designed challenge experiments may thus not only hasten the development of a COVID-19 vaccine, but also increase the likelihood that the vaccines that are eventually introduced are more effective, have fewer side effects, and hold a lot of promise.[3]

From the beginning, challenge experiments have been used to investigate infection and immune processes. They could be used to confirm SARS-CoV-2 immunity testing, uncover immune protection correlates, and examine the hazards of transmission posed by affected people. These findings could have a meaningful effect on the pandemic's overall public health response.[4]

BACKGROUND

Human volunteers are deliberately exposed to infectious pathogens in infectious human challenge research. Nonetheless, such a study may appear to be at odds with the medical guiding principle of "no harm." Challenge research must be undertaken within an ethical framework that allows for really informed consent. The importance of the information to be gathered must be demonstrated.[5, 16]

The data generated by traditional clinical trials are more rigorous, dependable, and safe, but these trials typically take longer to roll out an effective vaccine. On the other hand, there is a methodology known as the unconventional method that is used in clinical trials (Human challenge studies or human infectious studies). With no significant risks or concerns, HCTs have helped to produce vaccines for yellow fever, influenza, typhoid, cholera, and malaria (ongoing). Before being given to humans, vaccine candidates are tested for safety on a variety of animals. And the human subjects are constantly monitored and under constant monitoring.[6, 18]

Although human challenge trials are not necessary as part of any vaccine development program, there are a variety of reasons why a developer would wish to do "challenge-protection" research in humans rather than animals. Animal models are sometimes inaccurate in their representation of human disease, and many pathogenic organisms against which a vaccine developer might want to build a vaccine are not present in animal models. In some cases, human challenge trials can be conducted safely and ethically if they are properly designed and conducted.[7, 16] Refer to Figure No. 1 for Eight criteria for conducting challenge studies.[16, 17]

It's important to keep in mind that not all diseases for which vaccines might be developed are appropriate for human challenge trials. The human challenge with a virulent or even attenuated organism is not always regarded as ethical or safe. If an organism creates a disease with a high case fatality rate (or a long and unknown latency period) and no available medicines to prevent or improve disease and avoid death, then human challenge trials with that organism are not acceptable. A human challenge study, on the other hand, can be considered if the challenged organism has an acute onset, can be easily and objectively identified, and current effective treatments can be given at the right time to eliminate mortality.[7, 18]

HISTORY OF HUMAN CHALLENGE TRIALS

Human Challenge studies have ~~a~~ long history, including early research with smallpox, malaria, and yellow fever that changed the course of global public health. In the last 50 years, challenge studies have been safely performed in thousands of adult volunteers under the oversight of ethics committees. One of the early examples was Edward Jenner's vaccination of James Phipps. On 14th May 1796, Jenner injected the pus from a cowpox sore into cuts or wounds on the arm of a healthy boy, James Phipps. A few weeks later Jenner inoculated

Phipps with the pus from smallpox sore. Phipps did not suffer smallpox, the idea of vaccination, so the story goes, had been born. Since the beginning, challenge studies have been ethically demanding, because they directly flow out the Hippocratic principle of Primum nonnocere (first not harm). The first true challenge with an infectious agent was used to evaluate the safety of variolation for the prevention of smallpox. Later, in 1789, Edward Jenner emulated this study to show the effective use of vaccination against smallpox infection.[8,16]

The intentional infection of humans with pathogens and recording of such methods to achieve benefits dated back to the 18th Century in England. Even though the credit for initiating a modern science of vaccination is accorded to Edward Jenner (1749– 1823), who pioneered the usage of cowpox to prevent smallpox, began much earlier, in Asia and the Eastern Mediterranean, and was introduced to North America and England in the early 18th Century. Later in 1892, two scientists intentionally infected themselves with cholera bacteria. One developed clinical cholera, and this was selected as significant evidence linking the microbe with the disease. Another early human challenge study, testing a typhoid vaccine, in two 'Officers' of the Indian Medical Service' took place in 1896. In the late 19th and early 20th Centuries, many early challenge studies began to occur on a larger scale with increasing scientific rigor. Now challenge studies investigating be referred to as vector-borne diseases (e.g., yellow fever, dengue and, malaria).[3]

BENEFITS OF HUMAN CHALLENGE STUDIES[9, 18]

The challenge model has been proven to

- Enable expedited development of pipeline compounds.
- Offer robust efficacy data for candidate selection.
- Effectively translate animal studies data to human endpoints and relate healthy participant data to field outcomes.
- Accelerate both validation and discovery processes through concepts related to protective antibody levels and insights into innovative mechanisms of immunity.
- Human Challenge studies can be substantially shorter, and less expensive than other kinds of studies.

- Significantly reduce the number of volunteers that must be exposed to an experimental vaccine to determine its efficacy.
- These studies are commonly used in early-stage research for the selection of candidate interventions.
- Accelerate research programs with the aim of rapid development of effective interventions for use in at-risk populations.
- This challenge model requires a smaller sample size to obtain meaningful results.
- Predictions of effectiveness in later field studies.
- This challenge model is not only effective as a proof-of-concept for effectiveness, but also as proof-of-mechanism for novel targets (e.g.in asthma).

RISKS OF HUMAN CHALLENGE STUDIES[7, 16, 18]

- Human Challenge Studies are risky and the fact is that the pathogenesis of the disease or condition is poorly understood.
- There are two main risks, one is that of a serious and potentially fatal disease in the participants, and the other is that protection will not be mimicked in real-life exposure.
- There is no existing treatment available in case participants develop the disease.
- Huge implications if studies backfire.
- HCS involve particularly significant risks to participants and third parties; unless they have a clear scientific rationale.
- The level of risk may depend upon pathogen or challenge strain, study population, whether volunteers will be inpatients or outpatients.
- Risks comprise of two components: the probability of harm occurring, and the degree of that potential harm.

PHASES OF HUMAN CHALLENGE TRIALS IN VACCINE DEVELOPMENT

Clinical trials of vaccines and other treatments usually proceed in four phases.

➢ **Phase I trials:** These trials include safety testing to make sure the vaccine isn't actively dangerous;

➢ **Phase II trials:** It is a small-scale efficacy trial, designed to test if the vaccine is protective against infection;

➢ **Phase III trials:** It is an expanded, larger-scale efficacy trial with more varying groups of people, like the aged or people with pre-existing conditions, whose immune systems might operate differently.

➢ **Phase IV trials:** These studies assess drugs after they're officially on the market and being used.

In most Phase II and Phase III trials for vaccines, participants are exposed to the disease being targeted only in the course of their regular lives. That creates a potential problem in a condition like the Covid-19 outbreak. If you're a healthy person who's doing social distancing, you possibly aren't going to get infected or if you are, it'll probably take some while for the infection to occur. That makes it hard to do an actual comparison between the vaccinated and unvaccinated groups. Maybe they both end up the same because not one person in either group was exposed to the pathogen. If that's the case, the study hasn't told us anything useful. Alternatively, satisfactory exposure to the virus might occur only after many months or a year, slowing down the testing activity. That's the case for using challenge trials, in which participants are instantly exposed to the virus, with no delays or uncertainty about the share of participants who have actually been exposed and thus have had their vaccinations tested satisfactorily.[10]

Human Challenge Trials are considered as a model by which "challenge-protection" can be evaluated and they represent one possible method for vaccine development. Consequently, all principles for clinical assessment of vaccines should apply, including approval by the NRAs and ethical committees, along with compliance to GCP. Human challenge trials are also a type of efficacy indicating study, but most would not be considered to be pivotal studies. Almost all would-be pilots in nature performed to get beneficial information to aid in the development of a vaccine. Numerous challenge trials might often be performed throughout vaccine development.[11]

POTENTIAL PURPOSES OF HUMAN CHALLENGE TRIALS[16, 17]

- Characterization of the challenge stock and model system: titration, kinetics, symptoms, shedding, and transmissibility.

- A better understanding of the pathogenesis and immunity to the organism to guide decisions on what type of immune responses a vaccine might need to cause to protect against that disease.

- Identification of potential immune correlates of protection.

- Identification of the optimal trial designs for conventional pivotal efficacy trials (e.g. Case definitions, study design aspects, endpoints); generation of right hypotheses to be formally tested in traditional efficacy studies.

- Proof-of-concept as to whether a specific vaccine candidate might deliver protection or not.

- Down or up selection among various potential lead vaccine candidates to advance only the best to large pilot or pivotal efficacy studies and to eliminate those not worth advancement.

- Comparison of vaccine performance in endemic settings against an efficacy trial population, including assessing the impact of prior immunity in the context of prevalent endemic diseases.

- Support for emergency use of an investigational vaccine like in an influenza pandemic.

ETHICAL FRAMEWORK FOR HUMAN CHALLENGE STUDIES[12]

Human Challenge Trials possess significant risks for study participants, research professionals, and society as a whole. Volunteers, developers, regulators, and other stakeholders would need to weigh in on whether the risks outweigh the possible benefits.

- It should be limited by choosing volunteers with a low risk of developing a serious disease, providing cutting-edge medical treatment, and carefully selecting the virus strain and mode of administration.

- HCTs must use an informed consent procedure to ensure that participants acknowledge they will be exposed to an infectious pathogen with the risk of becoming ill and suffering damage and that this could cause them to get ill and suffer disease symptoms, including uncertain long-term effects and even death.

- Participants must realize that after they have been exposed to the virus, they will only be able to leave the study facility once they are no longer a danger to others, even if they decide to withdraw from the data collection aspect of the trial.

- In addition, bioethicists and researchers should carefully balance the benefits of compensation (e.g., honoring volunteers by allowing them to participate) against its possible disadvantages.

Modern HCS researchers normally take great care to keep participant risks to a minimum (e.g., through the choice of challenge strain and close monitoring, early diagnosis, and treatment of participants). If the risks of HCS are deemed appropriate, there appears to be agreement that intentional infection is permissible if certain ethical requirements are met. People are placed in danger as part of research for the good of others.[13] Refer to Figure No. 1 for Ethical concern in terms of human challenge studies.[16, 17] Nonetheless, HCS are ethically sensitive and pose important questions, such as those about

(I) The types and extent of benefits would be sufficient to justify bringing healthy volunteers at risk.

(II) How the eventual benefits of HCS can be communicated to participants and local populations.

(III) The appropriate level of burdens (including risks) to which healthy volunteers may be subjected.

(IV) Fair participant selection/exclusion, especially when vulnerable individuals are being recruited or excluded.

(V) Sufficient monetary compensation for participants

(VI) The need for additional ethical standards, rules, or processes, as well as/or evaluation procedures (e.g., special committees)

(VII) Appropriate challenge strain selection, development, and regulation.

(VIII) HCS's role(s) in the development of new therapies.

(IX) The importance of community involvement in raising public consciousness about challenge studies and ensuring that they are socially acceptable in the communities where they are conducted.

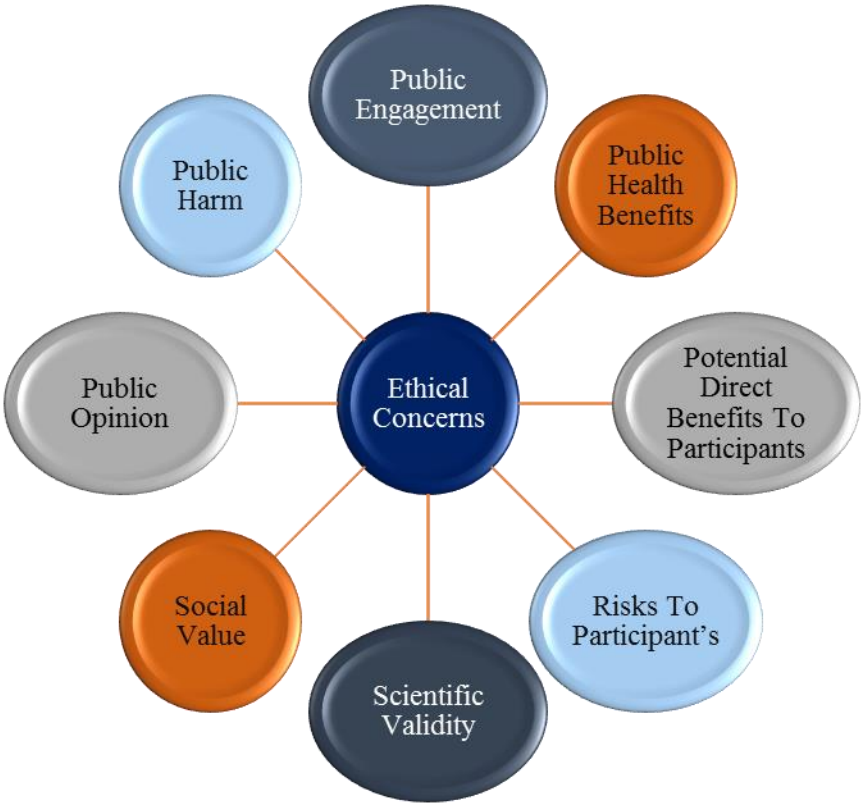

Figure No. 1: Ethical concern in terms of human challenge studies

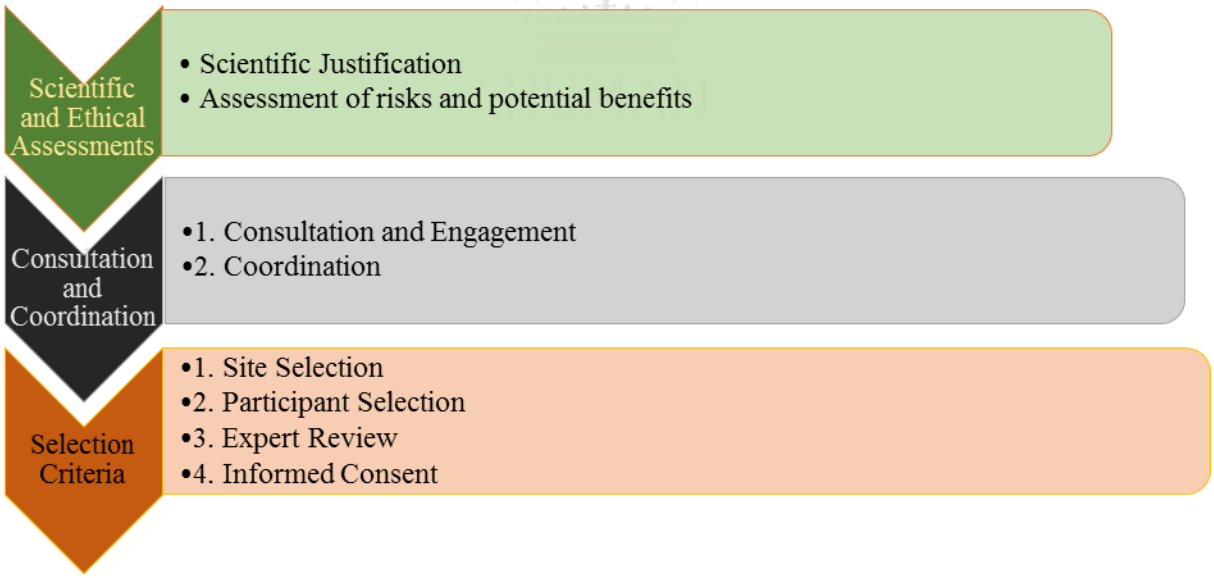

Figure No. 2: Eight criteria for conducting challenge studies

REGULATORY CONSIDERATIONS ON HUMAN CHALLENGE TRIALS

Standard regulations regulate HCS, including those governing the scientific conduct of research and those governing the development and use of investigational interventions, such as vaccines and medicines.[14] HCS may be subject to strict regulations relating to the development and use of a challenged organism, as well as additional regulations in certain situations if the organism is genetically modified. This section focuses on the regulation of challenge species because the general rules regulating research and the use of investigational vaccines do not apply to HCS, as well as HCS's position in regulatory development pathways leading to the approval of new vaccines and/or treatments. Refer to Table No. 1 for Regulatory bodies and/or specific regulations relevant to challenge organisms.

Human Challenge Trials for Vaccine Development: Regulatory Considerations, published by the WHO Expert Committee on Biological Standardization in 2016, is a short guidance paper. Overall, it is proposed that HCS be performed in the same manner as a (non-HCS) vaccine study, i.e., by observing normal clinical research guidelines (e.g., International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (CGP) procedures and local regulatory Clinical Trial Authorization (CTA) procedures for the conduct of clinical trials). While the document acknowledges that local regulations, such as those regulating genetically modified organisms, can vary.[15]

Table No. 1: Regulatory bodies and/or specific regulations relevant to challenge organisms

International Regulatory Agency	**Relevant Regulation**
WHO	Human Challenge Trials for, Vaccine Development: regulatory considerations (2016)
United Kingdom MHRA	Nil specific challenge strain regulation
United States of America US FDA	CGMP (for both challenge strain and other investigational products)
Europe European Medicines Agency (EMA) Auxiliary Medicinal	Auxiliary Medicinal Products in Clinical Trials (2017)

CHALLENGES IN CONDUCTING HCS[7]

- The majority of practical problems revolve around research design.
- Direct comparisons of HCS and field trials in terms of the time taken to generate results predicting vaccine effectiveness, the number of participants involved, and the associated benefits and risks of testing should be included in assessments of appropriate vaccine research strategies.
- These comparisons may be difficult, and epidemiological modeling will be required to inform ethical decisions using quantitative data.
- The choice and availability of a suitable challenge strain are critical to the setup of a human challenge study.
- Dose and route of infection is another challenge for experimental design in Human challenge studies.

- Most infections have a low natural attack rate and are often associated with mild or subclinical infections identified solely by serological responses.

- HCS which provides specific or otherwise difficult to obtain findings of asymptomatic infection, route, and risk of transmission during the early stages of illness, and the risk of re-infection is essentially the biggest concern in human challenge studies.

- One of the practical problems with human challenge trials is that efficacy outcomes do not always provide an adequate basis for licensing requirements on their own. But, in combination with standard Phase III trials, they may enable us to more rapidly weed out ineffective vaccine candidates or promote the development of promising candidates.

- Study participants are quarantined in a clinical trials unit as researchers monitor their immune responses and whether they develop symptoms.

DISCUSSION

Major advances

- Vaccines are assessed in a variety of challenge models to determine which ones have the greatest efficacy and can be used in field trials.

- Research into the pathogenesis of such infections and the creation of new therapies.

- Development of best studies with ethical and regulatory frameworks for use of human challenge models to improve public health through research with the relevant model system for human health.

Future opportunities

- To promote the production of new vaccines and treatments by developing new human challenge models and capabilities in existing models.

- To investigate natural and vaccine-induced infection resistance using emerging technologies such as RNAseq.

- To adapt challenge models to test putative virulence factors or antigens for vaccine production using genetically modified organisms.

- To build challenge strain libraries or repositories, as well as to encourage research investigators to share protocols and develop model frameworks.

- To develop or create challenge models in relevant populations, such as those living in endemic geographic areas, who may have significantly different and more relevant responses to infection, such as genetic history, prior exposure, or a different microbiome.

- Create a multinational ethical structure for challenge studies by maximizing the use of collaborative work between regulatory agencies.

SUMMARY

It is noted that human challenge trials have been, and can be performed successfully in low- and middle-income settings, according to the researchers. The same criteria as in more developed countries will apply. The investigators need to be qualified, an independent ethics committee review is required, and assurance of compliance with the local NRA's requirements and regulations are needed. If relevant, assurance of compliance with the national agency that regulates Genetically Modified Organisms, as well as bio-safety committees, may also be needed if applicable. If a controlled inpatient setting is required for the given study, this will also need to be in place. In addition to general principles for all clinical trials in human subjects, there are some unique and important operational aspects to the conduct of a human challenge trial.

Ideally, a human challenge study to establish the challenge model (i.e., without the use of an investigational medicinal product) should meet the same standards as a vaccination study – i.e., GCP compliance – and should be subject to approval or concurrence under a Clinical Trial Authorization by national regulatory authorities and ethics committees based on reliability. However, in the country where the challenging research will be undertaken, there may be no governmental framework in place to establish such expectations.

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