EXPERT COMMITTEE ON BIOLOGICAL STANDARDIZATION
Geneva, 17 to 21 October 2016

Human Challenge Trials: Scientific and regulatory considerations

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this draft is to provide information about the proposed WHO document on Human Challenge Trials: Scientific and regulatory considerations to a broad audience and to improve transparency of the consultation process.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee. Written comments proposing modifications to this text MUST be received by 23 September 2016 in the Comment Form available separately and should be addressed to the World Health Organization, 1211 Geneva 27, Switzerland, attention: Department of Essential Medicines and Health Products (EMP). Comments may also be submitted electronically to the Responsible Officer: Dr Ivana Knezevic at email: knezevici@who.int.

The outcome of the deliberations of the Expert Committee will be published in the WHO Technical Report Series. The final agreed formulation of the document will be edited to be in conformity with the "WHO style guide" (KMS/WHP/13.1).

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This guidance document published by WHO is intended to be scientific and advisory in nature. Each of the following
sections constitutes guidance for national regulatory authorities (NRAs) and for manufacturers of biological products. If an
NRA so desires, this document may be adopted as definitive national requirements, or modifications may be justified and made by the
NRA. It is recommended that modifications to this document be made only on condition that the
modifications ensure that the product is at least as safe and efficacious as that prepared in
accordance with the principles set out below.
1. Background and purpose

In July 2014, WHO held a consultation (1) to undertake a revision of the document *Clinical evaluation of vaccines: regulatory expectations* which had been adopted by the WHO Expert Committee on Biological Standardization in 2001. One area that was considered to be missing from the original version of this document, and which should be added in the revision, was the subject of human challenge trials. Human challenge trials are trials in which participants are intentionally challenged (whether or not they have been vaccinated) with an infectious disease organism. This challenge organism may be close to wild-type and pathogenic, adapted and/or attenuated from wild-type with less or no pathogenicity, or genetically modified in some manner.

Also discussed at the 2014 consultation was the matter of whether this addition to the document should be incorporated into the main text, where it would not be overlooked, but where it might also be thought to suggest that human challenge trials might be required, which is not the case. Alternatively, the information could be contained in an appendix with some mention in the main text to direct the reader to the appendix in case they had interest in this topic. It was generally agreed that the information should be placed in an appendix, and this was done. However, after several rounds of public consultation, comments and further revisions by the drafting group, the WHO consultation held on 3 May 2016 determined that, even as an appendix, the text might confuse some readers into thinking that human challenge trials are required. Thus, it was agreed that the appendix should be separated from the main document and published as a web document that would provide separate guidance for persons interested in the topic. An effort was made to continue the link between the main document on clinical evaluation of vaccines and the separate web document on human challenge trials. This was done to ensure that readers would understand that the document on human challenge trials should be read in the context of the larger document on clinical evaluation and to provide a bridge to certain terminology defined therein.

2. Scope

The scope of this document is to provide guidance to national regulatory authorities (NRAs), manufacturers, vaccine developers, investigators, independent ethics committees, and potentially
biosafety committees and national agencies that regulate genetically modified organisms (GMOs) if separate from the NRA. Only issues relevant specifically to the design and conduct of clinical trials enrolling healthy adult humans capable of truly informed consent and that involve the intentional exposure and potential infection with an infectious disease organism are discussed. All other issues common to the design, conduct and evaluation (assessment) of vaccine clinical trials may be found in the document *Clinical evaluation of vaccines: regulatory aspects*, which is to be considered by the WHO Expert Committee on Biological Standardization in October 2016.

3. Introduction

Although human challenge trials are not a required element of every vaccine development programme, there are many reasons why a developer may wish to conduct with humans a “challenge-protection” study that might normally be conducted in animals. Animal models are often quite imprecise in reflecting human disease, and many infectious organisms against which a developer might wish to develop a vaccine are species-specific for humans. Human challenge trials may be safely and ethically performed in some cases, if properly designed and conducted. Tremendous insight into the mode of action and the potential for benefit in the relevant species – humans – may be gained from challenge trials. However, there are also limitations to what challenge trials may be able to ascertain because, like animal model challenge-protection studies, a human challenge trial represents a model system. Because there are often such significant limitations to animal models, the model system of the human challenge trial may significantly advance, streamline and/or accelerate vaccine development (2).

It will be important to consider the regulatory framework in which the human challenge trial may be conducted because, in some countries, challenge stocks are expected to be regulated in the same manner as vaccines and are expected to be studied with authorization in accordance with clinical trial regulations, whether or not an investigational vaccine is to be used in the same clinical investigation protocol. For instance, a challenge trial might be conducted to titrate the challenge organism in humans before using the challenge in a vaccine study, in order to know
the proper dose of the challenge organism to give and to characterize the symptoms, kinetics, shedding, transmissibility and so forth to be expected from the challenge. In cases when challenge should be studied in compliance with clinical trial regulations, there is greater clarity about regulatory expectations, including the quality of the challenge stock to be used, because the clinical trial regulations or requirements would apply. However, in many countries, because the challenge stock is not itself a medicinal product, such characterization/model development studies would not come under the NRA’s review and authorization. Thus, much less clarity exists on regulatory expectations and quality matters in such cases.

It should be understood that a pathogenic challenge strain will not have the “safety” of a hopefully innocuous vaccine. However, its quality should be comparable to a candidate vaccine at the same clinical trial phase. Ideally, a human challenge study should also match the same expectations for conduct of a vaccine study – i.e. compliance with good clinical practice (GCP) and approval of a clinical trial authorization (CTA). However, there may be no regulatory framework to promulgate such expectations in the country where the challenge study is to be conducted. Trial sponsors, vaccine developers, researchers and others should determine from the relevant NRA what regulatory expectations they may have when clarity does not exist and when the human challenge study is intended to support the development of a vaccine candidate they would like to ultimately license (i.e. gain marketing authorization or registration).

It is also important to note that not all diseases for which vaccines might be developed are suitable for conducting human challenge trials. In many cases, human challenge with a virulent or even an attenuated organism would not be considered ethical or safe. For example, if an organism causes a disease with a high case fatality rate (or there is a long and uncertain latency period) and there are no existing therapies to prevent or ameliorate disease and preclude death, then it would not be appropriate to consider human challenge trials with such an organism. However, a human challenge trial might be considered when the disease an organism causes has an acute onset, can be readily and objectively detected, and existing efficacious treatments
(whether curative or palliative) can be administered at an appropriate juncture in disease development to prevent significant morbidity (and eliminate mortality).

4. Purposes of human challenge trials

A vaccine developer may conduct human challenge trials to accomplish one or more of a number of aims. The aims of the study determine which clinical phase the study is in. Human challenge trials are often a type of efficacy study, but most would not be considered to be pivotal efficacy studies. Almost all would be pilot in nature, performed to gain useful information to aid in the development of a vaccine. Several challenge trials might often be performed during the course of vaccine development.

Potential purposes of human challenge trials could include one or more of the following:

- characterization of the challenge stock and model system: titration, symptoms, kinetics, shedding, transmissibility, etc;
- clearer understanding of the pathogenesis of and immunity to the organism in order to guide decisions on what (type and/or quantity) immune responses a vaccine might need to elicit in order to protect against that disease – i.e. insight for vaccine design (studies for this purpose may be referred to as experimental medicine studies);
- identification of potential immune correlates of protection (ICPs, which would then require validation in a traditional efficacy study);
- identification of the optimal trial design for traditional pivotal efficacy trial(s) (e.g. case definitions, endpoints, study design aspects);
- generation of appropriate hypotheses to be formally tested in traditional efficacy trials;
- proof-of-concept as to whether a particular vaccine candidate might provide protection or not;
- down- or up-selection among various potential lead vaccine candidates to advance only the best to large pilot or pivotal efficacy trials and to eliminate those not worth advancement;
• de-risk or “left-shift”\(^1\) risk of failure in a vaccine development programme;
• comparison of vaccine performance in endemic settings versus an efficacy trial population,\(^2\) including evaluating the impact of prior immunity in the context of prevalent endemic diseases and conditions;
• support for emergency use of an investigational vaccine (e.g. in an influenza pandemic);
• a basis for licensure (this purpose would be a rare exception rather than the rule);
• exploration post-licensure of whether immunity to vaccination wanes, and if or when booster doses might be required for durable protection;\(^3\)
• others.

No single study could accomplish all of the above aims. For instance, if the human challenge model system does not adequately mimic the wild-type disease and the situation in which a vaccine would need to protect, then a human challenge trial would not be usable as a primary basis for licensure.

5. Purpose influences study design, which influences regulatory use and decision-making

As in all studies, the aim(s) of the human challenge trial guides the study design. Consequently, even for the same disease, the challenge model may vary according to the purposes and design of the study to be conducted. In some cases (e.g. to identify appropriate efficacy trial design and case definitions), the challenge model may need to mimic wild-type disease as closely as feasible. In other cases, consideration might be given to the use of an attenuated challenge organism (e.g. a previous vaccine candidate) or a model system in which objective early signs

\(^1\) When a timeline of vaccine development is viewed as a graph from early to the left to late to the right, shifting the risk of failure earlier, or left, in the timeline could result in significant cost- and resource-savings and could minimize lost opportunity costs by abandoning an unpromising candidate before committing greater expenditures to higher-phase clinical trials, not to mention minimizing risk to human subjects by not conducting large efficacy studies of vaccines that would not prove efficacious.

\(^2\) The target population in a particular country may have a higher rate of individuals with, for instance, sickle cell trait, different nutritional status or greater parasitic load in “normal” flora, any of which might affect immune responsiveness and thus efficacy (benefit), compared to the efficacy trial population, or safety (greater risks) in the endemic setting. Either would have an impact on the risk/benefit decision-making.

\(^3\) This might entail a challenge study in adults to extrapolate when children might need booster doses.
(e.g. parasitaemia, viraemia) signal the onset of disease symptoms. These signals could trigger initiation of treatment to prevent actual disease onset or morbidity. Initiation of treatment should be based on pre-specified criteria in the study protocol.

Another important consideration for a human challenge model system would be its usefulness for positive or negative prediction. If used for down-selection, de-risking or to identify vaccine candidates that would not warrant advancement to large human efficacy studies, the usefulness for negative prediction should be high. If intended to be used for evidence of vaccine efficacy, the usefulness for positive prediction of the model system might need to be nearly as compelling and credible as a traditional pivotal efficacy trial might be. Whether the purpose of the study or studies is to provide supportive evidence for licensure or to help inform and design traditional efficacy studies or vaccine design, human challenge trials may contribute to the preponderance of evidence upon which regulators could take a clinical trial or licensure decision. Thus, the purpose of the study would influence the design, which would in turn influence conclusions and decisions that might be made from the study results by regulators.

6. Operational aspects

There are some unique and important operational aspects to the conduct of a human challenge trial. Most often, human challenge trials are undertaken in special facilities that are designed and operated in a manner that can prevent the spread of the challenge organism to people outside the study or to the environment. These clinical facilities are capable of providing continuous monitoring and medical attention at the appropriate point(s) in time after the challenge is given. In addition to providing immediate access to appropriate medical care and treatment, the facilities are often designed to prevent the spread of disease, particularly when the challenge organism is a genetically modified organism or an organism that is not endemic to the locality. These facilities may need to be operated in a manner that permits all waste (including excrement) to be collected and decontaminated before release. All staff, including janitorial and administrative staff, might be required to work in personal protective gear appropriate for the
pathogenicity of the challenge organism and its potential hazard to the environment. It should be noted that not all human challenge trials require such a high level of control. When the challenge organism is attenuated and the wild-type organism is likely to be present in the locality anyway, it may be adequate to conduct human challenge trials in an outpatient setting or with minimal procedures to prevent spread (e.g. use of BCG vaccine as a challenge organism, use of bandaging that could cover and prevent spread from an intramuscular injection – so long as the organism is not shed by other means).

It may be necessary to ensure housing of controls and vaccinees together if an objective of the human challenge trial is to identify potential for transmissibility. In such a situation, only the vaccinees or unvaccinated participants might be challenged, and the controls, who were not challenged, would be monitored for evidence of acquiring the challenge organism through contact with the challenged vaccinees. In this way, transmissibility of the challenge organism may be determined. In order to achieve the study objective of identifying transmissibility, it would be necessary to conduct the study in-house even if the challenge organism was attenuated and the wild-type organism was present in the locality.

It should be noted that human challenge trials have been, and can be, successfully conducted in low- and middle-income settings. The same standards would apply as in more developed countries. The investigators need to be qualified, independent ethics committee review is required, and assurance of compliance with the local NRA’s requirements and regulations is needed. If relevant, assurance of compliance with the national agency that regulates GMOs, and/or local biosafety committees, may also be needed. If a controlled inpatient setting is required for the given study, this would also need to be in place.

7. Some key ethical considerations
Ethics in clinical trials, as in medicine, follow the precept of “do no harm”. Review of the proposed human challenge study by an independent ethics committee is essential. By their nature (i.e. intentional infection of humans with disease-causing organisms), human challenge trials would seem to contradict this basic precept. Further, clinical trials should be designed and conducted in a manner that minimizes risks to human subjects while maximizing the potential for benefit. Consideration must be given to both potential individual risks and benefits, as well as to potential societal benefits (and risks, such as release into the environment of a pathogen that might not otherwise be present). Provisions in clinical trial ethics are made for situations in which there may be greater-than-minimal risk but no (or little) potential for individual benefit, when knowledge may be gained to the benefit of the larger societal population with whom the potential trial participant shares significant characteristics.

Ethical considerations about challenges in clinical trials should be thoroughly evaluated. In particular, the use of placebo in vaccine trials was the main topic of the WHO Expert Consultation in January 2013 and a set of considerations for NRAs and ethics committees is provided in the WHO meeting report (3). These considerations are intended to facilitate review of proposed use of placebo in vaccine trials on a case-by-case basis. Such principles, discussed by the meeting participants as reported, may be a model for considering how ethical principles apply to human challenge trials.

Acknowledgement is due to the reality that some persons are greater risk-takers than others, while some persons are quite risk-averse and would not accept the risk of receiving a challenge. The key to asking individuals to accept the risk from a challenge study, in which they have little potential to receive individual benefit, is the element of informed consent. Healthy adults may consent when they are well-informed and understand what risks they are accepting to take, even if those risks may be considerably greater than minimal (e.g. accepting that they will develop an acute, but manageable, disease that will resolve but in the meantime may cause considerable morbidity, such as severe diarrhoea managed with fluid and electrolyte replacement). There could be some potential for direct benefit if the trial participant becomes immune to the disease.
caused by the challenge (or wild-type) organism but, conversely, pre-existing immunity upon exposure to wild-type virus in the future may be harmful. Thus, in appropriate situations, it may be considered ethical to ask healthy and informed adults to consent to volunteer and participate in a human challenge trial whether they will receive an investigational vaccine that may or may not protect them from the challenge organism, a placebo that will not protect them, or only the challenge organism itself. However, accepting such risks requires absolutely that the elements of voluntary consent are based on truly being informed. It is for this reason (i.e. the need for truly informed consent) that consideration of conducting human challenge studies in children, or in any other vulnerable population which would have diminished capacity to give informed consent, would not be deemed acceptable at this time.

The need to minimize risks to subjects in clinical trials calls for the investigators to give due consideration to whether or not the challenge organism need be pathogenic or not, or to what degree. As noted above, the aim or purpose of the study may drive this decision about pathogenicity or attenuation, but the ethics of minimizing – to the extent that is feasible within the frame of sound science – any risks to human subjects should bear due consideration in this regard. It should also be obvious that the credibility of the data to support regulatory decision-making needs to be taken into account when deciding how pathogenic or attenuated the challenge organism need be.

References


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