Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations

Proposed revision of WHO TRS 924, Annex 1

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 early draft is to provide information about the proposed Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations, 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 15th March 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 on Biological Standardization 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" (WHO/IMD/PUB/04.1).
Recommendations and guidelines published by 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. If an NRA so desires, these Guidelines may be adopted as definitive national requirements, or modifications may be justified and made by the NRA. It is recommended that modifications to these Guidelines be made only on condition that modifications ensure that the vaccine is at least as safe and efficacious as that prepared in accordance with the recommendations set out below. The parts of each section printed in small type are comments or examples for additional guidance intended for manufacturers and NRAs, which may benefit from those details.
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Appendix 1. Human challenge trials
1. **Introduction**

This guideline is intended to replace *WHO Technical Report, Series No. 924, Annex 1 Guidelines on clinical evaluation of vaccines: Regulatory Expectations*, which was adopted by the Expert Committee on Biological Standardization (ECBS) in 2001 (1). This document of 2001 has served as a basis for setting or updating national requirements for the evaluation and licensing of a broad range of vaccines as well as for WHO vaccine prequalification.

Following on the establishment of the document of 2001, more than 20 vaccine-specific documents that include a section on clinical evaluation have been adopted by the ECBS, all of which are intended to be read in conjunction with TRS 924, Annex 1 (2). These include documents that address polio vaccines [OPV, IPV], whole cell pertussis and acellular pertussis vaccines, meningococcal conjugate vaccines for serotypes A and C, pneumococcal conjugate vaccines and vaccines intended to prevent diseases due to rotaviruses, dengue viruses, human papillomaviruses and malaria parasites.

This guideline has been prepared to reflect the scientific and regulatory experience that has been gained from vaccine clinical development programs since the adoption of the above mentioned version in 2001. Many challenging issues surrounding appropriate and feasible vaccine clinical development programs for specific types of vaccines have arisen in the intervening period. For example, there has been increasing recognition of the potential need to base initial licensure of certain vaccines on safety and immunogenicity data only (i.e. it is not feasible to generate pre-licensure efficacy data) and in the absence of an established immunological correlate of protection (ICP).

This guideline is intended for use by national regulatory authorities (NRAs), companies developing and holding licences for vaccines, clinical researchers and investigators. It considers the variable content of clinical development programs, clinical trial designs, the interpretation of trial results and post-licensing activities. The content of the various sections is intended to assist in the preparation and approval of clinical trial applications, applications for initial licensure and
applications to support post-licensure changes as well as to provide guidance on post-licensure activities, such as pharmacovigilance and estimation of vaccine effectiveness.

The main changes (modification or expansion of previous text and additional issues covered) in this revision compared to the above mentioned version of TRS No. 924, Annex 1, 2001 (1) include, but are not limited to, the following:

**Immunogenicity**

- General principles for comparative immunogenicity studies, including selection of the comparators, endpoints and acceptance criteria for concluding non-inferiority or superiority of immune responses
- Situations in which age de-escalation studies may be inappropriate
- Assessing the need for and timing of post-primary doses
- Using different vaccines for priming and boosting
- Assessing the ability of vaccines to elicit immune memory or to cause hypo-responsiveness
- Using immunogenicity data to predict vaccine efficacy, with or without bridging to efficacy data
- The derivation and uses of immunological ICPs
- Vaccination of pregnant women to protect them and/or their infants

**Efficacy**

- Role and potential value of human challenge studies
- Need for and feasibility of conducting vaccine efficacy studies
- Selection of appropriate control groups in different circumstances
- Comparing extended with parent versions of vaccines
- Predicting vaccine efficacy when there is no ICP and vaccine efficacy studies are not feasible
- Preliminary and confirmatory vaccine efficacy studies and their design
- Vaccines with modest efficacy and/or that provide a short duration of protection
• Extrapolating data between geographic/genetically diverse populations
• Role of sponsors and public health authorities in generating vaccine effectiveness data

Safety
• Detailed consideration of the collection and analysis of safety data from clinical trials
• Consideration of size of the pre-licensure database by type of vaccine and its novelty
• Consideration of the safety database by population sub-group
• Special safety considerations by vaccine construct
• Circumstances of limited safety data pre-licensure
• Use of vaccine registries and disease registries
• Particular issues for vaccine pharmacovigilance activities

Due to the fact that a separate document on nonclinical evaluation of vaccines was established in 2003 (3), the section on that topic in the 2001 version has been removed. Furthermore, the structure of the document has changed. In particular, a number of methodological considerations have now been incorporated into relevant sections and subsections rather than being described in a separate section. In line with the changes made in the document, the Glossary and References have been updated.

The WHO has also made available several other guidelines of relevance to clinical development programs for vaccines. These should be consulted as appropriate and include:
• Good clinical practice for trials on pharmaceutical products (4)
• Good manufacturing practice for pharmaceutical preparations (5)
• Good manufacturing practice for biological products (6)
• Guidelines on nonclinical evaluation of vaccines (3)
• Guidelines on nonclinical evaluation of vaccine adjuvants and adjuvanted vaccines (7)
• Guidelines on procedures and data requirements for changes to approved vaccines (8)
• Guidelines for independent lot release of vaccines by regulatory authorities (9)
• Recommendations for the evaluation of animal cell cultures as substrates for the manufacture of biological medicinal products and for the characterization of cell banks (10)
Furthermore, guidance on various aspects of pre-licensure clinical development programs for vaccines and post-licensure assessment is also available from several other bodies, such as the International Conference on Harmonization (ICH), the European Medicines Agency (EMA), the United States Food and Drug Administration (FDA) and the United Kingdom Medical Research Council (MRC). These WHO guidelines are not intended to conflict with, but rather to complement, these other documents.

2. **Scope**

This guideline considers clinical development programmes for vaccines that are intended to prevent infectious diseases in humans by eliciting protective immune responses that are sufficient to prevent clinically apparent infections. It includes vaccines that may be given before exposure or shortly after known or presumed exposure to an infectious agent to prevent onset of clinical disease. Protective immune responses may be directed against one or more specific antigenic components of micro-organisms or against substances produced and secreted by them (e.g. toxins) that are responsible for clinical disease.

The guideline is applicable to vaccines which contain one of more of the following:

- Microorganisms that have been inactivated by chemical and/or physical means
- Live microorganisms that have been rendered avirulent in humans as a result of attenuation processes or specific genetic modification
- Antigenic substances that have been derived from micro-organisms. These may be purified from micro-organisms and used in their natural state or may be modified (e.g. detoxified by chemical or physical means, aggregated or polymerized).
- Antigens that have been manufactured by synthetic processes or produced by live organisms using recombinant DNA technology.
• Antigens (however manufactured) that have been chemically conjugated to a carrier molecule to modify the interaction of the antigen with the host immune system.
• Antigens that are expressed by another micro-organism which itself does not cause clinical disease but acts as a live vector (e.g. live viral vectored vaccines, live attenuated chimeric vaccines).

In addition, although naked DNA vaccines are not specifically discussed in this guideline the principles and development programs outlined are broadly applicable.

This guideline does not apply to:
• Therapeutic vaccines (i.e. used for treatment of disease)
• Vaccines intended for any purpose other than prevention of infectious diseases and the consequences of infectious diseases.

3. Glossary

The definitions given below apply to the terms used in this guideline. They may have different meanings in other contexts.

Adverse event (AE)
Any untoward medical occurrence in a trial subject. An AE does not necessarily have a causal relationship with the vaccine.

Adverse event following immunization (AEFI)
Any untoward medical occurrence that follows immunization using a licensed vaccine outside of a clinical trial setting. An AEFI does not necessarily have a causal relationship with the use of the vaccine. The AEFI may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

Attack rate
The proportion of the population exposed to an infectious agent who become (clinically) ill.


**Blinding**

A procedure in which one or more parties involved in a clinical trial are kept unaware of the treatment assignment(s). Double blinding refers to the vaccinees/care-givers, investigator(s) and sponsor staff being unaware of the treatment assignment during the conduct of the trial and at least until after completion of the primary analysis.

**Booster dose**

A dose that is given at a certain time interval after completion of the primary series that is intended to boost immunity to, and therefore prolong protection against, the disease that is to be prevented.

**Case ascertainment**

The method adopted in a trial of vaccine efficacy for detecting cases of the infectious disease intended to be prevented by vaccination.

**Case definition**

The pre-defined clinical and laboratory criteria that must be fulfilled to confirm a case of a clinically manifest infectious disease in a study of vaccine efficacy or effectiveness.

**Clinical trial application**

An application submitted to a NRA by a sponsor for the purposes of gaining authorization to conduct a clinical trial of an investigational or licensed vaccine at a trial site within the NRA’s jurisdiction. The contents and format of the application will vary as required by the relevant NRA(s).

**Cluster randomization**

Randomization of subjects into a clinical trial by group (e.g. by households or communities) as opposed to randomization of the individual subject.

**Geometric mean concentration**

The average antibody concentration for a group of subjects calculated by multiplying all values
and taking the $n$th root of this number, where $n$ is the number of subjects.

**Geometric mean titre**

The average antibody titre for a group of subjects calculated by multiplying all values and taking the $n$th root of this number, where $n$ is the number of subjects.

**Good clinical practice (GCP)**

GCP is a process that incorporates established ethical and scientific quality standards for the design, conduct, recording and reporting of clinical research involving the participation of human subjects. Compliance with GCP provides public assurance that the rights, safety, and well-being of research subjects are protected and respected, consistent with the principles enunciated in the Declaration of Helsinki and other internationally recognized ethical guidelines, and ensures the integrity of clinical research data.

**Good manufacturing practice (GMP)**

GMP is the aspect of quality assurance that ensures that medicinal products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the product specification.

**Immunological correlate of protection (ICP)**

An Immunological Correlate of Protection (ICP) is most commonly defined as a type and amount of immunological response that correlates with vaccine-induced protection against a clinically apparent infectious disease and is considered predictive of clinical efficacy. For some types of vaccines the ICP may be the type and amount of immunological response that correlates with vaccine-induced protection against infection (e.g. hepatitis A and B vaccines). The ICP may be mechanistic (i.e. causative for protection, such as antibody that effects virus neutralization or serum bactericidal antibody) or it may be non-mechanistic (i.e. non-causative, an immune response that is present in those protected by vaccination, but not the cause of protection (such as serum IgG against VZV in the context of prevention of herpes zoster).

**Immune memory**
An immunological phenomenon in which the primary contact between the host immune system and an antigen results in a T-cell-dependent immune response, often referred to as priming of the immune system. Effective priming results in development of memory B-cells and an anamnestic immune response to post-primary doses, which are commonly referred to as booster doses.

**Immunogenicity**

The capacity of a vaccine to elicit a measurable immune response.

**Non-inferiority trial**

In the context of vaccine clinical development programs, non-inferiority trials may have the primary objective of showing that the immune response(s) to one or more specific antigenic components in a candidate vaccine are not inferior to immune responses to corresponding antigenic components in a licensed vaccine. Alternatively, the primary objective may be to demonstrate that a candidate vaccine has non-inferior efficacy to a licensed vaccine.

**Pharmacovigilance**

A practice of detecting, assessing, understanding, responding to and preventing adverse drug reactions, including reactions to vaccines, in the post-licensure period.

**Posology**

The vaccine posology for a specific route of administration and target population includes:

- The dose content and volume delivered per dose
- The dose regimen (i.e. the number of doses to be given in the primary series and, if applicable, after the primary series)
- Dose schedule (i.e. the dose intervals to be adhered to within the primary series and between the primary series and any further doses)

**Post-licensure safety surveillance**

A system for monitoring AEFI s in the post-licensure period.

**Post-primary doses**
Additional doses of vaccine given after some time interval following the primary series of vaccination, which may or may not boost the immune response.

**Primary vaccination**

First vaccination or series of vaccinations intended to establish clinical protection.

**Protocol**

A document that states the background, rationale and objectives of the clinical trial and describes its designs, methodology and organization, including statistical considerations and the conditions under which it is to be performed and managed. The protocol should be signed and dated by the investigator, the institution involved and the sponsor.

**Randomization**

In its simplest form, randomization is a process by which \( n \) individuals are assigned to a test \( (n_T) \) or control \( (n_C) \) treatment so that all possible groups of size \( n = n_T + n_C \) have equal probability of occurring. Thus, randomization avoids systematic bias in the assignment of treatment.

**Responder**

A vaccinee who develops an immune response (humoral or cellular) that meets or exceeds a pre-defined threshold value using a specific assay. This term is most often used when there is no ICP and when the clinical relevance of achieving or exceeding the pre-defined response is unknown.

**Responder rate**

The responder rate is the percentage of vaccinees achieving or exceeding the pre-defined level of response.

**Serious adverse event (SAE) or serious AEFI (SAEFI)**

An adverse event is serious when it results in death, admission to hospital, prolongation of a hospital stay, persistent or significant disability or incapacity, is otherwise life-threatening or results in a congenital abnormality/birth defect. SAEs are such events that occur during clinical trials. SAEFIs are such events that occur during post-licensure safety surveillance.
Seroconversion

A predefined increase in antibody concentration or titre. In subjects with no measurable antibody prior to vaccination seroconversion is usually defined as achieving a measurable antibody level post-vaccination. In subjects with measurable antibody prior to vaccination seroconversion is commonly defined by a pre-defined fold-increase from pre- to post-vaccination. The definitions may be adjusted depending on whether the lower limit of detection of the assay is or is not the same as the lower limit of quantification.

Sponsor

The individual, company, institution or organization that takes responsibility for the initiation, management and conduct of a clinical trial. The entity acting as a sponsor for a clinical trial is usually the same as that which applies for clinical trial approval. The sponsor of a clinical trial may not be the entity that applies for a license to place the same product on the market and/or the entity that holds the license (i.e. is responsible for post-licensing safety reporting) in any one jurisdiction.

Superiority trial

A trial with the primary objective of demonstrating that the immune response to one or more antigenic components in a group that receives a candidate vaccine is superior to the corresponding immune response in a control group.

Vaccine efficacy

An estimate of the reduction in the chance or odds of developing clinical disease after vaccination relative to the chance or odds when not vaccinated against the disease to be prevented. Vaccine efficacy measures direct protection (i.e. protection induced by vaccination in the vaccinated population sample).

Vaccine effectiveness

An estimate of the protection conferred by vaccination in a specified population that measures both direct and indirect protection (i.e. the estimate may reflect in part protection of non-
vaccinated persons secondary to the effect of the vaccine in the vaccinated population).

**Vaccine vector**

A vaccine vector is a genetically engineered micro-organism (which may be replication competent or incompetent) that expresses one or more foreign antigen(s) (i.e. antigens derived from a different micro-organism).

### 4. Vaccine Clinical Development Programs

**This Section considers:**

- Important considerations for clinical programs, including:
  - Consultations with regulatory authorities
  - Use of independent data review committees
  - Registering and reporting clinical trials
- Typical clinical development programs for new candidate vaccines, including:
  - Main objectives of the clinical development program
  - Factors that determine the extent and content of the program
  - Stages of typical development programs
  - Programs that do and do not include vaccine efficacy trials
  - Alternatives for estimation of vaccine efficacy
- Clinical evaluation trials after initial licensure

#### 4.1 General considerations

For a new candidate vaccine the main objective of the clinical development program is to accumulate adequate data to support initial licensure and appropriate use, as described in Subsection 4.2. The essential elements of the program are:

- To describe the interaction between the vaccine and the host immune response (Section 5)
- To identify safe and effective dose regimens and schedules (Sections 5 and 6)
- To provide estimates of vaccine efficacy by directly measuring efficacy or inferring efficacy
based on immune responses (Sections 5 and 6)

- To describe the safety profile (Section 7)
- To assess co-administration with other vaccines if this will be essential for use (Section 5)

After initial licensure, as described in Subsection 4.3:

- It is essential to monitor vaccine safety in routine use (Section 7).
- It is commonly appropriate to estimate vaccine effectiveness (Section 6)
- Depending on the content of the pre-licensure program, further trials of safety, immunogenicity and/or efficacy may be conducted and the data may be used to extend or otherwise modify the use of the vaccine via amendment of the prescribing information.

4.1.1 Consultation with National Regulatory Authorities (NRAs)

It is strongly recommended that dialogue with the appropriate NRAs occurs at regular intervals during the pre-licensure clinical development program to agree on the content and extent of the initial application dossier. This is especially important when:

a. The clinical program proposes a novel approach to any aspect of development for which there is no precedent or guidance available
b. The proposed program conflicts with existing guidance to which the NRAs involved would usually refer when considering the suitability of the program
c. There are particular difficulties foreseen in providing evidence to support an expectation of vaccine efficacy (i.e. there is no immunological correlate of protection and a vaccine efficacy study is not feasible)
d. There are other special considerations for the total content of the pre-licensure program. For example, when it is necessary to use different vaccine constructs for priming and boosting to achieve immune responses thought likely to be protective. In this case each constitutes a separate vaccine but the clinical data required to support their licensure for use in tandem is less than would be required for two vaccines intended to be used completely independently.

Further dialogue should ensue whenever additional clinical trials are planned with intent to modify the prescribing information. In addition, it should be considered whether changes to the
manufacturing process of a vaccine before or after initial licensure need to be discussed with
NRAs to establish whether or not specific clinical trials are required to support the changes.
Consultation with NRAs is also essential when issues of vaccine safety or effectiveness arise in
the post-licensure period to determine any actions that are needed.

4.1.2 Use of independent data monitoring committees

It is common in vaccine trials that a data safety monitoring board (DSMB) is appointed to
provide independent ongoing assessments of safety data. In the pre-licensure program for a new
candidate vaccine it may be appropriate to have a DSMB in place even for the initial exploratory
trials and dose-finding trials, especially if the vaccine consists of a new construct and/or when it
may be anticipated that it could be very reactogenic. For other vaccines it may be considered
useful to have a DSMB in place if available data from the same or similar vaccines point to the
possibility of important safety issues or if the trial will enrol particular populations (e.g. infants
and toddlers, pregnant women or immunocompromised subjects). A DSMB may not be
considered necessary for trials with vaccines that include only established antigenic components
and adjuvants for which no particular safety problems are anticipated or when a licensed vaccine
is being investigated using an alternative posology or in a new population. If the DSMB charter
includes recommending that trials are terminated early for safety reasons there should be
appropriate stopping rules in place.

In vaccine efficacy trials it may also be appropriate to appoint an independent data adjudication
committee consisting of individuals with expertise relevant to the infectious disease to be
prevented. For example, such a group could be used to provide an independent review of the
eligibility of individual vaccinees for inclusion in the primary analysis population and/or to
identify cases of clinically apparent infections that meet the pre-defined case definition. If such a
committee is appointed to oversee one or more trials the protocol and statistical analysis plan
should clarify whether the conclusions of the adjudication committee will be used to conduct the
primary analysis and any secondary analyses that are pre-defined.

In some situations, it may be appropriate to appoint an independent data monitoring committee
to review the results of pre-planned interim analyses of safety and/or efficacy data when a certain proportion of the intended sample size has reached a certain stage of participation. It may be appropriate that the DSMB or some other independent data monitoring committee takes on this responsibility. Protocols and statistical analysis plans may define futility criteria to be applied to the results of one or more interim analyses that, if met, would result in a recommendation from the independent committee to terminate the trial. Whenever an interim analysis is planned, expert statistical input should be obtained to ensure that appropriate adjustments are made to protect the power and integrity of the trial.

4.1.3 Registering and reporting clinical trials

Before any clinical trial is initiated (i.e. before the first subject receives the first medical intervention in the trial) its details must be registered in a publicly available, free to access, searchable clinical trial registry. The registry should comply with individual NRA requirements and as a minimum should comply with the WHO international agreed standards.

The entry into the clinical trial registry site should be updated as necessary to include final enrolment numbers achieved and the date of actual study completion (i.e. the last data collection time point for the last subject for the primary outcome measure). If clinical trials are terminated prematurely the entry should be updated to reflect this with a report of the numbers enrolled up to the point of termination.

The key outcomes of a clinical trial must be posted in the results section of the entry in the clinical trial registry within 12 months of study completion and/or posted on a publicly-available, free-to-access, searchable website (e.g. that of the trial sponsor or Principal Investigator).

Each NRA may have specific requirements for reporting the results of completed trials and the status of ongoing clinical trials conducted with a specific product within and without their jurisdiction. Whatever these requirements, each regulatory submission (whether for clinical trial approval, to support initial licensure or a post-licensure modification or to provide a product safety update report) should include a listing of all completed and ongoing trials conducted with
the product by the sponsor. It is recommended that any trials that are known to the sponsor (e.g. from searching registries or from publications) that were initiated by persons other than the sponsor (e.g. by a public health body or academic institution or by another company that used the product as a comparator) should also be listed.

4.2 New candidate vaccines

Examples of new candidate vaccines from the regulatory standpoint include:

i. Vaccines that contain only new antigenic components (i.e. not previously used in licensed vaccines)

ii. Vaccines that contain both new (i.e. not in any licensed vaccine) and known (i.e. already in licensed vaccines) antigenic components

iii. Vaccines that contain a new adjuvant, with known and/or new antigenic components

iv. Vaccines that contain only known antigenic components that have not previously been combined all together into a single vaccine, with or without a known adjuvant

v. Vaccines that contain only known antigenic components ± known adjuvants in a combination that is already licensed but the vaccine is produced by a different manufacturer. This includes situations in which seed lots or bulk antigenic components used to make a licensed vaccine are supplied to other manufacturers for their own vaccine production.

For new candidate vaccines the content and extent of pre-licensure clinical development programs will reflect how much is already known about the antigenic components and adjuvants in the product. Some of the most important factors include:

a. Number of the antigenic components (e.g. from the same or from several infectious organisms)

b. Nature of the antigenic components (e.g. manufactured with or without genetic modification, live attenuated, live vectored)

c. Inclusion of an adjuvant

d. Disease(s) to be prevented

e. The available options for predicting vaccine efficacy (e.g. inferring efficacy based on
established immunological correlates of protection or conducting vaccine efficacy trials)

f. Age range and population for use (e.g. infants, elderly, pregnant women)
g. Route of administration
h. Likelihood of co-administration with other vaccines in routine use
i. Vaccine-specific safety issues that may be anticipated

4.2.1 Safety and immunogenicity trials

The safety and immunogenicity of a new candidate vaccine should be evaluated in all pre-licensure clinical trials. In the earliest stage of clinical development the primary objective of a trial is usually to describe safety although immunogenicity data are also collected. In later trials the primary objective is usually to address specific immunogenicity issues and the assessment of safety may be a co-primary or secondary objective. In vaccine efficacy trials evaluations of safety and immunogenicity are usually secondary objectives (see Subsection 4.2).

4.2.1.1 Initial trials

These are commonly referred to as Phase 1 trials.

The clinical program for new candidate vaccines commences with an exploration of safety and of the interaction between the antigens proposed for inclusion in the candidate vaccine and the human immune system. In most cases the first clinical trials are conducted in healthy young adults before proceeding to conduct trials in other age groups and/or in subjects with underlying conditions. Depending on the perceived benefit and risks of vaccination it may not be appropriate or necessary to apply an age de-escalation approach (e.g. to move from adults to adolescents, then to children aged 6-12 followed by younger children, toddlers and finally infants) to sequential trials or groups within trials. For example, if a vaccine has negligible potential benefit for older children it may be acceptable in some cases to proceed from trials in adults to trials in infants and toddlers.

It is usual that these trials explore different doses of antigenic components and, if applicable, the
effect of adding an adjuvant in various amounts. For vaccines that contain more than one new antigenic component the first trials may evaluate each one given alone before selecting possible doses for use in combinations. When new antigenic components are to be added to a licensed product the immune response to separate administrations and to the proposed combination product are compared. For vaccines that contain only known antigenic components and adjuvants the initial trials focus on the effects of combining them into a single formulation or the effects of mixing immediately prior to injection (e.g. using a liquid formulation of some component to reconstitute a lyophilized presentation of the others). Depending on the initial results, sequential trials may explore formulations with adjusted amounts of one or more antigenic components and/or the adjuvant.

4.2.1.2 Further trials

These are commonly referred to as Phase 2 trials.

Further safety and immunogenicity trials are conducted to build on the Phase 1 trial results. In most cases these trials are conducted in subjects who are representative of the intended target population for the vaccine at the time of initial licensure.

These trials are usually designed to provide sufficient immunogenicity data to support selection of one or more candidate formulations for further trial i.e. to select the amounts of antigenic components and, where applicable, adjuvants in each dose. They may provide adequate data to determine the number of doses and dose intervals but the final vaccine posology is sometimes established only after completion of confirmatory immunogenicity trials or vaccine efficacy trials.

4.2.1.3 Confirmatory (or pivotal) trials

In many vaccine clinical development programs the confirmatory (or pivotal) trial(s) involve an estimate of vaccine efficacy as described in Subsection 4.2.2.
In instances where vaccine efficacy trials do not need to be, or cannot be, conducted (see Subsection 4.2.2), the confirmatory (or pivotal) trial(s) usually assess the immunogenicity of the final selected vaccine formulation and posology in each target population. In this setting, they are commonly referred to as Phase 3 safety and immunogenicity trials. It is usual that the investigational formulations used in these confirmatory safety and immunogenicity trials (as well as in confirmatory efficacy trials; see below) should be manufactured using validated processes and should undergo lot release in the same way as intended for the commercial product.

4.2.2 Efficacy trials

Vaccine efficacy trials have the primary aim of evaluating the protective efficacy of a candidate vaccine against an infectious disease. The immunogenicity data collected during vaccine efficacy trials can be used to evaluate the relationship between immune parameters and efficacy and may enable identification of immune correlates of protection (see Subsection 5.4). These trials also provide an opportunity to collect extensive safety data using the final intended formulation and dose regimen in the target population.

Preliminary vaccine efficacy trials may be conducted to explore the magnitude of protection that may be possible and to inform the design of confirmatory vaccine efficacy trials (e.g. by evaluating efficacy of different dose regimens and/or by estimating efficacy based on a range of efficacy variables). If conducted, these are commonly referred to as Phase 2b trials. They are also sometimes referred to as pilot efficacy trials or proof of concept efficacy trials.

Confirmatory vaccine efficacy trials that are designed and powered to provide statistically robust estimates of vaccine efficacy are commonly referred to as Phase 3 (or pivotal) efficacy trials or sometimes as field efficacy trials.

The need for and feasibility of evaluating the protective efficacy of a candidate vaccine should be considered at an early stage of vaccine development because the conclusion will determine the overall content of the pre-licensure clinical program and impact on its duration. In all application dossiers that do not include an evaluation of vaccine efficacy the sponsor should
provide a sound justification for the lack of such data, taking into account the following:

a) Efficacy data are not required

Vaccine efficacy trials are not necessary if it is established that clinical immunological data can be used to predict protection against disease. For example, when there is an established immunological correlate for protection against a specific disease (e.g. anti-toxin levels against diphtheria and tetanus toxins, antibody against hepatitis B surface antigen) the candidate vaccine should be shown to elicit satisfactory responses based on the relevant correlate(s).

b) Efficacy data are usually required

Vaccine efficacy trials are usually required whenever a candidate vaccine is developed with intent to protect against an infectious disease and one or more of the following apply:

- There is no established immunological correlate of protection that could be used to predict the efficacy of the candidate vaccine.
- There is no existing licensed vaccine of documented efficacy against a specific infectious disease to allow for immunobridging of a candidate vaccine to the efficacy of a licensed vaccine.
- Immunobridging to the documented efficacy of a licensed vaccine against a specific infectious disease is not considered to be possible because there is no known relationship between specific immune response parameters and efficacy.
- There are sound scientific reasons to expect that vaccine efficacy cannot be extrapolated from the population(s) included in the prior efficacy trial(s) with a candidate vaccine to one or more other populations.
- There are sound scientific reasons to expect that vaccine efficacy that has been demonstrated for the candidate vaccine against infectious disease due to specific strains (e.g. serotypes, sub-types) cannot be extrapolated to other strains.

c) Efficacy data cannot be provided
In some instances in which efficacy data are usually required it may not be feasible to conduct efficacy trials. For example, if the candidate vaccine is intended to prevent an infectious disease that:

- Does not currently occur (e.g. smallpox)
- Occurs in unpredictable and short-lived outbreaks that do not allow enough time for the conduct of appropriately designed trials to provide a robust estimation of vaccine efficacy (e.g. some viral haemorrhagic fevers)
- Occurs at a rate that is too low for vaccine efficacy to be evaluated in a reasonably sized trial population and period of time. This situation may apply:
  
  a. Due to natural rarity (e.g. plague, anthrax, meningitis due to *N. meningitidis* type B) of the infectious disease
  
  b. Due to rarity of the infectious disease resulting from the widespread use of effective vaccines. In this case the numbers required to conduct an adequately powered analysis of the relative efficacy of a candidate vaccine vs. a licensed vaccine may be too large to permit completion in any reasonable timeframe.
  
  c. When the aim is to evaluate vaccine efficacy against serotypes or subtypes of an organism that occur rarely (e.g. pneumococcal conjugate vaccines and human papillomavirus vaccines).

If it is not feasible to perform vaccine efficacy trials and there is no immunological correlate of protection, it may be possible to support an assumption of the likely efficacy of a vaccine by deriving a marker of protection from one or more of the following:

i) Nonclinical efficacy trials

ii) Passive protection trials (i.e. effects of normal or hyper-immune human gamma globulin, use of convalescent sera) that may point to the sufficiency of humoral immunity for prevention of clinical disease and suggest a minimum protective antibody level that could be used as a benchmark in clinical trials with candidate vaccines

iii) Trials of the acquisition of natural immunity that may support an approach as in ii)

iv) Human challenge trials

v) Comparison of immunological responses with those seen in past trials of similar vaccines with proven protective efficacy (e.g. acellular pertussis vaccines) even though
the relationship between immune responses to one or more antigenic components and efficacy remains unknown

4.2.3 Pivotal safety trials

Safety is an important secondary endpoint in all trials with the primary objective of assessing immunogenicity or efficacy. In rare cases, the assessment of safety may be the primary or co-primary objective in a pre-licensure Phase 3 (pivotal trial) that has immunogenicity and/or efficacy as secondary objectives, as described in Subsection 7.2.3.

4.3 Post-licensure clinical evaluations

For all licensed vaccines safety data are collected as part of routine pharmacovigilance. On occasion, additional pharmacovigilance in the form of trials designed to address specific safety issues that were identified as potential concerns from pre-licensure trials may be conducted post-licensure (see Section 7).

Whether or not vaccine efficacy trials were conducted prior to initial licensure it is usual to evaluate vaccine effectiveness during routine use or by means of trials specifically designed to provide estimates of effectiveness (see Subsection 6.3).

Further clinical trials are commonly conducted after first licensure and are sometimes performed to address commitments made to NRAs. These trials may or may not be intended to support modifications of the prescribing information and may include:

a. Extension phases of trials that commenced before first licensure (e.g. to continue follow-up of safety, efficacy and/or immune response, to evaluate the effects of further doses)

b. Trials that evaluate the use of alternative dose regimens (e.g. reducing the number of doses) and/or schedules (e.g. extending the interval between doses)

c. Trials in additional populations (e.g. different age groups, populations with factors that could affect their immune response, such as pregnancy, prematurity and immunosuppression)
d. Trials to support changes in vaccine manufacture with potential to affect safety, efficacy or immune response

e. Trials to support co-administration with other vaccines

The nomenclature for these types of trial is variable. If these additional trials are conducted in wholly new populations or with substantially different vaccination regimens, especially when they are intended to provide support for changes to the prescribing information, they are commonly referred to as Phase 2 or 3 trials. Trials that are intended to support more minor changes, such as adding alternative dose regimens or extending the age range, are commonly referred to as Phase 3b trials. Other types of post-licensure trials, such as those in which vaccines are given in accordance with licensed uses and regimens, are more often referred to as Phase 4 trials. These include trials that are specifically designed to address specific safety issues or to estimate vaccine effectiveness.

5. Immunogenicity

This Section considers:

- The range of immunogenicity data that may be collected throughout the pre- and post-licensure clinical development program
- Collection of specimens for immunogenicity trials
- Characterization of the immune response to a new candidate vaccine
- Selection of the immune parameters to be measured
- Assays for measuring humoral and cellular immune responses
- Identification and uses of immunological correlates of protection
- Objectives and designs of immunogenicity trials
- Considerations for some specific types of immunogenicity trials, including:
  - Trials to identify formulations and posologies (primary and post-primary)
  - Comparative immunogenicity trials to bridge efficacy
  - Trials to extend or modify use
  - Co-administration trials
  - Trials in which pregnant women are vaccinated
5.1 General considerations

Immunogenicity trials are conducted at all stages of pre-licensure vaccine development and additional trials are commonly conducted in the post-licensure period. In all trials the evaluation of immune responses rests on the collection of adequate specimens at appropriate time intervals and measurement of immune parameters most relevant to the vaccine using validated assays.

In the clinical development program for new candidate vaccines that contain micro-organisms or antigens not previously included in human vaccines immunogenicity trials should provide a detailed understanding of the immune response to vaccination. Subsequent pre-licensure and post-licensure clinical trials commonly evaluate and compare immune responses between trial groups to address a range of objectives. Depending on the objectives, stage of development and trial population the comparisons may be made with one or more of placebo, other formulations or regimens of the same vaccine or licensed vaccines. In these trials the assessments and analyses of the immune responses are primary objectives whereas the assessments of safety may be co-primary or secondary objectives. In trials that are primarily intended to estimate vaccine efficacy, assessment of the immune responses is usually a secondary objective but it is important that data on immune responses are collected to support analyses of the relationship between immunogenicity and efficacy, which may lead to identification of immunological correlates of protection.

5.2 Characterization of the immune response

For micro-organisms and antigens that have not been used previously in human vaccines a thorough investigation of their interaction with the human immune response should be conducted as part of the overall clinical development program. For micro-organisms and antigens that are already in licensed vaccines it is not usually necessary to repeat these types of investigations but consideration should be given to conducting at least some trials in certain circumstances (e.g.
when a new adjuvant is to be added to known antigens, a different method of attenuation is used, a different carrier protein is used for antigen conjugation or an antigen previously obtained by purification from cultures is to be manufactured using recombinant technology).

The range of investigations conducted should take into account what is known about the immune response that results from natural exposure and whether or not this provides partial or complete protection that is temporary or lifelong. The range of investigations should also consider the characteristics of the infecting micro-organism (e.g. whether there are multiple subtypes that cause human disease) and the content of the vaccine (14). Investigations may include some or all of the following:

- Determination of the amount, class, sub-class and function of antibody elicited by the vaccine
- Description of the magnitude of the humoral and cell-mediated immune response to initial and sequential doses and changes in the magnitude of responses with time elapsed since vaccination
- Assessment of the ability of the vaccine to elicit a T-cell dependent primary immune response, with induction of immune memory (i.e. priming of the immune system) giving rise to anamnestic responses i) on natural exposure ii) after further doses of the same vaccine and/or iii) after further doses of a vaccine that contains closely related but non-identical micro-organisms or antigens (i.e. cross-priming)
- Assessment of the specificity and cross-reactivity of the immune response
- Assessment of changes in antibody avidity with sequential doses, which may be useful when investigating priming
- Evaluation of factors that could influence the immune responses (e.g. presence of maternal antibody, pre-existing immunity to the same or very similar organisms, natural or vaccine-elicited antibody against a live viral vector)

5.3 Measuring the immune response

5.3.1 Collection of specimens
Immune responses to vaccination are routinely measured in serum (humoral immune responses) and blood (cellular immune responses). For some vaccines it may be of interest to explore immune responses in other body fluids that are relevant to the site at which the target microorganism infects and/or replicates (e.g. in nasal washes or cervical mucus), especially if it is known or suspected that the systemic immune response does not show a strong correlation with protective efficacy for the type of vaccine under trial (e.g. intranasal vaccination against influenza). Nevertheless, to date specimens other than sera have not provided data that have been pivotal in regulatory decision making processes and have not resulted in identification of ICPs. Therefore the rest of this section focuses on the collection of sera.

Pre-vaccination samples should be collected from all subjects in the early immunogenicity trials after which it may be justifiable to omit these samples or to obtain them from subsets (e.g. if the initial trials indicate that antibody is rarely detectable or quantifiable prior to vaccination in the target population). Pre-vaccination sampling remains essential if it is expected that the target population will have some degree of pre-existing immunity either due to natural exposure and/or their vaccination history since the assessment of the immune response will need to take into account seroconversion rates and increments in geometric mean titres or concentrations from pre- to post-vaccination. Pre-vaccination sampling is also necessary if it is known or suspected that pre-existing immune status may have a positive (e.g. because pre-existing antibody reflects past priming) or negative (e.g. due to maternal antibody interfering with primary vaccination with certain antigens in infants) impact on the magnitude of the immune response to vaccination.

The timing of post-vaccination sampling should be based on what is already known about the peak immune response and antibody decay curve after initial and, if applicable, sequential doses (e.g. for vaccines that elicit priming the rise in antibody after a booster dose is usually much more rapid compared to earlier doses). For antigens not previously used in human vaccines sampling times may be based initially on nonclinical data and then adjusted when antibody kinetic data specific to the antigen(s) under trial have been generated. As information is accumulated the number and volume of samples taken from individual vaccinees may be reduced to the minimum considered necessary to address the trial objectives.
5.3.2 Immunological parameters

Immunological parameters are measures that describe the humoral (e.g. antibody concentrations or antibody titres depending on the assay output) or the cell-mediated (e.g. percentages of sensitised T-cells) immune response. To date, immunological parameters other than those that measure the humoral immune response have not played a pivotal or major role in vaccine licensure so that the focus is usually on determination of antibody levels.

- For known micro-organisms or antigens in a candidate vaccine the range of parameters to be measured in clinical trials is usually selected from prior experience and whether or not there is an established ICP.
- For micro-organisms or antigens not previously included in human vaccines the selection of parameters to be measured should take into account what is known about natural immunity. For some infectious diseases the nature of the immune response to infection in animal models may also be useful for parameter selection. In later clinical trials, after characterization of the immune response, the parameters to be measured may be modified.

5.3.2.1 Humoral immune response

The humoral immune response is assessed from the post-vaccination appearance or increase from pre-vaccination in antibody directed at specific micro-organisms or antigens in the vaccine.

- Most weight is usually placed on functional antibody responses (e.g. serum bactericidal antibody [SBA], toxin or virus neutralizing antibody, opsonophagocytic antibody [OPA]) but there may not be an appropriate assay available (e.g. for typhoid vaccines based on the Vi polysaccharide) or the only available assays may have low feasibility for application to large numbers of samples (e.g. because they are very labor intensive or require high-level biocontainment facilities).
- Alternatively, or in addition to the determination of functional antibody, the immune response may be assessed by measuring total antibody (e.g. total IgG measured by ELISA) that binds to selected antigens (or, on occasion, to specific epitopes). Only a proportion of the total antibody detected may be functional.
The following should be taken into consideration when deciding how to measure the humoral immune response:

a. If a strong correlation has already been established between total and functional antibody responses to a specific micro-organism or antigen it may be acceptable to measure only total IgG in further trials (e.g. antibody to tetanus toxin)

b. For antigens for which there is an established ICP it may suffice to measure only the relevant functional antibody (e.g. SBA for meningococcal vaccines) or total IgG (e.g. for antibody to tetanus toxin) response

c. If the ICP is based on total IgG there may be instances in which there is still merit in measuring functional antibody (e.g. for antibody to diphtheria toxin for which a micro-neutralization assay is available)

d. If there is no ICP the functional antibody response should be measured if this is feasible

e. Occasionally there may be more than one immunological parameter that measures functional antibody but one is considered to be a more definitive measure than the other (e.g. neutralizing antibody to influenza virus vs. antibody that inhibits haemagglutination), in which case the more definitive parameter may be determined at least in a subset

f. For some vaccines against certain viruses there is a potential that some of the total antibody detected has no protective effect (e.g. is non-neutralizing) but it could enhance cellular infection by wild-type virus and result in an increased risk of severe disease after vaccination (e.g. this may apply to dengue vaccines). To assess this possibility the routine measurement of total antibody to assess the humoral immune response to vaccination should be supported by other detailed investigations.

5.3.2.2 Cell-mediated immune response

For some types of infectious disease (such as tuberculosis) the assessment of the cell-mediated immune response may have a major role in the assessment of the interaction between the vaccine and the human immune system. In many other settings the evaluation of the cellular immune response may serve to support the findings based on the humoral immune response (e.g. when assessing the benefit of adding an adjuvant or when evaluating the degree of cross-priming elicited by a vaccine).
The cell-mediated immune response is most commonly assessed by detecting and quantifying sensitized T-cells in blood from vaccinees. These investigations may also serve to characterize the predominant cytokines released and to detect differences in sensitization between T-cell subpopulations. There are several methods that may be used. These are commonly based on measuring the production of a range of cytokines following in-vitro stimulation of T-cells with individual or pooled antigens.

To date, the methodologies used for these and alternative types of assays have been variable and non-standardized. Nevertheless, the results may provide useful comparisons between treatment groups within any one study (e.g. could describe the effect, if any, of an adjuvant) based on comparing rates of “responders” defined by a magnitude of change in the assay readout from pre- to post-vaccination. If there are marked discrepancies in the patterns of responses observed between cell-mediated and humoral responses (e.g. if adding an adjuvant does have a major effect on antibody levels but does not increase the percentages of sensitized cells in one or more T-cell subsets) the findings should be carefully considered and discussed.

5.3.3 Assays

Assays of functional or total antibody that are used to report immune responses to vaccination (whether to the candidate vaccine or to co-administered vaccines) in trials intended to support licensure (i.e. in confirmatory trials) may be:

- Commercially available assays specifically designed and intended for quantification of antibody that are considered acceptable to NRAs (i.e. have been marketed following a robust regulatory review by the same or by other NRAs).
- In-house assays that have been validated according to similar principles recommended for quantitative lot release assays in the ICH Q2 (R1) document Validation of Analytical Procedures: Text and Methodology (15). In-house assays that are used in early trials that explore the immune response may be regarded as an exception and may report data using assays that have yet to be validated or which are not subsequently validated.
- In-house assays that have been shown to be comparable to a reference assay (e.g. to an assay
established in a WHO reference laboratory or to an assay that is established in a recognized public health laboratory and which has been used previously to support clinical trials that have been pivotal for licensure).

In each case, it is expected that WHO International Standard reagents will be used in assay runs if these exist or omission of their use should be adequately justified.

Commercial assays suitable for quantification of the cell-mediated response to vaccination are not currently available but may be used in future. In-house assays that are used to detect and quantify cell-mediated immunity may be difficult to fully validate, in which case the results should not be used to make specific claims regarding clinical effect.

Clinical trial protocols should specify which assays will be used and in which laboratories. Clinical trial reports should include at least a summary of the assay methodology and its commercial or other validation status. For in-house assays the validation reports should be provided.

It is preferable that the same assays are used in the same laboratories throughout the clinical development program (including pre-and post-licensure trials) for an individual vaccine. It is also preferable that each assay (whether it measures the response to the candidate vaccine or to a concomitant vaccine) is run by one central laboratory. If this is not possible (e.g. because different laboratories have to be used, commercial or in-house assays change over time or a switch is made between in-house and commercial assays) the new and original assays should be shown to be comparable. As a minimum it is recommended that a selection of stored sera (e.g. covering a range of low to high results when using the previous assay) are re-run using the previous and new assays in parallel. The number of sera re-tested should be sufficient to support a statistical assessment of inter-assay variability.

The micro-organisms (e.g. in assays of SBA, OPA and virus neutralization) and the antigens (e.g. in ELISAs and for in-vitro stimulation of sensitized T-cells) used in the assay may affect both the result and the interpretation of the result. For example:

- It is important to use purified antigen to avoid the possibility that the assay detects and
measures antibody to any extraneous antigenic substances that may be in the vaccine.

- For vaccines that contain antigens from multiple strains of the same species (e.g. multiple bacterial capsular types) separate assays are needed to determine the immune response to each antigen.

- Although it is usually acceptable to conduct routine testing using the same micro-organisms or antigens present in the vaccine it may be very informative to perform additional testing, at least in subsets of samples, using circulating wild-type organisms or antigens derived from them in the assay. It is not expected that these additional assays will necessarily be validated since they are exploratory in nature. The results of additional testing can provide an indication as to whether the results of routine testing could represent an over-estimate of the immune response to circulating strains. This additional testing can also provide an assessment of the cross-reactivity of the immune responses elicited by the vaccine to other organisms of the same genus or species (e.g. to different flaviviruses, to different clades of influenza virus or to different HPV types) and guide the need to replace or add strains or antigens in a vaccine to improve or maintain its protective effect.

### 5.4 Identification and use of immunological correlates of protection

#### 5.4.1 Immunological correlates of protection and their uses

To date, all established ICPs are based on humoral immune response parameters that measure functional or total IgG antibody. Examples of well-established ICPs include those for antibody to diphtheria and tetanus toxoids, polioviruses, hepatitis B virus and *H. influenzae* type b (Hib) polysaccharide (PRP) (16). In most cases, established ICPs have been shown to correlate with prevention of clinically apparent infectious disease but for some pathogens the ICP correlates with prevention of documented infection (e.g. hepatitis A and hepatitis B).

In some cases the ICP is a measure of the functional antibody response but if a strong correlation is shown between the results of assays of functional and total antibody, it may be possible to derive an alternative ICP based on total antibody (see Subsection 5.3.3).
Subsections 5.5.2 and 5.5.3 consider trial endpoints and the approach to analysis and interpretation of immunogenicity data in the presence or absence of an ICP and situations in which alternative approaches may be appropriate. For example, for some infectious diseases vaccine-elicted protection against clinical disease shows a broad correlation with a specific immunological parameter (e.g. with serum neutralising antibody elicited by HPV vaccines) but no cut-off value has been identified that shows a strong statistical correlation with protection in the short or longer-term in individuals or populations. In some other instances there is an indication of a threshold value that seems to broadly predict protection but the evidence is insufficient to regard this as an ICP applicable to a specific or to several different sub-populations or organism subtypes (e.g. IgG to specific pneumococcal serotypes). For some other infectious diseases there is no correlation that is well established between vaccine-elicted protection and measurable immune parameters (e.g. for acellular pertussis vaccines).

5.4.2 Establishing an ICP

Documentation of the immune response to natural infection, the duration of protection after clinically apparent infection (i.e. whether natural protection is life-long [solid immunity], temporary or absent) and the specificity of protection (i.e. whether the individual is protected only against specific subtypes of a micro-organism) should be taken into account when attempting to establish an ICP from clinical data. For example, to date, widely-accepted clinical ICPs have been established based on one or more of:

- Serosurveillance and disease prevalence in specific populations
- Passive protection using antibody derived from immune humans or manufactured using recombinant technology
- Efficacy trials
- Effectiveness trials
- Investigation of vaccine failure in immunosuppressed populations

In the majority of cases clinical ICPs have been determined from vaccine efficacy trials that were initiated pre-licensure, often with long-term follow-up of subjects that extended into the post-licensure period. Efficacy trial protocols should plan to collect sufficient information to allow for
analyses of the relationship between immune parameters and protection against clinically
apparent disease. As a minimum this requires collection of post-vaccination samples from all or
from a substantial subset of the vaccinated and control groups. Serial collection of samples over
the longer-term along with follow-up surveillance for vaccine breakthrough cases has also served
to support identification of ICPs.

To investigate the predictive capacity of a putative ICP protocols should pre-define the
assessments to be applied to all cases of the disease to be prevented that occur in the vaccinated
and control groups. These assessments should include investigation of the immune status of
subjects and microbiological studies with the infecting micro-organisms whenever these have
been recovered. For breakthrough cases from which there are both post-vaccination sera and
organisms recovered it is recommended that functional antibody should be determined (or, if not
possible, total antibody) for individuals against their own pathogen. An exploration of vaccine-
elicted cell-mediated responses in individuals against their own pathogen may also be useful
and, for some types of infectious diseases (such as tuberculosis), may be very important to
further understanding of vaccine-associated protection. These data may be very important to
investigate the broad applicability of the ICP depending on host and organism factors.

A single clinical ICP identified from a vaccine efficacy trial in a defined population may not
necessarily be applicable to other vaccine constructs intended to prevent the same infectious
disease. In addition, an ICP may not be applicable to other populations and disease setting. For
example, putative ICPs have sometimes differed between populations of different ethnicities
with variable natural exposure histories for subtypes of a single micro-organism. Thus the
reliance that is placed on a clinical ICP, even if regarded as well-supported by the evidence,
should take into account details of the efficacy trials from which it was derived.

Clinical ICPs have also been derived from or further supported by analyses of effectiveness data.
The methods used to derive ICPs from effectiveness data have been very variable. In addition to
the factors that may affect the relevance of ICPs derived from efficacy trials, estimates drawn
from effectiveness data may in part reflect the type of immunization program in place and the
extent to which protection of individuals relies on herd immunity rather than the initial and
persisting immune response in the individual. The wider applicability of ICPs derived from such trials should be viewed in light of how and in what setting the estimates were obtained.

If it is not possible to derive a clinical ICP the interpretation of the human immune response data may take into account what is known about immunological parameters that correlate with protection in relevant animal models and any nonclinical ICPs that have been identified (e.g. from trials that assess passive protection and active immunization). This approach may be the only option available for interpreting immune responses to some new candidate vaccines. Nevertheless, ICPs derived wholly from nonclinical data should be viewed with caution and attempts should be made to obtain a clinical ICP whenever the opportunity arises (e.g. when the vaccine is used in an outbreak situation).

If conducted, human challenge trials may also provide preliminary evidence supporting an ICP. Nevertheless, these trials are usually conducted in non-immune healthy adults who are challenged with organisms that are not identical to, and do not behave like, virulent wild-types. Therefore these trials may point to a correlation between a specific immunological parameter and protection, which can be further investigated during the clinical development program.

5.5 Immunogenicity trials

5.5.1 Objectives

The objectives of pre-licensure and post-licensure clinical immunogenicity trials include (but are not limited to):

i) To select vaccine formulations and posologies (including primary and booster doses)

ii) To bridge the efficacy demonstrated in a specific population and using one vaccine formulation and posology to
   a) The same vaccine when used in other settings or with alternative posologies or
   b) A different vaccine intended to protect against the same infectious disease(s) as a licensed vaccine for which efficacy has been established

iii) To achieve the objectives as in ii) but in the absence of prior efficacy data to which a
bridge can be made

iv) To support co-administration with other vaccines

v) To support maternal immunization with the primary intent to protect the infant

vi) To support major changes to the manufacturing process

vii) To assess lot to lot consistency (8)

Subsections 5.5.2 and 5.5.3 address some general considerations for the selection of endpoints, the design of comparative immunogenicity trials and the analysis and interpretation of the results. Subsection 5.6 provides additional details of issues to take into consideration when designing, analyzing and interpreting comparative immunogenicity trials that have one or more of objectives i) to vii).

5.5.2 General considerations for trial designs

Immunogenicity trials are almost without exception comparative trials. Comparative trials include those in which all subjects receive the same vaccine formulation but there are differences between groups in how or to whom the vaccine is administered (e.g. using a different dose or dose interval, administering the vaccine to different age groups) and trials in which at least one of the trial groups receives an alternative treatment, which may be placebo and/or another licensed vaccine.

The design of comparative immunogenicity trials is driven by the characteristics of the vaccine, the trial objectives, the stage of clinical development, the trial population, the availability and acceptability of suitable comparators and what is known about immune parameters that correlate with protection (including whether or not there is an established ICP).

In comparative immunogenicity trials subjects should be randomized to one of the trial groups at enrolment. This also applies to trials that enroll sequential cohorts of subjects (e.g. in ascending dose trials in which at least some subjects are assigned to receive placebo or another vaccine). In some cases it may be appropriate that subjects who meet certain criteria (e.g. completed all assigned doses in the initial part of the trial) are re-randomized at a later stage of the trial to
receive a further dose of a test or control treatment.

Whenever possible, comparative immunogenicity trials should be double blind. If the vaccines to be compared are visually distinguishable, it is preferable that designated persons at each trial site administer the products. Vaccinees (or their parents/guardians) and all other trial staff should remain unaware of the treatment assignment. If this is not feasible, or if the vaccines to be compared are given by different routes or at different schedules, the assays should be conducted by laboratory staff unaware of the treatment assignment.

In trials intended to provide only descriptive analyses of the immunogenicity data the trial sample size is usually based on considerations of feasibility and collection of sufficient safety data to support the design of sequential trials. Trials that aim to assess superiority or non-inferiority between vaccine groups should be sized according to the intended power and the pre-defined margins.

5.5.2.1 Endpoints

The choice of the primary trial endpoint and the range of other endpoints for immunogenicity trials should take into account Subsections 5.2, 5.3 and 5.4. Protocols should pre-define the primary, secondary and any other (which may be designated tertiary or exploratory) endpoints. Trial protocols may pre-define multiple co-primary endpoints:

- For vaccines intended to protect against multiple subtypes of the same micro-organism (e.g. human papillomavirus vaccines, pneumococcal conjugate vaccines)
- For combination vaccines, including vaccines that contain multiple micro-organisms (such as measles, mumps, rubella vaccine) or multiple antigens (such as combination vaccines used for the primary immunization series in infants)

The following should be taken into consideration when selecting the primary endpoint(s) following primary vaccination:

i. When an ICP has been established the primary endpoint is usually the percentage of
vaccinees that achieves an antibody level at or above the ICP, which is sometimes referred

to as the seroprotection rate.

ii. When there is no established ICP the primary endpoint is usually based on the parameter

that is known or could be anticipated to best correlate with efficacy (e.g. a measure of

functional antibody or, if no functional assay is available, a measure of total IgG).

➢ In some instances there may not be an ICP but there may be evidence to support

application of a threshold value (i.e. the primary endpoint may be the percentage of

vaccinees that achieves antibody levels at or above the threshold value, which is

sometimes referred to as the responder rate).

➢ If there is no ICP or threshold that could be applied it may be appropriate that the primary

endpoint is based on the seroconversion rate or on some other definition of the magnitude

of the immune response that differentiates responders from non-responders. Comparisons

of post-vaccination seropositivity rates may also be informative if pre-vaccination rates

are very low.

For assessment of the immune response following administration of a vaccine to subjects who

are already primed against one or more micro-organisms or antigens in the vaccine an

anamnestic immune response is anticipated so that seroprotection, seroconversion (when defined

by fold-rise from pre- to post-boost) and seropositivity rates after the booster dose will likely be

very high. In these cases the most sensitive immunological parameter for detecting differences

between groups may be the geometric mean concentration or titre.

After primary vaccination and after any additional doses the results of all immunological

parameters measured should be reported, including seroprotection (if defined), seropositivity and

seroconversion rates, geometric mean concentrations or titres and the reverse cumulative

distributions, regardless of the pre-defined primary endpoint.

5.5.2.2 Exploratory trials

In the initial stages of vaccine clinical development, and when commencing further vaccine
development to substantially modify the initial prescribing information, exploratory trials are commonly conducted to provide preliminary data on safety and immunogenicity. The assessment of the immune response may be designated as co-primary with safety or secondary. Exploratory trials are not usually powered or designed to address specific hypotheses. To obtain a clear picture of safety, these trials may include a placebo group if this is considered to be acceptable (e.g. a placebo group is commonly used in initial trials with a new candidate vaccine in healthy adults).

5.5.2.3 Superiority trials

Trials intended to detect superiority of immune responses are most often conducted during the selection of candidate vaccine formulations and posologies for further clinical investigation. It is common that these trials plan to assess whether a specific candidate vaccine formulation elicits superior immune responses compared to no vaccination against the disease to be prevented and/or compared to alternative formulations of the candidate vaccine. Initial dose selection trials are not usually formally powered to demonstrate superiority but this may be considered for larger trials that are intended to select a final formulation and posology for further investigation.

Superiority trials are also conducted when an adjuvant is proposed for inclusion in the vaccine, in which case it is usually expected that the immune response to at least one of the antigenic components of an adjuvanted formulation should be superior to that for a non-adjuvanted formulation that is otherwise identical. However, if addition of an adjuvant is intended to reduce the amount(s) of antigen(s) required (which may increase vaccine production capacity) it may suffice that the adjuvanted formulation with the reduced antigen dose is shown to be at least as immunogenic (i.e. non-inferior) as a non-adjuvanted formulation containing a higher dose.

Some trials may be designed to assess superiority between certain groups and non-inferiority between others or to assess superiority of immune responses to single or multiple antigenic components. For example, whilst adding an adjuvant may improve the immune responses to one or more antigenic components it should also not have a negative effect that is of potential clinical significance on the immune responses to all other antigenic components. In addition, a trial may
be designed to establish that specific immune responses are at least non-inferior between trial
groups and, if the pre-defined non-inferiority criteria are met, to then assess whether the
responses are superior.

5.5.2.4 Non-inferiority trials

Most comparative immunogenicity trials are intended to show that the test vaccinated groups
achieve comparable immune responses to the selected reference groups. Not all such trials need
to be formally designed and powered to demonstrate non-inferiority but trials that are intended to
be pivotal (i.e. the application for licensure or to modify the license is to be based mainly or
wholly on the trial) should be adequately designed and powered to demonstrate non-inferiority
using a pre-defined and justifiable non-inferiority margin. It is recommended that protocols and
statistical analysis plans for each trial are developed in conjunction with an appropriately
experienced statistician.

Factors to consider regarding the stringency of the non-inferiority margin include the clinical
relevance of the endpoint, seriousness of the disease to be prevented and the vulnerability of the
target population. More stringent margins may be appropriate when the vaccine is intended to
prevent severe or life-threatening diseases and will be used in particularly vulnerable populations
(e.g. infants and pregnant women). If a new candidate vaccine is known to offer substantial
benefits in terms of safety or improved coverage, less stringent margins may be considered. In
contrast, a more stringent margin could be considered when there is a potential for a downward
drift in immunogenicity such as that which could occur when a new candidate vaccine can be
compared only with vaccines that were themselves approved based on non-inferiority trials (see
Subsection 5.6.2.1). As a result of these considerations it is possible that different non-inferiority
margins may be considered appropriate to interpret immune responses to any one specific
antigenic component in different settings.

As a general rule, for the purposes of establishing non-inferiority between vaccine groups
based on GMT or GMC ratios for antibody titres or concentrations, it is suggested that the
lower bound of the 95% confidence interval around the ratio (test vs. reference vaccine) should
not fall below 0.67. Under certain circumstances, NRAs may consider allowing a lower bound of 0.5. The criterion should be selected taking into account whether or not an ICP has been identified. In addition, any marked separations between the reverse cumulative distributions of antibody titres or concentrations should be discussed in terms of the potential clinical implications, even if these occur only at the lower or upper ends of the curves.

When comparing seroprotection rates, seroconversion rates or percentages of vaccines with immune responses that are above a pre-defined threshold, sponsors frequently select a non-inferiority margin of 10%, which gives modest sample sizes. There is very rarely any justification provided for this margin nor is there any discussion of the possible consequences of a candidate vaccine eliciting seroprotection or seroconversion rates or percentages with responses above a pre-defined threshold that are lower those in the licensed vaccine group to such an extent that the lower 95% confidence interval around the difference (test – reference) approaches -10%. If a sponsor does pre-define such a margin without adequate justification, the implications of the actual 95% confidence intervals that are observed should be reviewed in light of the considerations described above.

5.5.3 Analysis and interpretation

A statistical analysis plan should be finalized before closing the trial database and unblinding treatment assignments (if these were blinded). This should include any planned interim analyses, which should be adequately addressed in terms of purpose, timing and any statistical adjustments required.

The immunogenicity data from all subjects with at least one result for any immunological parameter measured in the trial should be included in the clinical trial report. The analysis of the immune response based on any one parameter is commonly restricted to all subjects with a pre-vaccination measurement (if this is to be obtained from all subjects) and at least one post-vaccination measurement. Protocols may also restrict the primary analysis population to subjects with pre- and post-vaccination results who received all the assigned doses within pre-defined windows around the intended schedule and had no other major protocol violations (e.g. met the
inclusion and exclusion criteria). Other analysis populations of interest may be pre-defined in accordance with the primary or secondary objectives (e.g. age sub-groups, pre-vaccination serostatus). Whatever the pre-defined primary analysis population, all available immunogenicity data should be presented in the clinical trial report.

If a trial fails to meet the pre-defined criteria for superiority and/or non-inferiority with respect to any of the antigenic components the possible reasons for the result and the clinical implications should be carefully considered before proceeding with clinical development or licensure. The considerations may take into account the basis for setting the pre-defined criteria (e.g. does failure to meet the criteria strongly imply that lower efficacy may result), the comparisons made for all other immune parameters measured (e.g. were criteria not met for only one or a few of many antigenic components of the vaccine), any differences in composition between the test and the comparator vaccines that could explain the result, the severity of the disease(s) to be prevented and the overall anticipated benefits of vaccine, including its safety profile. Subsection 5.6 provides some further examples and issues to consider.

Additional analyses of the data that were not pre-specified in the protocol and/or the statistical analysis plan (i.e. post hoc analyses) should generally be avoided. If conducted, they should usually be viewed with caution although the results may stimulate further clinical trials to investigate specific issues.

5.6 Specific considerations for trial design and interpretation

This Subsection should be read in conjunction with Subsection 5.5

5.6.1 Selection of formulation and posology

The vaccine formulation is determined by the numbers of micro-organisms or amounts of antigens and, if applicable, adjuvant that is to be delivered in each dose as well as the route of administration.
The vaccine posology for a specific route of administration includes:

- Dose content (as for formulation) and volume delivered per dose
- Dose regimen (number of doses to be given in the primary series and, if applicable, after the primary series)
- Dose schedule (dose intervals within the primary series and between the primary series and any further doses)

The vaccine posology for any one vaccine may vary between target populations (e.g., age groups and according to prior vaccination history) in one or more aspects (content, regimen or schedule).

The following sections outline the immunogenicity data that are usually generated to support the vaccine formulation and posology and to assess the need for, and immune response to, additional doses of the vaccine after completion of the primary series. Section 7 addresses the importance of the safety profile when selecting vaccine formulations and posologies.

5.6.1.1 Selecting the formulation and posology for initial licensure

The vaccine formulation and posology that is initially approved should be supported by safety and immunogenicity data, with or without efficacy data, collected throughout the pre-licensure clinical development programme. At the time of initial licensure the data should at least support the formulation and posology for the primary series, which may consist of one or more doses.

Depending on the intended formulation of the new candidate vaccine the following considerations may apply:

i) Whenever a new candidate vaccine contains any micro-organisms or antigens not previously used in human vaccines, with or without others already used in human vaccines, the initial trials usually explore the immune responses to different amounts of each of the new micro-organisms or antigens when given alone in non-immune healthy adult subjects. These trials should describe the dose-response curve and may indicate a plateau for the immune responses above a certain
dose level. The next trials usually evaluate immune responses to further doses at various dose intervals to evaluate the kinetics of the immune response as well as any increment in immune response that is achieved by further doses. The transition from trials in healthy adults to trials in subjects in the target age range at the time of initial licensure (if this is not confined to young adults) should occur as soon as this can be supported taking into account the safety profile.

However, evaluating the immune response to each of the new micro-organisms or antigens alone may not be a feasible undertaking. For example, if the vaccine construct is manufactured in such a way that production of individual antigens is not feasible then the evaluation of the appropriate vaccine dose may be based solely on studies with the entire construct. Another example concerns vaccines intended to protect against multiple subtypes of an organism. In this case, the use of micro-organisms or antigens that could be regarded as broadly representative in the first trials may provide some idea of the likely response to other subtypes. Further trials may then explore formulations that contain increasing numbers of the subtypes with the objective of assessing the effect of combining them into a single product on the immune response.

ii) For new candidate vaccines that contain known antigenic components not previously combined together into a single vaccine the initial trials are usually conducted in subjects within the age ranges approved for licensed vaccines that contain some or all of the same antigenic components. The aim is to demonstrate non-inferiority of immune responses to each of the intended antigenic components when combined into a candidate formulation with co-administration of licensed vaccines that together provide all of the same antigenic components. The same approach applies whenever the antigenic components are not combined into a single formulation but the contents of more than one pre-formulated product have to be mixed immediately before administration to avoid a detrimental physico-chemical interaction.

iii) For new candidate vaccines that contain known and one or more new antigenic components the initial trials may aim to demonstrate non-inferiority of immune responses to each of the known antigenic components when combined into a candidate formulation with separate administrations of known and new antigenic components. It may also be informative to include a control group that receives co-administration of known and new antigenic components. The
exact design depends on the availability of a single licensed vaccine containing the known antigenic components or whether more than one licensed vaccine has to be given.

iv) For any vaccine formulation to which an adjuvant is to be added there should be adequate data already available (which may apply to known adjuvants) or data should be generated (new adjuvants or when using any adjuvant with a new antigenic component) to demonstrate that addition of the adjuvant elicits a superior immune response to one or more antigenic components without a potentially detrimental effect on any other antigenic components. Alternatively, data should demonstrate that including the adjuvant allows for the use of a much lower dose of an antigenic component to achieve the desired level of immune response. Trials should evaluate a sufficient range of combinations of antigenic components and adjuvant to support the final selected formulation.

v) The total data generated should be explored to identify the criteria to be applied for the determination of an appropriate shelf-life of the vaccine. This is usually of particular importance to vaccines that contain live micro-organisms. Depending on data already generated, it may be necessary to conduct additional trials with formulations known to contain a range of micro-organism numbers or antigen doses to identify appropriate limits at end of shelf-life.

vi) Comparative immunogenicity trials may be needed to determine schedules appropriate for specific target populations, taking into account the urgency to achieve protective immunity (i.e. based on diseases to be prevented and their epidemiology). The data generated across all the trials should determine the minimum period that should elapse between doses and the effects of delaying doses to support acceptable windows around scheduled doses. Additionally, for some vaccines it may be useful to explore the shortest time frame within which doses may be completed without a detrimental effect on the final immune response (e.g. for vaccines for travelers who may need to depart at short notice and for vaccines intended to provide post-exposure prophylaxis).

The assessment of the effects of dose interval and the total time taken to complete the primary series is a particular issue for vaccines intended for use in infants due to the very wide range of
schedules in use in different countries (e.g. 3-dose schedules include 6-10-14 weeks and 2-4-6 months). In general, experience indicates that the magnitude of the post-primary series immune responses broadly correlates with the age of infants at the time of the final dose. If a trial using a 6-10-14 weeks or 2-3-4 months schedule demonstrates highly satisfactory immune responses it is reasonable to expect that schedules that either commence later in infancy, use longer dose intervals and/or in which the final dose is given at 5-6 months or later will also be highly satisfactory. In contrast, the results of the latter types of schedules cannot be used to support use of earlier and more condensed schedules.

vii) All of the data generated in accordance with points i) to vi) should be taken into account when selecting the final formulation and posology or posologies. The selection process is more straightforward if there are established ICPs that can be applied to interpretation of the results for at least some of the antigenic components. In the absence of an ICP, which frequently applies to new micro-organisms or antigens, the posology may be selected from considerations of any plateau effects that are observed and the safety profile of various doses and regimens.

It is not unusual that the final selected formulation and posology to some extent represents a compromise between immunogenicity and safety or, for combination vaccines, between the potential benefits of a vaccine that can protect against multiple types of infectious disease with some negative effects on immune response that may occur. These negative effects may result from a physicochemical interaction between vaccine components and/or a negative immune interference effect for some antigenic components with or without a positive immune interference effect for some others. The rationale for the final selection requires careful discussion in the application dossier.

5.6.1.2 Amending or adding posologies after initial licensure

Clinical trials conducted after first licensure may be designed to address one or more of the following:

a. Change the number of doses or dose intervals. In this case the control group should be vaccinated using the licensed posology and the trial should be conducted in a population
for which the vaccine is already licensed.

b. Use of the licensed posology in a new population (e.g. in subjects who are younger or older than the currently licensed age group; in subjects with specific underlying conditions, such as immunosuppression). In this case the trial should compare use of the licensed posology in the new target population and the population for which the vaccine is already licensed.

c. Use of an alternative to the licensed posology in a new population. In this case the alternative posology administered to the new population should be directly compared with the licensed posology in the licensed population.

d. Support alternative routes of administration for the licensed formulation (e.g. adding subcutaneous or intra-dermal injection to intra-muscular use).

Post-licensure clinical trials may also be conducted to support changes in formulation. Formulation changes other than adding or removing a preservative or removing thiomersal from the manufacturing process usually result in a modified product that is considered to be a new candidate vaccine from a regulatory standpoint (i.e. it would require a new application dossier and adequate trials to support separate licensure).

5.6.1.3 Post-primary doses

a. Need for post-primary doses

The need to administer additional doses, and the timing of these doses, may be determined before and/or after first licensure.

To date, very few licensed vaccines are recommended only for use in a primary series. Examples include inactivated hepatitis A vaccines and hepatitis B vaccines containing recombinant surface antigen [HBsAg] for which very long term follow-up continues to suggest that additional doses are not necessary to maintain protection in those who had a robust immune response to the primary series. For all other vaccines one or more additional doses of the same or another vaccine that protects against the same disease(s) is recommended or the prescribing information
states that it is not yet known whether further doses will be necessary.

If experience with other similar vaccines clearly indicate that additional doses of a new candidate vaccine will be needed the clinical development program should incorporate this in the overall assessment of immune responses.

If it is not known whether post-primary doses of a new candidate vaccine will be needed to maintain protection it is preferable that this should be determined from long-term follow-up of subjects who were enrolled in efficacy trials and/or from post-licensure effectiveness trials. Although the long-term monitoring of antibody persistence is important, these data alone cannot determine if another dose is needed unless there is evidence or a strong reason to expect that failure to maintain circulating antibody above a certain level (e.g. above the ICP if there is one) is associated with risk of breakthrough disease (even when the primary series of the vaccine elicited an immune memory response).

Until it is clear whether or not additional doses are needed, it is prudent to plan to obtain data on the immune response to additional doses at different intervals after the last dose of the primary series so that data are available should it become clear that an additional dose is required.

b. Assessment of priming during the primary series

Not all vaccines elicit a T-cell-dependent immune response that results in priming of the immune system and an anamnestic response to further doses. The administration of post-primary doses of a new candidate vaccine that contains one or more micro-organisms or antigens not previously used in human vaccines provides an opportunity to assess whether there was successful priming of the immune system during the primary series, in which case subsequent doses will serve to boost the immune response (see Subsection 5.2).

When assessing the immune response to additional doses and determining whether or not the primary series elicited immune memory the following should be taken into account:

a. Trials in which additional doses are administered may be extension phases of primary series
trials or new trials in subjects with documented vaccine histories.

b. When assessing whether the primary series elicited immune memory the optimal design is to compare subjects who previously completed a full primary series of the candidate vaccine with a control group consisting of subjects not previously vaccinated. Control subjects should be matched for age and for any host or demographic factors that might impact on their immune response (e.g. they should be resident in similar areas so that any natural exposure is likely similar).

c. If the new candidate vaccine elicited immune memory in the primary series the immune response to the additional (i.e. booster) dose should usually be superior to that observed in individuals who have not been vaccinated against the disease to be prevented based on comparisons of the geometric mean concentrations or titres of antibody. The percentages that achieve seropositivity or seroprotection (as defined) may not be different between the two groups if a single dose of the vaccine is highly immunogenic even in unprimed individuals.

d. The immune response to the additional dose in primed and unprimed subjects may also be differentiated based on the rapidity of the rise in antibody levels (faster in primed) and in terms of antibody avidity (greater in primed).

e. If the immune response as measured by geometric mean antibody concentrations or titres in the primed group is not superior to that in controls this does not always mean that the primary series did not elicit immune memory. For example, this may occur when natural priming has occurred in a substantial proportion in the control group that was not previously vaccinated against the disease to be prevented, in which case the rapidity of response and measurements of avidity may also not be distinguishable between groups. If natural priming has occurred it may or may not be detectable from pre-vaccination antibody levels in the control group.

f. If an immune memory response is elicited in the primary series it may be possible to achieve a robust anamnestic response using a much lower dose of an antigenic component compared to the primary series. A lower boosting dose may also provide a better safety profile (e.g. as occurs with diphtheria toxoid).

g. For polysaccharide-protein conjugate vaccines that elicit immune memory it may be informative to compare boosting with the same type of conjugate used for priming with an
alternative conjugate (e.g. to prime with a tetanus toxoid conjugate and boost with a
CRM197 conjugate and *vice versa*).

h. It may also be informative to assess the ability of a candidate vaccine to achieve cross-
priming by using heterologous antigenic components for priming and boosting. This may be
assessed by comparing boosting with the same vaccine used to prime with administration of
a formulation (which may be a licensed vaccine or an unlicensed product manufactured
specifically for the trial) containing a different micro-organism or antigen that is known to
be closely related but not identical to that in the vaccine (e.g. material derived from an
influenza virus of a different clade).

i. Elicitation of an immune memory response to a vector for an antigen after the first dose(s)
may interfere with or wholly prevent the immune response to the antigen after subsequent
doses (e.g. this may be observed when using adenoviruses capable of infecting humans as
live viral vectors). It is essential to understand whether or not this occurs since it may
necessitate the use of a different vector for the antigen or an entirely different vaccine
construct to deliver subsequent doses.

j. There are some antigens that not only do not elicit an immune memory response but also
demonstrate hypo-responsiveness to further doses. The best known examples are some of
the unconjugated meningococcal and pneumococcal polysaccharides (17, 18). In the past
these were sometimes administered to assess whether corresponding conjugated
polysaccharides had elicited immune memory in the primary series based on the premise
that this would better mimic the immune response to natural exposure compared to
administration of a further dose of the conjugate. This practice is not recommended since it
is possible that a dose of unconjugated polysaccharide could result in blunted immune
responses to further doses of the conjugate.

5.6.2 Using immunogenicity data to predict efficacy

Immunogenicity data may be used to predict efficacy with varying levels of confidence when:

a. There is a well-established ICP that can be used to interpret the immune responses to a
specific antigenic component (see Subsections 5.4 and 5.5). Comparative
immunogenicity trials are recommended since they provide a control for interpretation of
any unexpected findings and for safety. Depending on the objectives the comparator may be the same vaccine used as currently licensed or a licensed vaccine that has been widely used with no known problems regarding its effectiveness and which contains all or as many as possible of the same antigenic components as the candidate vaccine.

b. It is possible to use immune responses to bridge to estimates of vaccine efficacy obtained from well-designed clinical trials (i.e. to conduct bridging trials); see Subsection 5.6.2.1.

c. There is no ICP nor is it possible to bridge to a prior demonstration of efficacy; see Subsection 5.6.2.2.

5.6.2.1 Bridging to efficacy data

There are two main situations to consider. In both cases comparative immunogenicity trials designed to demonstrate non-inferiority are recommended. The choice of comparator is a critical factor for interpretation of the results.

i) Modifying the use of the same vaccine for which efficacy has been estimated

As described in Section 6, vaccine efficacy trials are usually conducted in specific target populations, characterised by factors such as age, region (which may define endemicity for some infectious diseases) and health status, using the intended final vaccine posology. Before or after initial licensure trials may be conducted with the aim of extending the use of the vaccine to other populations and/or to support alternative posologies.

When a different age group or posology is proposed or when extending use from immunocompetent to immunocompromised subjects it is usually very clear that a bridging trial is necessary. Whether or not a bridging trial is necessary to support use in regions other than where the estimate of efficacy was obtained requires careful consideration. Such trials should be required for licensure only if there are compelling scientific reasons to expect that the immune response to the vaccine, and therefore its efficacy, could be significantly different due to host factors (such as common underlying conditions that may affect immune responses) and/or geographical factors (such as distributions of subtypes of organisms, levels of natural exposure
and for trials in infants the possibility that high levels of maternal antibody could interfere with
responses to the primary series).

The usual trial design involves a direct comparison between the new population and/or posology
and a control group in which subjects representative of the efficacy trial population receive the
previously studied posology. It may also be acceptable that an indirect comparison is made with
the immunogenicity data that were obtained during the efficacy trial, in which case the vaccine
formulation and assay used should be the same as used in the efficacy trial whenever possible.

a. If the vaccine used in the efficacy trial is no longer available the comparator should be as
similar as possible to the original. Over time, it may be that the only bridge back to the
efficacy data is via a comparison with a licensed vaccine that was itself licensed based on a
bridging efficacy trial. As the number of bridging steps that has occurred between the
original efficacy data and the licensed comparator vaccine increases, so the reliance that may
be placed on a demonstration of non-inferiority to predict efficacy is weakened. This
consideration also applies when the vaccine for which efficacy was estimated has been
extended based on bridging efficacy for the shared subtypes (e.g. when additional subtypes
have been added) and the extended vaccine has replaced the original vaccine in the market.

b. If the assay has changed and has not been or cannot be directly compared to the original
assay used during the efficacy trial it may be possible to re-assay stored sera collected
during the prior efficacy trial in parallel with the sera from the new trial population.

If it remains unknown which immunological parameter best correlates with efficacy it is
preferable that the primary comparison between vaccines is based on functional antibody
whenever this is feasible.

ii) Inferring the efficacy of a new candidate vaccine

In this case the main evidence of efficacy for licensure comes from one or more bridging
efficacy trials. The same considerations regarding primary comparison, choice of comparative
vaccine and assay apply as described above.
If the new candidate vaccine is an extended version of a licensed vaccine and/or it contains additional subtypes of an organism not included in a licensed vaccine the interpretation of the immune responses to the unshared types in a comparative immunogenicity trial is not straightforward. Approaches that could be considered include comparing immune responses to each additional subtype with a mean response across all subtypes or the lowest response to an individual subtype included in the vaccine for which efficacy was demonstrated. Both of these approaches may provide a route to licensure but the limitations of these comparisons to predict efficacy should be taken into account when considering the overall benefit-risk relationship for the new vaccine and the collection of effectiveness data in the post-licensure period is recommended.

5.6.2.2 Other approaches

When there is no ICP nor is it possible to bridge to a prior demonstration of efficacy licensing a new candidate vaccine is problematical. This situation is most likely to apply to new vaccines against rare infectious diseases such as some viral haemorrhagic fevers, for which outbreaks do not occur in substantial numbers of persons or are of short durations, and some micro-organisms that could be used for bioterrorism purposes. Another important situation is the development of influenza vaccines against potential pandemic strains.

Approaches may include establishing a nonclinical model of efficacy that is thought to be relevant to the human infection and identifying which immunological parameter best correlates with protection (and if possible a putative ICP), trials of natural infection and protection against further disease and any passive protection data that may be available from nonclinical or clinical trials. If a vaccine has already been licensed based on evidence derived from one of these approaches any changes to the vaccine usage is subject to the same issues.

Although licensure of vaccines based on these approaches means that it is not likely to be possible to achieve a high level of confidence in the level of efficacy in humans, having available vaccines that have already been subjected to a full review of quality and nonclinical data as well
as at least some safety and immunogenicity data in humans does mean that they could be ready for rapid use in an emergency situation. Nevertheless, for these products it is particularly essential that protocols are developed in advance of any such emergency so that adequate data can be collected to assess efficacy/effectiveness whenever the opportunity arises.

5.6.3 Co-administration trials

Comparative immunogenicity trials intended to support co-administration of a vaccine with one or more other vaccines (i.e. administration at the same time but using different limbs for injection or multiple routes of administration) should demonstrate non-inferiority for immune responses to each of the co-administered antigenic components (see Subsection 5.5.3). The immunological parameters applied to each comparison may differ depending on vaccine content. It should be noted that co-administration may also enhance the immune response to certain antigens but so far there have not been instances in which this has been regarded as a cause for concern since the safety of co-administration has been acceptable.

When there are multiple licensed products containing the same antigenic components that could be co-administered with the vaccine under trial (e.g. combination vaccines intended for the routine infant primary immunization series) it is not feasible nor should it be necessary to conduct trials with each licensed product. The vaccine(s) chosen for trial should be as representative as possible of the range of licensed products.

An exception arises when there are several different types of polysaccharide-protein conjugate vaccines available that may be co-administered with the vaccine under trial. This is usually only an issue when the vaccine under trial contains protein that is the same as, or similar to, that in available conjugates. In this case it is important to appreciate that the results obtained with any one conjugate may not be applicable to other types of conjugate (e.g. lack of immune interference with a tetanus toxoid conjugate does not rule out that this could occur with a CRM197 conjugate).

If multiple doses of the co-administered vaccines are needed it is usual that the comparison
between groups is made only after completion of all doses. The schedule at which the vaccines are co-administered may also be an issue if there are several possible alternatives (e.g. as applies to vaccines for the primary immunization series in infants and for vaccines against hepatitis A and B). Consideration may be given to using a schedule that is most likely to detect an effect if there is one.

These trials usually have the following designs:

- Randomized parallel group trials in which different groups of subjects receive the vaccine under trial alone, the vaccine intended for co-administration and both together. If there is more than one additional vaccine that may be co-administered at the same time additional groups should receive each of these vaccines alone. In this case it is useful for interpretation of any observed effects to also add groups that each receives the vaccine under trial with one of the additional vaccines as well as a group that receives them all together.

- Randomized trials that use a staggered administration design. This approach is necessary when it is not possible to withhold any antigenic components to be co-administered (e.g. during the infant primary schedule). In these trials one group receives the co-administered vaccines at a chosen schedule while the control group receives either the vaccine under trial or the vaccine to be co-administered at the same schedule as the test group and the other vaccine is given one month later (or other appropriate interval). For completeness, an additional control group may be used in which the order of staggered vaccine administrations is reversed. The final dose and sampling occurs at least one month later compared to the co-administration group which, in infants, could have some impact on the magnitude of the immune response.

5.6.4 Immunization of pregnant women

5.6.4.1 Aims of immunization during pregnancy

Immunization during pregnancy may be undertaken with the primary aim to:

a. Protect the mother. For any candidate vaccine under development for prevention of an
infectious disease in which the target population includes adolescents and adults there is a need to consider the importance of generating data in pregnant women to support its use. The considerations should take into account the nature of the vaccine construct (e.g. does the vaccine contain a live organism that is replication-competent), whether pregnant women can reasonably avoid exposure to an infectious agent (e.g. by not travelling) and whether they may have the same risk of exposure but a greater risk of experiencing severe disease compared to non-pregnant women of the same age.

b. Protect the infant from an infectious disease for a limited period after birth by means of trans-placental transfer of maternal antibody. In this case there may be a potential benefit to the mother (e.g. influenza, acellular pertussis) or no or negligible potential benefit to the mother (e.g. respiratory syncytial virus and Streptococcus Group B).

5.6.4.2 Dose-finding in pregnancy

For new candidate vaccines intended for use in pregnant women and for licensed vaccines not authorized for use in pregnancy the first clinical trials to support this use should be conducted in non-pregnant adults, including or consisting only of women of child-bearing age (19). Once there are adequate relevant nonclinical data with satisfactory findings and some data on immune responses in non-pregnant women data should be obtained from pregnant women, covering a representative age range, so that the effects of pregnancy on the immune response can be evaluated. The doses tested initially in pregnant women should be based on the non-pregnant adult data but may need to be adjusted (in terms of antigen dose or dose regimen) after review of results from initial trials due to the effects of pregnancy on the immune system. Additional considerations for dose-finding when the aim is primarily to protect the infant are provided in Subsection 5.6.4.3.

In all trials conducted in pregnant women adequate mechanisms should be in place to document the outcome of the pregnancy, including the duration of gestation at time of delivery, the condition of the infant at birth and the presence of any congenital conditions. Depending on the type of vaccine, it may also be considered appropriate to collect information on developmental
milestones at least during the first few years of life.

5.6.4.3 Passive protection of infants

Transfer of IgG across the placenta does not occur to any extent until the third trimester. If the vaccine is not expected to benefit the mother, then administration in the third trimester should be studied. If the aim is also to provide some benefit to the mother, administration earlier in pregnancy should be studied. In this case, since the immune response to vaccination changes as pregnancy progresses and women do not always access healthcare early on, the effect of dosing at different times during pregnancy should be evaluated.

If it is expected that a substantial proportion of adults are likely to already have evidence of humoral immunity against the infectious disease to be prevented so that the aim of vaccination during pregnancy is to increase the amount of antibody transferred to the fetus, the trials in pregnant women may need to include exploration of doses and, if more than one dose is needed, dose intervals in seropositive as well as seronegative adults.

When the aim is primarily to protect the infant, dose-finding trials in pregnant women should include measurement of antibody levels in cord blood samples taken at delivery. The number of samples obtained should be sufficient to provide an estimate of inter-individual variability. In addition, efforts should be made to collect cord blood data that cover a range of times between maternal vaccination and delivery, that allow for evaluation of the effects of unexpected early delivery and which measure the impact of placental dysfunction (e.g. based on infants of low birth weight for their gestational age). The cord blood levels in infants born to vaccinated mothers who receive the final selected vaccine posology should be clearly superior to that in infants born to mothers who were not vaccinated, regardless of the pre-vaccination serostatus of the mothers. Secondary analyses could examine whether this finding also applies within subsets of mothers who were seronegative or seropositive prior to vaccination.

The duration of detectable maternal antibody in infants should be documented. To avoid multiple bleeds in individual infants this may be documented by randomization of mothers such that their
Infants are sampled only once or a few times at staggered defined intervals so that the total data are used to describe the antibody decay curve. These data are particularly important when it is planned that passive protection via maternal antibody will be followed by active vaccination of infants against the same antigen(s).

If there is an immune correlate of protection established for the infectious disease to be prevented the aim of the immunogenicity trials should be to identify a maternal vaccination regimen that results in cord blood levels that exceed the ICP in a high proportion of new born infants. If there is no ICP, an efficacy trial in infants is usually needed (see Section 6).

5.6.5 Changes to the manufacturing process

Changes made to the product composition (e.g. addition of, removal of, or change in adjuvants or preservatives) or manufacture (changes to process, site or scale) during the pre-licensure clinical development program or after licensure do not always need to be supported by comparative clinical immunogenicity trials between the prior and the newer products.

For example, it is common that the scale of manufacture changes during the pre-licensure development program but this step alone would not be expected to have a clinically significant effect in the absence of other changes. In addition, the later confirmatory trials usually use product from final scale process. Also, any clinical effects of changes to the manufacturing process during the pre-licensure program may be evident from the results of sequential trials in similar populations or may not matter if the pivotal immunogenicity and/or efficacy trials use vaccine made using the final process. If this is not the case, and for all changes that are made post-licensure, consideration must be given to whether a clinical trial to compare vaccine manufactured using the prior and new processes is required. This decision must be taken on a case by case basis after a full evaluation of the in-vitro and any nonclinical in-vivo data describing and supporting the change. It is usually acceptable that a single lot of vaccine made using each process is sufficient for the comparison.

In the post-licensure period there may be many changes to the manufacturing process over time.
Over time it is possible that each one of these was considered too minor to merit conduct of a clinical trial but the product that results from multiple minor changes could be substantially different to that which was initially licensed. When considering the potential impact of what seems to be a relatively minor change to the production process that, not alone, would merit a clinical trial it may be important to consider the full history of changes that have been allowed without clinical data and to consider whether the sum total of changes could have a clinical impact. In this situation, when many years have passed, a clinical trial of the current compared to the original licensed vaccine will not be possible. If disease surveillance suggests that there could be a problem with vaccine effectiveness, a clinical trial that compares the current vaccine with another licensed vaccine for which there is a lot of clinical experience may be considered useful.

5.6.6 Lot-to-lot consistency trials

Some NRAs request lot-to-lot consistency trials during the pre-licensure clinical development program for all new candidate vaccines. Where these trials are not requested as a routine they may be considered for certain types of vaccines where there is inherent variability in manufacture of the product. If requested, the rationale for conducting the trial and the objectives should be very clear.

In these trials the usual expectation is that 95% confidence interval around each pairwise comparison of the post-vaccination geometric mean concentrations/titres falls within pre-defined limits. The clinical implications of results that show that one or more comparisons do or do not meet the pre-defined criteria set around the ratios are unknown and interpretation of the results should take into account all of the available immune response data.
6. Efficacy and effectiveness

This Section considers:

- Approaches to determination of efficacy
- Human challenge trials
- Preliminary and confirmatory (pivotal) efficacy trials
- Design and conduct of efficacy trials, including control groups
- Approaches to determination of vaccine effectiveness

6.1 Approaches to determination of efficacy

6.1.1 Human challenge trials

In some settings it may be useful and appropriate to obtain an initial assessment of vaccine efficacy from human challenge trials in which vaccinees are deliberately exposed to an infectious agent in a controlled setting. Human challenge trials are not always feasible or appropriate, as discussed in Appendix 1. When they can be performed, human challenge trials have potential to streamline and so accelerate vaccine development. They may be of particular use:

- When there is no appropriate nonclinical model (e.g. when a candidate vaccine is intended to protect against an infectious disease that is confined to humans).
- When there is no known immunological correlate of protection.
- When vaccine efficacy trials (as described above and in detail in the sections that follow) are not feasible.

Like all model systems human challenge trials have limitations in terms of their relevance to natural infection and their ability to predict protection under very variable circumstances (e.g. in terms of time elapsed between vaccination and exposure to a pathogen and the impact of pathogen dose on development of clinically apparent infection). Nevertheless, they may suffice to rule out vaccines or doses that seem unlikely to have useful protective efficacy and to select the most promising formulations and regimens for further trial. See Appendix 1 for further information.
Later on in the clinical development program, usually after safety and immunogenicity trials have identified one or more potentially effective vaccination regimens for further evaluation, vaccine efficacy may be assessed against naturally acquired infectious disease.

6.1.2 Preliminary efficacy trials

Based on the available safety and immunogenicity data it may be considered appropriate to evaluate vaccine efficacy initially in dose-finding trials (which may include different doses and/or different numbers of doses or dose intervals) or in small-scale trials that evaluate a single vaccination regimen before proceeding to confirmatory (pivotal) trials.

Whenever possible the general features of these trials (such as case definitions and method of case ascertainment) should resemble those expected to be applied in confirmatory trials of efficacy. However, it is sometimes the case that preliminary efficacy trials are used to inform the final design of confirmatory efficacy trials. For example:

- By applying various case definitions the results may be used to identify or refine the most appropriate case definition for confirmatory trials.
- By exploring efficacy in specific subgroups in preliminary trials the confirmatory trials may be designed to ensure adequate numbers of cases per subgroup of interest.
- The method of case ascertainment used may be assessed for feasibility in larger trials with a greater number of, and more geographically widespread, trial sites.
- The immunogenicity and efficacy data may be used to support a provisional assessment of potential correlates of protection.

If the candidate vaccine is intended to prevent a severe and/or life-threatening infectious disease for which there is no, or at least no very satisfactory, vaccine already available, individual NRAs may agree to accept an initial application for licensure based on one or more preliminary efficacy trial or trials. In these cases it is essential that sponsors and NRAs should discuss and agree the main features of the design of the trials before initiation, including the sample size, so that, subject to promising results, the data may be considered robust and sufficient.
The availability of a vaccine licensed on the basis of preliminary efficacy data has potentially important implications for the acceptability and feasibility of initiating or completing confirmatory efficacy trials that include a control group that does not receive active vaccination. These issues should be discussed between NRAs and sponsors so that expectations for provision of confirmatory efficacy data are agreed prior to the start of any trials that could potentially support initial licensure.

6.1.3 Confirmatory (pivotal) efficacy trials

A single confirmatory vaccine efficacy trial or more than one trial may be conducted, depending on considerations described in Subsection 6.2 below.

In pivotal efficacy trials, the primary objective is usually to estimate vaccine efficacy over a pre-defined time frame after completion of the primary vaccination schedule, which may comprise one or more doses. Confirmatory trials may evaluate a single or more than one vaccination regimen and may or may not include evaluations of efficacy before and after booster doses. As applicable to the individual candidate vaccine, a range of secondary efficacy objectives may be defined although the trial will not be formally powered for these analyses.

6.2 Design and conduct of efficacy trials

The protective efficacy of a vaccine against a specific infectious disease is usually defined as the reduction in the chance of developing the disease after vaccination relative to the chance when not vaccinated as determined in a prospective randomized controlled trial. Vaccine efficacy (VE) is therefore derived from the proportionate reduction in disease attack rate (AR) between the control group that did not receive vaccination against the infectious disease potentially preventable by the candidate vaccine (ARU) and the vaccinated (ARV) group(s). VE can be calculated from the relative risk (RR) of disease among the vaccinated group as (ARU-ARV/ARU) x 100 and (1-RR) x 100.
Much less often, vaccine efficacy may be determined in a prospective randomized trial in which the efficacy of the candidate vaccine is compared to that of a licensed vaccine intended to prevent the same infectious disease.

The following sections consider issues that apply to both types of trial, including some specific trial designs that may be considered along with some issues for analysis of the data. Details of statistical methodologies are beyond the scope of this guidance and only broad principles are described.

6.2.1 Selection of trial sites

Vaccine efficacy trials require the presence of a sufficient burden of clinical disease to enable estimates to be obtained from feasible numbers of subjects and within a reasonable timeframe. The infectious disease to be prevented may occur at sufficiently high rates to enable efficacy trials to be conducted only in confined areas. Even when the disease to be prevented is more widespread, it may be necessary to confine efficacy trials to specific affected areas for reasons that may include feasibility of dealing with multiple NRAs and ethics committees, need to ensure adequacy of monitoring and desire to accumulate representative numbers of cases due to specific serotypes or subtypes.

Sponsors may have to conduct feasibility assessments to accurately ascertain clinical disease rates in various age subgroups of populations before selecting trial sites. Any nationally-recommended non-vaccine-related preventive measures that are in place (e.g. prophylactic drug therapy in high risk individuals or settings, use of insect repellents and bed nets) should be identified and the trial should be conducted against a background of these additional interventions.

Trial sites need to be sufficiently accessible to allow regular monitoring visits. Sponsors may have to engage in site capacity building exercises prior to trial initiation, including training of study personnel, and may need to provide essential infrastructure to support the trial (e.g. to ensure that there are adequate blood collection and processing facilities, refrigeration facilities
suitable for the vaccine and/or sera, competent laboratories, data handling capacity and communication methods to allow electronic randomization schemes, rapid reporting of safety data or other trial issues to the sponsor).

6.2.2 Candidate (test) vaccine group(s)

If previous data do not support selection of a single dose or regimen of the candidate vaccine for assessment of efficacy, trials may include one or more groups in which subjects receive the candidate vaccine (e.g. more than one dose or schedule may be evaluated). In some instances one or more placebo doses may need to be interspersed with candidate vaccine doses to enable matching of all regimens under trial in a double-blind design (e.g. if 2 or 3 doses of the candidate vaccine are to be compared with the control group).

6.2.3 Control (reference) group(s)

Control groups comprise all subjects who do not receive the candidate vaccine. Usually only one control group is enrolled in any one trial. On occasion, it may be considered important to include more than one of the possible types of control groups that are discussed below.

6.2.3.1 Control groups not vaccinated against the infectious disease to be prevented

In most cases vaccine efficacy trials employ a control group that does not receive vaccination against the disease to be prevented by the candidate vaccine. In double-blind trials the control group may receive:

- A true placebo (i.e. material without any pharmacological activity). This has the advantage of providing safety data against a control that has no pharmacologically active components. However, the use of an injectable placebo may not be acceptable to one or more of NRAs, ethics committees, investigators, trial subjects or their parents/guardians at least in some age groups (e.g. there may be particular objections raised against true placebo injections in
infants). In contrast, there is usually no objection to use of a true placebo when the candidate vaccine is administered orally or by nasal installation.

- If a true placebo is not acceptable to one or more of the above interested parties the control group may receive a licensed vaccine that has no effect on the infectious disease to be prevented by the candidate vaccine but may have some benefit for recipients. In some cases both licensed vaccine and placebo doses may have to be used to match the candidate vaccine regimen. Due to distinctive visual characteristics or markings on presentations of licensed vaccines it may not be possible to wholly maintain double-blind conditions. In this case those site staff who prepare and/or administer trial vaccines should not otherwise be involved in trial conduct. Difficulties may also arise if the candidate vaccine is injected in a different fashion (i.e. subcutaneous, intradermal, intramuscular) to the only suitable licensed vaccine(s) that could be given to controls. In this case it may be possible to screen the administration site to prevent vaccine recipients and care-givers observing the specific method of injection.

- A licensed vaccine that has an effect on the infectious disease to be prevented only when due to some of the total serotypes or subtypes in the candidate vaccine. In this case the licensed vaccine provides a control group that is not vaccinated against the additional types in the candidate vaccine (i.e. unshared types).

If there are major objections to use of placebo injections but there is no potentially beneficial licensed vaccine that would be suitable for the target age group, the control group may be randomized to receive no vaccine. This is an undesirable situation and should be regarded as a last resort since it precludes the use of any form of blinding of trial personnel or participants (including care-givers).

6.2.3.2 Control groups vaccinated against the infectious disease to be prevented

In this case the control group receives a vaccine that is already licensed to prevent the same infectious disease as the candidate vaccine. This approach is used when it is not acceptable to
employ a control group that is not vaccinated against the infectious disease to be prevented because there is at least one available licensed efficacious vaccine that is recommended for use in areas where the disease occurs.

On occasion, the control group receives a vaccine that may prevent the same infectious disease as the candidate vaccine but only when due to some of the total serotypes or subtypes in the candidate vaccine. Therefore the control group is vaccinated against the shared types but is not vaccinated against the unshared types.

If there is more than one licensed vaccine that could be used it is important that selection of the control vaccine takes into account the available evidence supporting its efficacy and, if relevant, whether it appears to have similar efficacy against all serotypes or subtypes of the pathogen involved. It is also necessary to discuss the choice of comparator with NRAs in countries where the sponsor will seek a licence for the candidate vaccine to ascertain the acceptability of an estimate of relative efficacy against a product that may be unlicensed or, at least, not the product in widespread use. This is especially important if one multi-country pivotal trial will be conducted, in which case the same vaccine should be given to the control group at all trial sites. If it is not possible to use the same control vaccine in all regions where efficacy is to be evaluated consideration should be given to conducting different efficacy trials with different vaccines used in the control groups.

On occasion, there may be at least one licensed vaccine available in one or more countries to prevent the same infectious disease as the candidate vaccine but there may be other countries in which the disease of interest occurs in which:

- No such vaccine is yet licensed and/or
- No such vaccine is included in the routine immunization schedule and/or
- There are sound reasons to consider that no licensed vaccine is likely to provide useful efficacy (e.g. because the licensed vaccine does not cover or is known/expected to have poor efficacy against the serotypes or subtypes that are most prevalent in a specific region).

In these situations, after careful consideration by all interested parties (i.e. sponsor, NRAs, ethics
committees, local public health authorities and investigators) it may be deemed appropriate to use a control group that is not vaccinated against the disease to be prevented.

6.2.4 Trial designs

6.2.4.1 Randomization

The unit of randomization is most often the individual. Alternatives include the household or the cluster under trial (e.g. a school population or a local community). Randomization of groups or clusters rather than individuals may be preferred:

- When a vaccination program is to be conducted in a geographical area or community
- When it is logistically easier to administer the vaccine to groups than to individuals
- When vaccination is anticipated to reduce transmission of the infectious agent

6.2.4.2 Types of trial design

The absolute protective efficacy of a vaccine is most commonly assessed in prospective randomized trials that compare rates of clinically apparent disease (e.g. an acute clinical illness) or established infection (e.g. chronic infection that is known to predispose to serious clinical disease) between a candidate vaccine group and a control group.

The simplest design involves randomization of equal numbers of subjects to each of the candidate vaccine group and the control group (i.e. 1:1). In trials that employ a control group that is not vaccinated against the disease to be prevented but there are clinical data already available to strongly support the likely efficacy of a candidate vaccine, it may be appropriate (subject to statistical considerations and an assessment of the impact on the total trial sample size) to use unbalanced randomization to reduce the chance that subjects will be randomized to the control group (e.g. 2:1 or 3:1 so that the majority of trial subjects receive the candidate vaccine).

Trials may plan to follow up trial subjects for the primary efficacy endpoint for a fixed period of time after the last dose of the primary series. The time at which the primary analysis is conducted
is based both on the anticipated rate of occurrence of the primary efficacy endpoint in the control
group and the feasibility of retaining subjects on trial for prolonged periods. Alternatively, based
on anticipated rates of the primary efficacy endpoint in the control group and an expected or
minimum desirable level of efficacy of the candidate vaccine, a case-driven approach may be
taken. In this design the primary analysis is conducted once a pre-specified number of total cases
(i.e. in a double-blind setting based on the anticipated numbers in test and control group required
to demonstrate the projected vaccine effect) has been detected.

Alternative designs that allow for a comparison with a control group that is not vaccinated
against the disease to be prevented, at least in the short-term, may include (but are not limited to)
the following:

i) In a step-wedge trial the candidate vaccine is administered to pre-defined groups in a
sequential fashion. Each pre-defined group is a unit of randomization. These may be
geographical groups or groups defined by host factors (e.g. age) or other factors (e.g. attendance
at a specific school or resident within a specific healthcare catchment area). Such a design may
be chosen when there is good reason to anticipate that the vaccine will do more good than harm
(affecting the equipoise associated with randomization to a control group that is not vaccinated
against the disease to be prevented) and/or when it is impossible to deliver the intervention
simultaneously to all trial participants. This design may also be used to evaluate vaccine
effectiveness (see Subsection 6.3).

ii) In a ring vaccination trial the direct contacts of a case, and sometimes secondary contacts,
may be randomized to vaccine or control or may be randomized to receive immediate
vaccination or vaccination after a delay period (20). This type of pre-exposure cohort trial
usually requires smaller sample sizes than prospective randomized controlled trials. The trial
design assumes that there is an equal chance of vaccinees and non-vaccinees being infected and
developing the infectious disease as a result of contact with an index case.

These types of trials may be particularly applicable when the infectious disease to be prevented
is associated with a relatively high incidence of secondary cases in susceptible populations.
Therefore the use of this trial design requires prior knowledge of the infectivity of the infectious agent and proportion of infections that are clinically apparent as well as the general susceptibility of the trial population.

The follow-up period for subjects after contact with the index case should cover the upper limit of the incubation period, taking into account the period during which the index cases were infectious and the contact period. The inclusion period for new cases and controls and their contacts should be set at a maximum of six months following the detection of the first case. Inclusion over a longer period may introduce bias in favour of vaccine efficacy, because the exposure to the infecting pathogen and thus the risk of infection will be reduced in the vaccinated groups or clusters compared with that in groups or clusters that are not vaccinated against the disease to be prevented.

iii) There are some situations in which the vaccine is not intended, or at least not primarily intended, to protect the vaccinees themselves against a clinically apparent infectious disease. The most common example is the vaccination of mothers during the last trimester of pregnancy, when IgG most efficiently crosses the placenta, to protect the infant during the early months of life (see Subsection 5.6.4). This strategy may or may not be followed by active immunization of infants, provided that suitable vaccines exist. If vaccine efficacy is measured in infants the unit of randomization is the mother.

6.2.5 Clinical endpoints

Preliminary efficacy trials may have an objective to identify the primary and/or secondary endpoints for confirmatory trials. Therefore the primary endpoint in preliminary efficacy trials may be different to that selected for confirmatory efficacy trials.

6.2.5.1 Primary endpoints

In most instances, the focus of vaccine efficacy trials is on the prevention of clinically apparent infections that fit the primary case definition based on clinical and laboratory criteria. The
primary endpoint is also usually defined by the timeframe in which the case occurred in relation to dosing.

If an organism is able to cause a range of infections (e.g. from life-threatening invasive infections to common infections that are not serious if adequately treated), the primary endpoint in any one trial should be carefully selected in accordance with the proposed indication(s).

A candidate vaccine may contain antigens derived from one or several types (serotypes, subtypes or genotypes) of the same species. It is also possible that there may be some potential for cross-protection against types not included in the vaccine (e.g. as observed with rotavirus vaccines and human papilloma virus vaccines). For these types of vaccines it is usual that the primary endpoint comprises cases due to any of the types included in the vaccine and the trial is powered for this composite endpoint. It is not usually possible to power the trial to formally assess efficacy against individual types in the vaccine or to assess cross-protection against types not in the vaccine.

Alternative primary endpoints may include:

- Clinical manifestations of latent infection (e.g. herpes zoster)
- Established chronic infections that may be asymptomatic but predispose to infection-related disease later in life (e.g. chronic hepatitis B infection; persistent infection with HPV)
- Other markers that predict progression to clinically apparent disease (e.g. histological changes that are established pre-ursors of malignant neoplasia)

6.2.5.2 Secondary endpoints

As applicable to the individual candidate vaccine and the definition of the primary endpoint, important secondary endpoints may include:

- Cases that occur after each dose, when the vaccine schedule includes multiple doses and/or a booster
- Cases due to each of the individual types of the species included in the vaccine
• Cases due to the species (i.e. regardless of whether caused by types that are and are not included in the candidate vaccine)
• Cases due to non-vaccine types
• Cases according to host factors (e.g. age, region)
• Cases meeting various criteria reflecting disease severity
• Duration and/or severity of the illness, which may include clinical (e.g. duration of fever or rash) and laboratory measurements (e.g. duration of shedding)

In accordance with Subsection 5.4, one important secondary objective should be to attempt to identify a correlate of protection or, at least, a threshold value.

There are no vaccines indicated for the prevention or interruption of carriage, implying an effect on transmission. In addition, there are no vaccines indicated for prevention of transmission. Eradication of carriage and/or reduction in disease transmission that is not directly linked to and/or accompanied by a clinical benefit of vaccination to the individual is not usually considered to be sufficient to support licensure. Sponsors contemplating trials in which these are primary endpoints are advised to consult widely with NRAs.

6.2.6 Case definition

As part of the pre-defined primary efficacy endpoint the protocol should describe the clinical and laboratory criteria that must be met to define a case.

- If a case is a clinically apparent infection it is essential that the definition includes core clinical features. It should also list acceptable sampling and laboratory processing methods to confirm the presence of the target pathogen and/or to detect infection by serological findings.
- If the endpoint is the result of infection (e.g. evidence of persistence of infection or a histological change) then details of sampling (frequency and method) and grading (if applicable) should be included.

Adequate case definitions should also be provided for secondary endpoints. For example, if the
primary endpoint is all clinically apparent infections due to the types in the vaccine the
secondary analyses may focus on cases that meet specific criteria for severity, cases that require
medical contact or hospitalization and cases that are due to organism types not actually included
in the vaccine.

Whenever possible, centralized laboratories should be used and standard shipping procedures
should be established for samples. If this is not feasible then information on assay performance
between laboratories should be obtained and presented. The sensitivity, specificity and
reproducibility of all the methods used should be included in the trial reports. If no well-
validated methods for establishing infection and/or progression of infection exist during the
period of pre-licensure clinical development then experimental laboratory methods could be
used. It would usually be expected that these experimental methods are validated before using
them to analyse specimens obtained during the pivotal trials.

See Subsection 4.1.2 regarding the use of an adjudication committee.

6.2.7 Case ascertainment

It is critical that the same methodology for case detection is applied in all treatment groups and
throughout the duration of the trial. Active case ascertainment usually requires frequent
monitoring and contact with vaccinees or their care-givers. Passive case ascertainment is usually
based on vaccinees or care-givers presenting to or otherwise contacting a local healthcare facility
due to the onset of specific symptoms. In this case it is common that contact is triggered by one
or more of a list of signs or symptoms given to trial subjects or their care-givers at the time of
randomization and they may be instructed to contact a specific healthcare facility. Alternatively
or in parallel, cases may be detected based on monitoring all local clinics and hospitals for cases.

For efficacy endpoints based on clinically apparent disease, the possible range of clinical
presentations will determine the mode of case ascertainment. For example, this may be hospital-
based for cases of life-threatening infections or community based for less severe infections. If
community based, case detection may depend on family practitioners and on first suspicion of
infection by vaccinated subjects themselves or their parents/guardians. In each case, it is critically important that the individuals who are most likely to initiate detection of a possible case should have clear instructions. These may need to cover issues such as criteria for stimulating contact with designated healthcare professionals, telephone contacts, initial investigations and further investigations once a case is confirmed.

For efficacy endpoints other than clinically apparent disease, it becomes critical that subjects are monitored at regular intervals to detect clinically non-apparent infections or changes in other selected markers (e.g. the appearance of histological changes). The frequency of visits, and acceptable windows around the visits, should be laid down in the trial protocol and must be carefully justified.

The appropriate period of case ascertainment during a trial requires special attention and will be determined mainly by the characteristics of the disease to be prevented and the claim for protection that is sought at the time of initial authorization. For infectious diseases that have marked seasonality, at least in some geographic locations, it is usual to plan for a primary analysis at least when all vaccinees have been followed through one complete season. In these settings it is usual to conduct an enrolment campaign over a very short period just before the expected season onset. However, it may be necessary to repeat the exercise before the next season to meet the pre-defined sample size, in which case the opportunity should be taken to collect all cases that occur in the second season for the initial vaccination campaign cohort.

6.2.8 Duration of follow-up

At the time of conducting the primary analysis for the purposes of obtaining initial licensure, the duration of follow-up in vaccine efficacy trials may be relatively short (e.g. 6-12 months) and insufficient to detect waning protection, if this exists. Therefore, case ascertainment should continue in the vaccine efficacy trial populations and/or waning protection should be assessed during post-licensure effectiveness trials. These data may serve to indicate the need for and optimal timing of booster doses and to estimate efficacy after booster doses.
6.2.9 Analysis of efficacy

6.2.9.1 Sample size calculation

The trial sample size should be calculated based on:

i. The selected primary efficacy endpoint, including the possibility that the primary endpoint may be a composite of cases due to any of the organism types included in the candidate vaccine;

ii. The primary analysis population (see below) and

iii. According to the primary hypothesis (i.e. superiority or non-inferiority and the pre-defined criteria).

If the primary analysis population represents a subset of the total randomized population the sample size calculation should include an adequate estimation of numbers likely to be excluded from the primary analysis for various reasons. In addition, if considered necessary, a blinded review of total numbers enrolled who are eligible for the primary analysis population may be conducted after a pre-defined number has been randomized so that the trial sample size can be adjusted accordingly.

6.2.9.2 Analysis populations

Clinical efficacy is usually assessed in the total randomized trial population (i.e. those who are assigned to receive vaccine and/or control) and in pre-defined subsets of the randomized population.

In maternal immunization trials of clinical efficacy it may be appropriate that trials are powered to assess vaccine efficacy only in the offspring. If a secondary or exploratory analysis is conducted in mothers the case definition will likely need to be different.

The pre-defined trial populations should include as a minimum:

- All randomized subjects (i.e. the full analysis set)
All vaccinated subjects regardless of the numbers of assigned doses actually received and whether or not they were administered within the pre-defined windows.

Subsets of all vaccinated subjects separated according to any evidence of prior exposure to the infectious disease under trial (e.g. baseline seropositivity vs. seronegativity).

The *per protocol* population should be confined to subjects who have generally complied with the protocol and have received all assigned doses within pre-defined windows. In addition, this population should be confined to those with no evidence of prior exposure to the infectious agent (or specific serotypes or subtypes) at baseline. Depending on the target pathogen this subset may also be defined based on prior vaccination history.

Other populations may be appropriate for some pre-defined secondary or exploratory analyses. For example:

- Those who completed specific numbers of assigned doses or received all doses within pre-defined windows around the scheduled trial visits, i.e. analyses of efficacy according to adherence to the vaccination regimen.
- Subgroups defined by demographic factors known or postulated to impact on vaccine efficacy.

### 6.2.9.3 Primary analysis

It is common in vaccine efficacy trials that the pre-defined primary analysis is based on estimating efficacy in the *per protocol* population and on rates of true vaccine failures, i.e. the calculation of efficacy takes into account only those cases with onset after a minimum time had elapsed after completion of the assigned doses. For example, depending on knowledge of the kinetics of the immune response, true vaccine failures may be limited to cases with onset more than a specified number of days or weeks after the final dose of the primary series. In addition, for a vaccine that contains antigens from only certain serotypes or subtypes, the primary analysis may be based on cases due to vaccine types only.

In trials that compare a candidate vaccine with a group that is not vaccinated against the disease
to be prevented the aim is to demonstrate that the lower bound of the 95% confidence interval around the estimate of vaccine efficacy is above a pre-defined percentage (which will always be above zero). The pre-defined percentage should be selected based on the sponsor’s expectation of the point estimate of vaccine efficacy and taking into account what might be viewed as the minimum level of efficacy that could be considered clinically important. The sample size calculation is based on this objective.

In trials that compare a candidate vaccine with an active control the aim is to demonstrate non-inferiority of the candidate vs. the control vaccine, with calculation of the 95% confidence intervals around the difference in rates of breakthrough infections. This requires a pre-defined non-inferiority margin, which should be justified in accordance with prior estimates of vaccine efficacy for the disease to be prevented, and level of alpha on which the sample size calculation depends. If the sponsor also intends to assess superiority of the candidate vaccine over the active control the statistical analysis plan should pre-define a hierarchical assessment so that superiority is assessed only after establishing that the non-inferiority has been demonstrated.

6.2.9.4 Other analyses

The full range of secondary and exploratory analyses will depend on the pre-defined endpoints. Some of these analyses may be conducted in specific predefined trial populations. For example, important sensitivity analyses to support the primary analysis include those based on all proven cases whenever they occurred after randomization and in each analysis population. If the schedule includes more than one dose then analyses should be conducted that count cases from the time of each dose for all subjects who were dosed up to that point.

If the primary analysis was confined to cases due to organism types included in the vaccine then additional analyses should evaluate efficacy based on all cases regardless of the serotype or subtype responsible. If there are sufficient numbers of cases, these analyses may provide some indication of any cross-protection provided by the antigens in the vaccine.

Depending on the case definition, other analyses may be based on cases that met some but not all
of the case definition criteria, cases that were severe and cases that required a medical consultation or hospitalization.

6.2.9.5 Other issues

Vaccines that contain antigens derived from several serotypes, subtypes or genotypes

As discussed in Section 4.3.5, it is not usually possible to power the trial to formally assess efficacy against individual types in the vaccine. Secondary or, at least, exploratory analyses should be planned to describe efficacy against the various types represented in the vaccine and, if there is an expectation of cross-protection, against types not included. If the data suggest unusually low efficacy against any type in the vaccine it may be necessary to explore this matter in further trials.

Magnitude of vaccine efficacy

The point estimate of vaccine efficacy and 95% confidence intervals that are obtained may indicate that a relatively modest proportion of cases can be prevented. This fact alone does not preclude licensure provided that the sponsor can substantiate that the vaccine efficacy observed represents an important clinical benefit. For example, if the vaccine prevents life-threatening infections for which there is no very effective specific therapy and for which no vaccine or no more effective vaccine is available.

Extrapolation of vaccine efficacy

Vaccine efficacy can only be estimated in geographical areas where there is sufficient disease to support trial feasibility. In most instances it is not necessary for any one NRA to request provision of efficacy data from within its own jurisdiction nor is it feasible to conduct a study that provides robust results within a single country. Any such requests should only be made when there are scientifically sound reasons to think that vaccine efficacy could be substantially lower compared to that observed in the areas where Phase 3 trials were conducted. In addition,
such requests should not be made if there is a good scientific justification to use immunobridging
to support extrapolations of efficacy between populations (see Section 5 on bridging efficacy).

6.3 Approaches to determination of effectiveness

Vaccine effectiveness reflects direct (vaccine induced) and indirect (population related)
protection during routine use. Thus, the assessment of vaccine effectiveness can provide useful
information in addition to any pre-authorization estimates of protective efficacy. Even if it was
not feasible to estimate the protective efficacy of a vaccine pre-authorization it may be possible
and highly desirable to assess vaccine effectiveness during the post-authorization period. The
information gained from assessments of vaccine effectiveness may be particularly important to
further knowledge on the most appropriate mode of use of a vaccine (e.g. need for booster doses
in at least some segments of the population to maintain adequate protection over time).

Vaccine effectiveness may be estimated:

i) In observational cohort trials that describe the occurrence of the disease to be prevented in
the target population over time. However, there is no randomization step and there is the
potential for considerable biases to be introduced. One such approach is the screening
method.

ii) During phased (e.g. in sequential age or risk groups) introduction of the vaccine into the
target population in which the groups might form the units of randomization (i.e. using a
stepped wedge design).

iii) Using other designs, of which a wide range has been used in different circumstances. For
example, using a case test-negative trial design. In this modification of a case control trial
subjects with symptoms suggesting the infectious disease under trial and seeking medical
care are tested for the infectious agent of interest. The cases are those who are positive and
controls are those who are negative for the pathogen of interest. If vaccinated cases are less
severely ill and seek care less frequently than cases that occur in individuals not vaccinated
against the disease to be prevented, then an appropriate adjustment for illness severity is
required to avoid bias in effectiveness estimates (21).
Vaccine effectiveness is affected by a number of factors, including:

- Vaccination coverage of the population
- Pre-existing immune status of the population
- Differences in types included in a vaccine compared to predominant circulating types
- Changes in circulating predominant types over time
- Transmissibility of the pathogen and any effect that introduction of routine vaccination may have had on transmission rates

It may not be possible or appropriate for sponsors to conduct trials to estimate vaccine effectiveness themselves since regional or national networks may be necessary to ensure that cases are reliably detected. For some types of disease the use of data collected by means of national or international registries may be appropriate. In addition, in some jurisdictions the estimation of vaccine effectiveness is not considered to fall within the remit of the license holder.

Whatever the local requirements and arrangements, sponsors should discuss the arrangements for ongoing disease surveillance and the potential for estimating effectiveness with public health authorities in countries where the vaccine is to be used and where appropriate surveillance systems are in place. The plans for estimation of effectiveness should also be agreed with NRAs at the time of licensure and the requirements for reporting of effectiveness data to the NRA either via the sponsor or directly from a public health authority should be clarified.

It may be that reliable estimates of effectiveness can only be obtained in certain countries in which vaccination campaigns are initiated and where there is already a suitable infrastructure in place to identify cases. Therefore, it would likely be inappropriate to extrapolate any estimates of effectiveness that are obtained to other modes of use (such as introducing the same vaccine to different or only to highly selected sectors of the population).

7. Safety

This Section considers:
7.1 General considerations

Safety should be assessed in all clinical trials that are conducted pre- or post-licensure. The assessment of safety may be the only primary objective, a co-primary objective or a secondary objective in a clinical trial. Since the methods for collection, analysis and interpretation of safety data during clinical trials contrast with those applicable to post-licensure routine safety surveillance they are considered separately.

In principle, many of the approaches to documenting and reporting safety data during clinical trials and the conduct of pharmacovigilance activities for vaccines are similar to those for all medicinal products. The sections that follow should be read in conjunction with the extensive guidance that is available from many publications and on the websites of WHO, CIOMS, the ICH and individual regulatory bodies. The focus of the sections is on some methods and practises that are different for vaccines compared to other medicinal products and on some issues that may need to be addressed due to the vaccine composition.

7.2 Assessment of safety in clinical trials

As described in Subsection 4.1.2 the use of a DSMB should be considered before commencing clinical trials. If the DSMB’s role includes recommending early termination of a trial there should be appropriate stopping rules in place.

7.2.1 Safety as a primary or secondary endpoint
7.2.1.1 Safety as a primary endpoint

In the early clinical trials with a new candidate vaccine the assessment of safety may be the only primary objective or a co-primary objective. It is very unusual that the assessment of safety is a primary objective in pre-licensure trials conducted later in the development program. Where this has occurred the focus has been on a specific safety issue (e.g. intussusception in pre-licensure trials with rotavirus vaccines that were developed after the first vaccine had indicated a potential association with vaccination). The assessment of one or more safety aspects is the primary objective in post-licensure safety trials, which involve detailed monitoring during routine immunization programs.

When the assessment of safety is the primary objective of a clinical trial it is usual that the primary analysis is based on a specific safety endpoint (e.g. rates of a certain adverse event [AE], rates of AEs within a specific system organ class [SOC] or rates of AEs that may be part of a clinical syndrome of interest). These trials should be powered to address the pre-specified hypothesis. The exception is in trials that are exploratory in nature, such as initial trials with new candidate vaccines intended to provide a preliminary assessment of the safety of ascending doses or sequential doses.

7.2.1.2 Safety as a secondary endpoint

In vaccine efficacy trials and in immunogenicity trials the assessment of safety is usually a secondary objective. These trials are not powered a priori to support formal statistical conclusions from analyses of rates of all or specific AEs between trial groups but simple statistical comparisons are commonly used as an initial screening for any differences in rates between groups of subjects. If such analyses are conducted they should be pre-specified in the protocol and in the statistical analysis plan. If there are any findings indicating statistically significant differences in rates of AEs (overall, by SOC or by PT) they need to be interpreted with caution due to the fact that the trial was not primarily designed to address pre-specified hypotheses regarding safety endpoints. Nevertheless, the findings may indicate that it is
appropriate to design and power further pre- or post-licensure clinical trials to further investigate and quantify the potential risks.

7.2.2 Recording and reporting adverse events

7.2.2.1 Methods

Adverse events and serious adverse events (SAEs) should be reported and recorded by investigators and sponsors according to detailed procedures described in the trial protocol and in accordance with requirements for expediting reporting to NRAs.

In safety and immunogenicity trials it is usually expected that all AEs, whether solicited or unsolicited, are collected for defined periods after each dose from all randomized subjects or all randomized subjects who received at least one dose of assigned treatment (see Subsections 7.2.2.2 and 7.2.2.3). In vaccine efficacy trials involving large numbers of subjects, taking into account the safety profile observed in the previous trials and the numbers from which detailed safety data have already been obtained, it may be acceptable that all AEs are collected from a randomized subset. In this case all SAEs and any pre-specified adverse events of special interest (AESIs) should be collected from all randomized subjects. It may also be acceptable that only SAEs and AESIs are collected during long-term safety follow-up.

7.2.2.2 Solicited signs and symptoms

After each dose of a vaccine or placebo, local and systemic solicited signs and symptoms should be documented for a pre-defined post-dose period by vaccinees or their care-givers by completing a daily diary record. These diaries should be filled in each day and users should receive instructions in their completion before vaccination commences. The duration of collection of data in diaries should be at least 5-7 days after each dose but longer periods (e.g. 10-14 days) may be appropriate for vaccines that contain live micro-organisms, depending on whether or not they are replication-competent.
For injectable vaccines the local signs and symptoms to be documented are usually pain, redness and swelling in all age groups. When two or more vaccines are given by injection at the same time, the diary card should ensure that separate data are recorded for each injection site (for example, these are usually into different limbs and therefore the diary card should contain separate records by right and left arm and/or leg). For vaccines given by other routes, alternative local signs and symptoms may be identified as representing local AEs (e.g. sneezing after intranasal dosing). The systemic signs and symptoms are determined by the age range in the trial (e.g. those appropriate for infants will not be wholly applicable to toddlers and older subjects) and the route of administration (e.g. nausea and vomiting could be solicited symptoms for vaccines given orally).

For subjective symptoms (e.g. pain, fatigue, myalgia) a simple scoring system should be included in the diaries to allow for a grading of severity. For objective signs, the quality of the information collected can be improved by methods such as issuing digital thermometers to each vaccinee or care-giver for application at a specific site (e.g. oral or axillary in infants, with recordings made at specific time of the each day) and using transparent plastic measuring devices to record the extent of redness and swelling.

Any self-administered treatments used to address signs or symptoms (such as antipyretic and analgesic medicines) and whether there was any contact with, or treatment administered by, a healthcare professional should be captured. If a supply of a specific anti-pyretic or analgesic was given out at the time of each dose for use as needed, or as instructed in accordance with the protocol, the post-dose usage recorded in the diary should be checked against returned supplies. If prior safety data suggest that pre-vaccination antipyretic use is appropriate, this can be administered and recorded by trial staff at the vaccination visit and the diary cards should collect any post-vaccination doses administered.

At each trial visit, whether it involves face-to-face or telephone contact between the vaccinee and/or care-giver and trial staff, the diary cards should be checked for level of completion and further instructions given as needed to improve data recording after the next dose is given. At face-to-face visits the prior vaccination site(s) should be inspected for any remaining signs such
as induration. Also, vaccinees or care-givers should be asked about the maximum extent of signs (e.g. to determine whether whole limb swelling occurred). Any unresolved local or systemic signs and symptoms should be recorded and action taken as appropriate.

7.2.2.3 Unsolicited AEs

In addition to signs and symptoms that are pre-specified for collection of data, vaccinees and/or their care-givers should be questioned at each trial visit for the occurrence of any AEs since the last visit. For each AE the timing of onset in relation to vaccination, whether a healthcare professional was consulted, whether hospitalisation occurred and any treatment that was given (prescribed or non-prescribed) should be captured. Sponsors may also wish to record any days off school or off work for vaccinees and days off work for their care-givers.

A checklist of symptoms that could possibly reflect the onset of a pre-specified AESI may be useful to identify potential cases of various syndromes (such as auto-immune diseases) at an early stage and to ensure that there is careful follow-up. In addition, questions should be posed to elicit whether certain AEs have occurred that could be anticipated in the age group studied. For example, to determine whether persistent inconsolable crying or hypotonic hypo-responsive episodes occurred in infants. Where well-established and widely-applied definitions of these and other AEs are available, the reports received should be classified using these criteria.

Although solicited signs and symptoms are AEs, it is usual that clinical trial reports tabulate safety data separately for these and for unsolicited AEs. The classification of AEs should use a standardised scheme, such as MedDRA, to categorise AEs by SOC and PT. If the classification scheme is updated during conduct of the trial the clinical trial report should indicate how the changes impact on the tabulations.

7.2.2.4 Other investigations

The collection of data on routine laboratory tests (haematology, chemistry and urinalysis) is not commonly perceived to be necessary in clinical trials with vaccines. If the sponsor or NRA
considers that there is a good rationale for obtaining these data at certain time points the results
should be generated in appropriately certified laboratories and reported using well-established
grading scales for abnormalities.

For vaccines that contain live organisms (including attenuated wild-types, organisms that have
been genetically engineered to render them non-virulent and/or non-replicative and live viral
vector vaccines) additional investigations related to safety should usually include the detection of
viraemia and assessments of shedding (quantity and duration). Organisms recovered from
vaccinees may also be subjected to genetic analyses to determine any instances of recombination
with wild types and reversion to virulence and/or replication competency.

In the case of vaccines administered to pregnant women measures of growth and development in
their infants may be important safety parameters.

7.2.3 Categorization of adverse events

7.2.3.1 Causality

Section 8.5 of the WHO Global Manual on Surveillance of Adverse Events Following
Immunization (22) recommends that in clinical trials the investigator should make a judgement
of relatedness to vaccination for all solicited signs and symptoms and unsolicited AEs. The
investigator’s assessment may also be commented on by the sponsor. The assessment of
relatedness to vaccination should take into account factors such as:

a) Plausibility of relatedness, taking into account the vaccine construct. For example, live
attenuated vaccines may be associated with modified manifestations of natural infection
(e.g. rashes).

b) Timing in relation to dosing. Whilst most vaccine-related AEs occur within 1-2 weeks after
a dose there may reasons to suspect that illnesses with onset many months after the last dose
could be related to prior vaccination. For example, for some powerful adjuvants there is a
hypothetical concern that rates of auto-immune diseases may increases in genetically-
predisposed sub-populations.
c) Concurrent illnesses common in the trial age group or documented in the case report form and the anticipated background rates, if known. This is a particular issue for vaccines administered to infants and young children in whom intercurrent illnesses are relatively common.

d) The frequency with which any one AE occurred in groups that received the candidate vaccine compared to groups that received another vaccine or placebo.

e) Any correlation between rates of any one AE and dose of antigenic components.

f) Changes in rates of any one AE with sequential doses.

g) The results of medical investigations (e.g. diagnostic tests for concurrent illnesses) and of autopsies (e.g. in cases of sudden infant death).

7.2.3.2 Severity

Sufficient data should be collected for each solicited sign and symptom and unsolicited AE to make an assessment of severity. Wherever possible widely used grading scales should be used and/or the same scales should be applied throughout the clinical development program.

7.2.3.3 Other categorization

The classification of AEs as serious and the categorisation of frequencies should follow internationally-accepted conventions, as described in Section 3.1.2 of the WHO Global Manual on Surveillance of Adverse Events Following Immunization (22). Frequencies of solicited signs and symptoms by subject and of AEs in each treatment group should be calculated based on the denominator of all vaccinated subjects in that group. Frequencies of solicited signs and symptoms after each dose should use the number that received each dose.

7.2.4 AE reporting rates within and between trials

During any one clinical development program the reporting rates for all and/or for specific types of AEs, whether solicited or unsolicited, in clinical trials may demonstrate:
i) Differences between candidate vaccines and control groups within a clinical trial. For example, differences in AE rates may be anticipated between a candidate vaccine and a placebo group or a group that receives a licensed vaccine that does not have a similar composition to the candidate vaccine. Any marked differences between a candidate vaccine and a licensed vaccine that has the same or very similar composition are generally not anticipated and may require further investigation.

ii) Differences between clinical trials that may be observed in one or both of the candidate vaccine and control groups for total or specific AE reporting rates. Whenever this occurs it is important to consider the possible explanations, taking into account whether or not the same effect on the pattern of reporting rates is observed in groups that receive candidate vaccines and licensed vaccines and whether the study was double-blind or open-label. These differences between trials may reflect real and anticipated differences in vaccine reactogenicity between trial populations (e.g. age-related differences for specific AEs, such as higher fever rates in trials conducted in infants and toddlers compared to those in older children and adults). In contrast, marked differences in reporting rates between trials conducted in similar age ranges but in different geographical locations would not usually be anticipated. When there is no clear explanation for the differences observed, consideration should be given to the possibility that there has been incomplete reporting of AEs and further investigation is merited.

7.3 Size of the pre-licensure safety database

A total database of 3000 subjects across all trials and populations provides a 95% chance of observing one instance of an AE that occurs on average in 1 in 1000 subjects. This number may be regarded as a generally applicable target for the minimum total pre-licensure safety database for a new candidate vaccine that contains one or more antigenic components not previously used in human vaccines. Nevertheless, this figure should not be applied to application dossiers for any type of new candidate vaccine without further considerations, which include the following:

a. Fewer than 3000 subjects may be acceptable if the new candidate vaccine consists only of antigenic components already licensed in other vaccines for which there is considerable
experience in routine use.

b. The total number exposed in clinical trials may cover many age sub-groups or a single age group may predominate. It may be acceptable that the majority of subjects included in the safety database come from a specific age range unless the available data point to some specific safety concerns that require further investigation in other age groups before licensure.

c. For specific types of vaccines (e.g. innovative constructs) or specific modes of use (e.g. in a population considered to be vulnerable or otherwise at high risk that could predispose them to certain adverse events) individual NRAs may require that considerably more than 3000 subjects are exposed prior to initial licensure.

d. Additional considerations may apply to vaccines that contain antigenic components not previously used in human vaccines but for which efficacy trials are not possible. A large pre-licensure safety database is highly desirable for a vaccine with potential to be administered to very large numbers in an emergency situation (e.g. influenza pandemic vaccines, vaccines against certain viral haemorrhagic fevers or smallpox vaccines). Nevertheless, the safety profile documented in the initial safety and immunogenicity trials may lead to some reluctance to unnecessarily expose large numbers of subjects in the absence of an immediate threat and/or to expose large numbers in particular population subsets. Therefore NRAs may consider licensing these types of vaccines based on a relatively small safety database provided that very detailed plans are in place at the time of licensure for monitoring of safety should it be necessary to give the vaccine to large numbers of individuals at some future time.

7.4 Post-licensure safety surveillance

The requirements of individual NRAs for reporting of safety data collected from post-licensure safety surveillance activities should be consulted. NRAs should provide publicly-available guidance regarding their requirements for the content and timing of periodic reports of safety data and for any expedited reporting considered necessary. License holders should demonstrate that they have adequate capability and appropriate staff to collect, interpret and act upon the safety data received.
It has become routine that at the time of initial licensure there are detailed proposals in place for post-licensure safety surveillance activities, often in the form of risk management plans. These documents and proposals are then routinely updated at intervals in line with additional data that become available. They usually outline the safety specification for the vaccine based on all available safety data at the time of submitting each version of the plan along with details of routine and proposed additional pharmacovigilance and risk minimisation activities.

When planning pharmacovigilance activities for a vaccine, it is important to take into account that in addition to routine pharmacovigilance (i.e. passive surveillance), important information may come from:

i) Data from enhanced safety surveillance (active surveillance) put in place by public health bodies when a vaccine is introduced into a national routine immunization program or when the use of a vaccine within a program changes significantly (e.g. an entirely different age group is vaccinated for the first time).

ii) Large databases that link information in patient records on vaccination history with occurrence of specific types of illness. These can be interrogated to explore links between specific vaccines and safety issues in the short and longer-term.

iii) Various types of registries intended to capture details of use in specific populations. For example, there are registries that collect information on exposure of pregnant women to various types of vaccines and the outcome of the pregnancy (including rates of spontaneous abortion, premature delivery and congenital malformations in the infants). There are also registries that capture specific types of disease that could be of relevance to specific types of vaccines.

The limitations of each of these approaches are well known, which underlines the need to consider all sources along with additional data that may come from post-licensure trials.

As with other medicinal products the same vaccine may be marketed by different license holders in various countries and regions so that systems need to be in place at the time of licensure to facilitate rapid sharing of safety information between companies, between companies and NRAs.
and between NRAs. An additional consideration for vaccines is that when a safety signal is identified for any one vaccine it may or may not be possible to ascribe the AEFIs observed to any one antigenic component of the vaccine or to an adjuvant. Furthermore, if there was concomitant administration of vaccines in some or all cases generating the signal it may not be possible to ascribe the AEFI to only one of the products co-administered. The same or very similar antigenic component(s) or adjuvant in the vaccine(s) from which the signal arose may be in several other licensed products marketed worldwide. Ultimately several different companies and NRAs without established data sharing agreements may need to be involved. As a result, the actions taken, if any, and the speed at which action has been taken, are sometimes very variable between countries. These issues underscore the need for efficient use of electronic databases to facilitate rapid data sharing.

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Appendix 1. Human Challenge Trials

There are many reasons a developer might 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 however, the model system of the human challenge trial may significantly advance, streamline, and/or accelerate vaccine development (1).

It will be important to consider the regulatory framework where the human challenge trial may be conducted, because in some countries, challenge stocks are expected to be handled in the same manner as vaccines and to be studied under a Clinical Trial Authorization (Approval, CTA), 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 know the proper dose of the challenge organism to give and to characterize the symptoms, kinetics, shedding, transmissibility, and so forth to expect from the challenge. In such cases (when challenge should be studied under CTA), there is greater clarity about regulatory expectations, including quality of the challenge stock to be used, as the CTA regulations or requirements would apply. However, in many countries, because the challenge stock is not itself a medicinal product, such studies would not be under the purview of the NRA’s review and approval and much less clarity exists on regulatory expectations and quality matters in such cases. Ideally, a challenge stock should match in quality terms what is expected of an investigational vaccine at the same clinical Phase of development (understanding that a pathogenic challenge strain will not have the “safety” of a hopefully innocuous vaccine). Likewise, ideally a human challenge study
should match the same expectations for conduct of a vaccine study, e.g., compliance with GCP, approval of a CTA. However, there may not exist a regulatory framework to promulgate such expectations in the country where the challenge study is to be conducted. Thus, it may be necessary for regulators to consider and develop an appropriate regulatory pathway or framework for the quality of the challenge stock and the conduct of the challenge study, when clarity is not apparent in their existing system. This may require new legislation to give regulators the necessary authority, and it is encouraged that regulators should have this authority. Trial sponsors, vaccine developers, researchers, and so on should determine from the relevant NRA what regulatory expectations they may have when clarity does not exist, if 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).

It is also important to note that not all diseases for which vaccines might be developed are suitable to consider conducting human challenge trials. In many cases, human challenge with a virulent or even a potentially attenuated organism would not be considered ethical or safe. For example, if an organism causes 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, when the disease an organism causes has an acute onset and 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), a human challenge trial might be considered.

1. Purposes of human challenge trials

A developer may conduct human challenge trials to accomplish one or more of a number of aims. The aims of the study determine what clinical Phase the study may be considered to be. Human challenge trials are often a type of efficacy study, but not all would be considered a “Phase 3” study. 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 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 accomplish 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 (ICP, which would then require validation in a traditional efficacy study)

• Identification of optimal trial design for Phase 3 traditional 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 that a particular vaccine candidate might be capable of protection or not

• Down- or Up-selection among various potential lead vaccine candidates to advance only the best to large Phase 2b or Phase 3 efficacy trials and to eliminate those that are unworthy of advancement

• De-risk or “left-shift”¹ risk of failure in a vaccine development program

• Comparison of vaccine performance in endemic settings vs. in efficacy trial population², including evaluating impact of prior immunity

• Support emergency use of an investigational vaccine, e.g. in a pandemic

• Basis for licensure (this purpose would generally be an exception rather than the rule)

• Exploration post-licensure whether immunity to vaccination wanes and if or when booster doses might be required for durable protection³

• Others

Not all situations would support accomplishing each of the aims above. For example, if the human challenge model system does not adequately mimic the wild-type disease and situation in which a vaccine would need to protect, then a human challenge trial would not be usable as a basis for licensure. But, it might still serve well one or more of the other purposes above. It

¹ When looking at a timeline of vaccine development graphed from early to the left and late to the right, shifting the risk of failure earlier in the timeline, or left, could result in significant cost (and resource)-savings and minimize lost opportunity costs by abandoning an unpromising candidate before taking greater expenditures from 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 Target population in a particular country may have a higher rate of individuals with e.g., sickle cell trait or different nutritional status or greater parasitic load in “normal” flora, any of which might affect immune responsiveness and thus, efficacy, compared to the efficacy trial population

³ This might entail challenge study in adults to extrapolate when children might need booster doses
might even be considered by regulators as supportive of licensure, but not a sole or primary basis.

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

Obviously, the aim of the human challenge trial guides its study design. Consequently, even for the same disease, the challenge model may vary depending on the purposes and design of the study to be conducted. In some cases (e.g. to serve as a basis for licensure or to identify appropriate efficacy trial design and case definitions), the challenge model might need to mimic as closely as feasible wild-type disease. In other cases, consideration might be given to use of an attenuated challenge organism (e.g., an earlier but under-attenuated vaccine candidate) or a model system in which objective early signs (e.g. parasitaemia, viraemia) signaling onset of disease symptoms, which could trigger initiation of treatment to prevent actual disease onset or morbidity.

Another important consideration for a human challenge model system would be its positive and negative predictive utility. If used for down-selection or de-risking, the negative predictive utility of the model to identify vaccine candidates that would not warrant advancement into large human efficacy studies should be high. If intended to be used for licensure, the positive predictive utility of the model system would need to be nearly as compelling and credible as a traditional efficacy trial might be. Thus, the purpose of the study would influence the design, which would in turn influence the conclusions about and the decisions that might be made from the study results.

3. Some key ethical considerations

Ethics in clinical trials, as in medicine, follow the precept of “do no harm.” By their nature (intentionally infecting humans with disease-causing organisms), human challenge trials would seem to fly in the face of this basic precept. Further, clinical trials should be designed and conducted in a manner that minimizes risks to human subjects while maximizing the potential to benefit. Consideration must be given both to 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, but when knowledge may be gained to the benefit of the larger societal population
with whom the potential trial participant shares significant characteristics. Justification for
asking trial participants to accept the risk from a challenge may take some considerations from
the justifications that support inclusion of placebos in controlled clinical trials.

Acknowledgement is due to the reality that some individuals are greater risk-takers than others,
while some individuals are quite risk-averse and would not be accepting of the risk of
receiving a challenge. Key to asking individuals to accept the risk from a challenge study in
which they may not except to receive individual benefit is the element of informed consent.
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, e.g. severe diarrhea managed with fluid and electrolyte replacement).
Thus, in appropriate situations, it can be considered ethical to ask 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 the elements of voluntary consent based on truly being informed.
It is for this reason (need for truly informed consent), consideration of conducting human
challenge studies in children or any other vulnerable population, who 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 due consideration to whether
or not the challenge organism need be pathogenic or not, or to what degree. As stated above,
the aim or purpose of the study may drive this decision, but the ethics of minimizing to the
extent feasible within the frame of sound science any risks to human subjects should also bear
due consideration in this regard. It should also be obvious that the credibility of the data to
 support regulatory decision-making need be taken into account.

References