

Annex 10

Human challenge trials for vaccine development: regulatory considerations

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Guidance documents published by the World Health Organization (WHO) are 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.

Abbreviations

GCP	good clinical practice
GMO	genetically modified organism
ICP	immune correlate of protection
NRA	national regulatory authority

1. Introduction

Infectious human challenge trials involve the deliberate exposure of human volunteers to infectious agents. Trial 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.

Human challenge trials have been conducted over hundreds of years and have contributed vital scientific knowledge that has led to advances in the development of drugs and vaccines. Nevertheless, such research can appear to be in conflict with the guiding principle in medicine to do no harm. A number of well-documented historical examples of human exposure studies would be considered unethical by current standards. It is essential that challenge trials be conducted within an ethical framework in which truly informed consent is given. When conducted, human challenge trials should be undertaken with abundant forethought, caution and oversight. The value of the information to be gained should clearly justify the risks to human subjects.

Although human challenge trials are not a required element of every vaccine development programme, there are many reasons why a developer may ask to conduct a “challenge-protection” study with humans, which 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. Considerable insight can then be gained into the mode of action and potential benefit of drugs and vaccines in humans. However, there are also limitations on what challenge trials may be able to ascertain because, as with animal-model challenge-protection studies, a human challenge trial represents a model system. Nevertheless, because there are often such significant limitations to animal models, the model system of a human challenge trial may significantly advance, streamline and/or accelerate vaccine development (1).

It is 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 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.

It will also be important to consider the regulatory framework in which the human challenge trial may be conducted. 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 example, a challenge trial might be conducted to titrate the challenge organism in humans (before using the challenge in a vaccine study) in order to determine the proper dose of the challenge organism to administer, and to characterize the symptoms, kinetics, shedding and transmissibility to be expected from the challenge. The dose of challenge organism is usually titrated to induce a relatively high attack rate while limiting disease severity. In cases where the 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 considered to be a medicinal product, such characterization/model development studies would not come under national regulatory authority (NRA) review and authorization. Thus, much less clarity would exist on regulatory expectations and issues of quality in such cases.

It should be understood that a pathogenic challenge strain will not have the “safety” of an intended safe candidate vaccine. However, its quality should be comparable to a candidate vaccine at the same clinical trial phase. Ideally, a human challenge trial to establish the challenge model (that is, without use of an investigational medicinal product) should also match the expectations for conducting a vaccine study – that is, compliance with good clinical practice (GCP) and subject to approval or concurrence under a Clinical Trial Authorization by NRAs and ethics committees on the basis of requirements appropriate for this type of study. If such a framework does not exist, countries are encouraged to establish an appropriate regulatory and ethical framework for challenge trials. 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 other involved parties should determine what regulatory expectations the relevant NRA 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 ultimately like to license (that is, obtain marketing authorization or registration).

2. Background

In July 2014, WHO held a consultation on Clinical evaluation of vaccines: regulatory expectations (2). One area that was considered to be an important element in facilitating vaccine development was human challenge trials. It was recognized that the regulation of such trials needed to be well-defined by NRAs and that vaccine developers and manufacturers needed to be aware of regulatory expectations in this area.

This WHO guidance document on human challenge trials should be read in conjunction with the updated WHO *Guidelines on clinical evaluation of vaccines: regulatory expectations* (3) which were adopted, along with the current document, by the WHO Expert Committee on Biological Standardization in October 2016.

3. Purpose and scope

The purpose of this document is to provide guidance to NRAs, manufacturers, vaccine developers, investigators and independent ethics committees – and potentially to biosafety committees and national agencies that regulate genetically modified organisms (GMOs) where separate from the NRA. The document only covers issues specifically relevant to the design and conduct of clinical trials that enrol healthy adult humans capable of truly informed consent, and that involve the intentional exposure to, and potential infection with, an infectious disease organism. All other issues common to the design, conduct and evaluation (assessment) of vaccine clinical trials may be found in the updated WHO *Guidelines on clinical evaluation of vaccines: regulatory expectations* (3).

4. Purposes of human challenge trials in vaccine development

Human challenge trials are considered as a model by which challenge protection can be evaluated and represent one possible approach for vaccine development.

Therefore, all principles for the clinical evaluation of vaccines should apply, including the need for approval by the NRA and ethical committees as well as compliance to GCP.

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

development of a vaccine. Several challenge trials might 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 in terms of titration, symptoms, kinetics, shedding and transmissibility;
- clearer understanding of the pathogenesis of, and immunity to, the organism in order to guide decisions on what immune responses (type and/or quantity) a vaccine might need to elicit in order to protect against that disease as part of gaining insight into 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 design for traditional pivotal efficacy trial(s) – for example, case definitions, end-points and other 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 of 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;

¹ When the 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 (left) in the timeline could: (a) minimize risk to human subjects by avoiding large efficacy studies of vaccines that would not prove efficacious; (b) result in significant cost and resource savings; and (c) minimize lost opportunity costs by abandoning an unpromising candidate before committing greater expenditures to higher-phase clinical trials.

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

- support for emergency use of an investigational vaccine (for example, during an influenza pandemic);
- provision of a basis for licensure (this purpose would be a rare exception rather than routine);
- post-licensure exploration of whether immunity following 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 example, if the human challenge model system does not adequately mimic the wild-type disease and the actual situation in which a vaccine would need to provide protection, then a human challenge trial would not be usable as a primary basis for licensure.

5. Study design of human challenge trials

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 (for example, 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 (for example, a previous vaccine candidate) or to a model system in which objective early signs (for example, parasitaemia or viraemia) signal the onset of disease. These signals could then trigger initiation of treatment to prevent actual disease onset or morbidity. Such initiation of treatment should be based on criteria pre-specified 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 degree of usefulness of the model system for negative prediction should be high. If intended to be used for evidence of vaccine efficacy, the degree of usefulness for positive prediction might need to be almost as compelling and credible as for a traditional pivotal efficacy trial. 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

³ This might entail a challenge study in adults to extrapolate when children might need booster doses.

evidence upon which regulators could take a clinical trial or licensure decision. Thus, the purpose of the study would influence its design, which would in turn influence the conclusions and decisions that might be made by regulators following consideration of the study results.

6. Operational aspects

In addition to general principles for all clinical trials in human subjects there are some unique and important operational aspects to consider when conducting a human challenge trial. Human challenge trials should be undertaken in accordance with a protocol, and in special facilities that are designed and operated in a manner that prevents the spread of the challenge organism to people outside the study or to the environment. These clinical facilities should be 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 should be designed to prevent the spread of disease, particularly when the challenge organism is a GMO 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 equipment appropriate for the pathogenicity of the challenge organism and its potential hazard to the environment, and should be informed of the potential risks. 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 appropriate procedures to prevent spread. Examples of such approaches and procedures include the use of BCG vaccine as a challenge organism, the use of bandaging to cover and prevent spread from an intramuscular injection (assuming the organism is not shed by other means) and the use of malaria challenge during winter months in a temperate region. There may be other circumstances in which a human challenge trial is undertaken, for example where the target organism of the vaccine to be developed is not present in the location where the target group for its indication lives (for example, in case of a traveller vaccine) – when the risk of spread of the organism is low, human challenge trials using appropriate procedures could be undertaken.

It may be necessary to ensure that controls and vaccinees are housed together if an objective of the human challenge trial is to identify the potential for transmissibility. In such a situation, only the vaccinees or unvaccinated participants would 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, the transmissibility of the challenge organism from challenged vaccinees 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, an independent ethics committee review is required, and assurance of compliance with NRA requirements and regulations is needed. If relevant, assurance of compliance with the national agency that regulates GMOs and/or with 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 include the precept of “minimizing risks to subjects and maximizing benefits” and clinical trials should be designed and conducted accordingly. Review of the proposed human challenge trial by an independent ethics committee is essential. By their nature (that is, intentional infection of humans with disease-causing organisms) human challenge trials would seem to contradict this basic precept. Consideration must therefore be given to both potential individual risks and benefits, as well as to potential societal risks and benefits, such as the 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 that benefits the larger societal population with whom the potential trial participant shares significant characteristics.

The ethical considerations concerning challenges in clinical trials should be thoroughly evaluated. During a WHO Expert Consultation held in January 2013 consideration was given to the way in which ethical principles should be applied to vaccine trials. The main consultation topic concerned the use of placebo in such trials, and a set of considerations for NRAs and ethics committees was provided in the meeting report (4) and subsequently published recommendations (5). Although specifically intended to facilitate review of the proposed use of placebo in vaccine trials on a case-by-case basis these considerations and recommendations are likely to have applicability to human challenge trials.

It has to be acknowledged that in reality some individuals are greater risk-takers than others, and that those who are risk averse would be unlikely to

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) lies in the element of informed consent. Healthy adults may consent when they are well informed and understand what the risks are that they are agreeing to take – even if those risks may be considerably greater than minimal (for example, 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 should the trial participant become immune to the disease caused by the challenge (or wild-type) organism but, conversely, pre-existing immunity upon exposure to the wild-type organism 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, it is an absolute requirement that accepting such risks and providing voluntary consent are based upon being truly informed. For this reason (the absolute requirement for truly informed consent) it is not deemed acceptable at this time to consider conducting human challenge trials in children, or in any other vulnerable population with diminished capacity to give informed consent. One possible exception to this principle that might be considered would be a challenge model that used a licensed live-attenuated vaccine as the challenge organism.

The need to minimize the risks to subjects in clinical trials calls for investigators to give due consideration to whether the challenge organism needs be pathogenic or not, or to what degree. As noted above, the aim or purpose of the study may drive decisions on pathogenicity or attenuation, but the ethical precept of minimizing risks to human subjects – to the maximum extent feasible within the framework of sound science – should be given due consideration. Key to such considerations is the credibility of the data to support regulatory decision-making, which also needs to be taken into account when deciding how pathogenic or attenuated the challenge organism needs to be.

Authors and acknowledgements

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The second draft was prepared by a WHO drafting group and posted on the WHO Biologicals website (as an appendix to the WHO Guidelines on clinical evaluation of vaccines) for a second round of public consultation from 1 February to 15 March 2016. Comments were received from: Dr B. Brock, Sanofi Pasteur, the USA (*provided the consolidated comments of the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)*); Dr K. Farizo, United States Food and Drug Administration, Center for Biologics Evaluation and Research, the USA; and Dr A. Rinfret, Health Canada, Canada.

At a WHO meeting of the Working Group on clinical evaluation of vaccines held in Geneva, Switzerland, 3 May 2016 it was concluded that this WHO guidance document should be provided as a separate document rather than as an appendix to the WHO Guidelines on clinical evaluation of vaccines. The meeting was attended by: Dr G. Coleman, Health Canada, Canada; Dr M. Darko, Food and Drugs Authority, Ghana; Dr D. Etuko, National Drug Authority, Uganda; Dr E. Griffiths, Consultant, Kingston-upon-Thames, England; Dr S. Kennedy, University of Liberia, Liberia; Dr J. McEwen, Therapeutic Goods Administration, Australia; Dr M. Powell, Medicines and Healthcare products Regulatory Agency, England; Dr R. Sheets, Consultant, Silver Spring (MD), the USA; Dr J. Southern, Medicines Control Council, South Africa; Dr Y. Sun, Paul-Ehrlich-Institut, Germany; Dr K. Zoon, National Institutes of Health, the USA; and Dr I. Knezevic, World Health Organization, Switzerland.

Based on the comments received during the public consultation and on the discussions of the above Working Group meeting, the document WHO/BS/2016.2288 was prepared by Dr R. Sheets and Dr I. Knezevic.

The document was then posted on the WHO Biologicals website for a third round of public consultation from 27 July to 16 September 2016 and comments received from: Dr J. Auerbach and Dr A. Podda, GSK Vaccines Institute for Global Health, Italy; Dr M. Gruber and Dr D. Pratt, United States Food and Drug Administration, Center for Biologics Evaluation and Research, the USA; Dr P. Njuguna, KEMRI Wellcome Trust Research Programme, Kenya; and Dr P. Smith, London School of Hygiene and Tropical Medicine, England.

Further changes were subsequently made to document WHO/BS/2016.2288 by the WHO Expert Committee on Biological Standardization.

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