

WHO/V&B/03.12  
ORIGINAL: ENGLISH

# Training manual on the critical regulatory function for vaccines: evaluation of clinical performance through authorized clinical trials

Prepared for national regulatory authorities of vaccine-procuring and vaccine-producing countries

By Gillian Chaloner-Larsson, Ph.D.  
GCL Bioconsult, Ottawa, Canada

Immunization Safety Priority Project  
Vaccines and Biologicals



World Health Organization

# **Training manual on the critical regulatory function for vaccines: evaluation of clinical performance through authorized clinical trials**

**Prepared for national regulatory authorities of vaccine-procuring and vaccine-producing countries**

**By Gillian Chaloner-Larsson, Ph.D.  
GCL Bioconsult, Ottawa, Canada**

Immunization Safety Priority Project  
Vaccines and Biologicals



World Health Organization

---

**The Department of Vaccines and Biologicals  
thanks the donors whose unspecified financial support  
has made the production of this publication possible.**

This publication was produced by the  
Access to Technologies Team  
of the Department of Vaccines and Biologicals

*Ordering code: WHO/V&B/03.12*  
*Printed: June 2003*

**This publication is available on the Internet at:**

[www.who.int/vaccines-documents/](http://www.who.int/vaccines-documents/)

**Copies may be requested from:**

World Health Organization  
Department of Vaccines and Biologicals  
CH-1211 Geneva 27, Switzerland

• *Fax:* + 41 22 791 4227 • *Email:* [vaccines@who.int](mailto:vaccines@who.int) •

© World Health Organization 2003

All rights reserved. Publications of the World Health Organization can be obtained from Marketing and Dissemination, World Health Organization, 20 Avenue Appia, 1211 Geneva 27, Switzerland (tel.: +41 22 791 2476; fax: +41 22 791 4857; email: [bookorders@who.int](mailto:bookorders@who.int)). Requests for permission to reproduce or translate WHO publications – whether for sale or for noncommercial distribution – should be addressed to Publications, at the above address (fax: +41 22 791 4806; email: [permissions@who.int](mailto:permissions@who.int)).

The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

The World Health Organization does not warrant that the information contained in this publication is complete and correct and shall not be liable for any damages incurred as a result of its use.

---

# Contents

<i>Abbreviations</i> .....	<i>v</i>
<i>Glossary</i> .....	<i>vii</i>
<b>Introduction</b> .....	<b>1</b>
<b>Notes for trainers</b> .....	<b>5</b>
<b>Indicator 1: Policy of GMP, GLP, GCP, ethical oversight of trials</b> .....	<b>6</b>
<b>Indicator 2: Written guidelines for the conditions under which clinical trials will be needed: consideration given to the application of clinical data to the local use of vaccines</b> .....	<b>19</b>
<b>Indicator 3: Published guidelines on the format for submission of clinical data</b> .....	<b>26</b>
<b>Indicator 4: Access to expertise in epidemiology and statistics to advise on set up and analysis of trials</b> .....	<b>34</b>
<b>Indicator 5: Access to experts in the product being tested (including experts in test methods)</b> .....	<b>49</b>
<b>Bibliography</b> .....	<b>58</b>



---

# Abbreviations

<b>ACT</b>	Advisory Committee on Training
<b>ADR</b>	adverse drug reaction
<b>AE</b>	adverse event
<b>AEFI</b>	adverse event following immunization
<b>BIMO</b>	Bioresearch Monitoring (US FDA)
<b>CBER</b>	US FDA Center for Biologics Evaluation and Research
<b>CIOMS</b>	Council for International Organizations of Medical Sciences
<b>CFR</b>	Code of Federal Regulations (USA)
<b>CPMP</b>	Committee for Proprietary Medicinal Products, European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit (EU)
<b>CRO</b>	Contract Research Organization
<b>CTD</b>	Common Technical Document. ICH harmonized guideline for the format of data to be submitted to the three members, Japan, USA, EU.
<b>DNA</b>	deoxyribonucleic acid
<b>rDNA</b>	recombinant DNA
<b>EFPIA</b>	European Federation of Pharmaceutical Industries' Associations
<b>EMA</b>	The European Agency for the Evaluation of Medicinal Products
<b>EU</b>	European Union
<b>FDA</b>	Food and Drug Administration (USA)
<b>GCP</b>	good clinical practice
<b>GLP</b>	good laboratory practice
<b>GMP</b>	good manufacturing practice

---

<b>GMT</b>	geometric mean titre
<b>GTN</b>	Global Training Network
<b>IB</b>	investigator's brochure
<b>ICH</b>	International Conference on Harmonisation.
<b>IND</b>	investigational new drug (application)
<b>IEC</b>	Independent Ethics Committee (also see IRB)
<b>IRB</b>	Institutional Review Board (also see IEC)
<b>ITT</b>	intent to treat
<b>JPMA</b>	Japan Pharmaceutical Manufacturers Association
<b>MHW</b>	Ministry of Health and Welfare, Japan
<b>NRA</b>	national regulatory authority
<b>ORA</b>	US FDA Office of Regulatory Affairs
<b>PhRMA</b>	Pharmaceutical Research and Manufacturers of America
<b>PMS</b>	post-marketing surveillance
<b>RCT</b>	randomized controlled trial
<b>SOP</b>	standard operating procedure
<b>TDR</b>	Tropical Disease Research (UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (now housed in WHO's Communicable Diseases cluster)
<b>VAERS</b>	vaccine adverse event reporting system
<b>WHO</b>	World Health Organization

---

# Glossary

<i>Adverse drug reaction (ADR)</i>	A response to a pharmaceutical product (including a vaccine) during subsequent clinical use following licensure that occurs at doses normally used and that were tested in humans during clinical trials.
<i>Adverse event (AE)</i>	Any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product; it does not necessarily have a causal relationship with the treatment.
<i>Adverse event following immunization (AEFI)</i>	Any untoward medical occurrence in a clinical trial subject administered a vaccine; it does not necessarily have a causal relationship with the vaccine /vaccination.
<i>Attack rate</i>	The proportion of those exposed to an infectious agent who become (clinically) ill.
<i>Audit</i>	A systematic examination, carried out independently of those directly involved in the clinical trial, to determine whether the conduct of a trial complies with the agreed protocol and whether the data reported are consistent with the records on site, e.g., whether data reported or recorded in the case report forms are consonant with those found in hospital files and other original records.
<i>Blinding</i>	A procedure in which one or more parties of the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s) being unaware, and double blinding usually to the subject(s), investigator(s) and, in some cases, data analyst(s) being unaware of the treatment assignment. This is to avoid bias in the evaluation of the results. Unblinding (breaking the code) is done after the data assessment.
<i>Booster vaccination</i>	Vaccination given at a certain time interval (at least 6 months) after primary vaccination in order to induce long term protection.

---

<i>Bridging study</i>	A study performed in the new region to provide clinical data on efficacy, safety, dosage and dose regimen in the new region that will allow extrapolation of the foreign clinical data package to the population in the new region.
<i>Case control study</i>	An observational study in which the exposure to a vaccine (in the case of vaccine studies) is determined retrospectively, and this exposure is compared between individuals who experience an event (the disease to be prevented by the vaccine), the cases, and individuals who do not (the controls).
<i>Case definition</i>	<p>A set of diagnostic criteria that must be fulfilled to be regarded a case of a particular disease:</p> <ol style="list-style-type: none"> <li>1) the symptoms from the infection experienced by the patient, sufficient to seek medical care or advice;</li> <li>2) the diagnosis suspected by the physician;</li> <li>3) confirmation by the laboratory.</li> </ol> <p>All three components should be addressed in the development of the case definition.</p>
<i>Case report forms</i>	A document that is used to record data on a clinical trial subject during the course of the clinical trial, as defined by the protocol. The data should be collected by procedures that guarantee preservation, retention and retrieval of information and allow easy access for verification, audit and inspection.
<i>Clinical protocol</i>	A document that states the background, rationale and objectives of the clinical trial and describes its design, methodology and organization, including statistical considerations, and the conditions under which it is to be performed and managed. The protocol should be dated and signed by the investigator, the institution involved and the sponsor. It can also serve as a contract.
<i>Cluster</i>	The occurrence of an unusual number of cases in person, place or time.
<i>Cohort study</i>	Retrospective or prospective study, in which the development of disease or infection or any other relevant event is observed in a defined group of subjects observed over time.
<i>Colonization</i>	The asymptomatic, often transient, presence of a microbe as a part of the normal microflora of a host (e.g. pneumococci on the mucosae of the upper respiratory tract).
<i>Combined vaccines</i>	<p>Products intended for protection against:</p> <ol style="list-style-type: none"> <li>1) a single infectious disease complex caused by different strains or serotypes of organisms;</li> <li>2) or protection against multiple infectious diseases;</li> <li>3) or combinations of 1 and 2.</li> </ol>

---

<i>Community investigation</i>	Population-based trial in predefined large segments of the population to investigate the impact of a treatment on a preventable infectious disease.
<i>Community surveillance</i>	Surveillance where the starting point is a health event occurring in the community and reported by a community worker or actively sought by the investigators. This may be particularly useful during an outbreak and where syndromic case definition can be used.
<i>Comparator product</i>	A pharmaceutical or other product (which may be a placebo) used as a reference in a clinical trial.
<i>Contact</i>	An individual who has had contact with a case of disease in a way that is considered as having caused significant exposure and therefore risking of infection.
<i>Control</i>	Any comparator suitable for validation of the trial. The comparator may be either an active treatment or a placebo control.
<i>Effectiveness</i>	Utility of a drug, vaccine or other treatment when used by the public at large under uncontrolled, real world conditions. See also vaccine effectiveness.
<i>Efficacy</i>	Prophylactic, therapeutic or pharmacological result of a drug, vaccine or other treatment in a controlled clinical situation. The assessment of efficacy needs: specification of the clinical endpoints measured; description of how the efficacy parameters are measured and recorded; times and periods of efficacy recording; description of special analyses and/or tests to be carried out. See also vaccine efficacy.
<i>Equivalence trial</i>	A trial with the primary objective of showing that the response to two or more treatments differs by an amount which is clinically unimportant. Showing that the true treatment difference is likely to lie between a lower and an upper equivalence margin of clinically acceptable differences usually demonstrates this.
<i>Experimental study</i>	Study in which the conditions are under direct control of the investigator. Such studies may include randomization of subjects to treatment or control groups and blinding of subject and investigator to the placement status.
<i>Exposure</i>	Someone who has met with an infectious agent in a way that we know from experience may cause disease.
<i>Foreign clinical data</i>	Clinical data generated outside of the target region (i.e. in the foreign region).

---

---

<i>Geometric mean titre (GMT)</i>	Calculation of the average titre for a group by multiplying all values and taking the <i>n</i> th root of this number, where <i>n</i> is the number of subjects.
<i>Good clinical practice (GCP)</i>	A standard for clinical studies which encompasses the design, conduct, monitoring, termination, audit, analyses, reporting and documentation of the studies and which ensures that the studies are scientifically and ethically sound and that the clinical properties of the pharmaceutical product (diagnostic, therapeutic or prophylactic) under investigation are properly documented.
<i>Good laboratory practice (GLP)</i>	A quality system concerned with the organizational process and the conditions under which non-clinical health and environmental safety studies are planned, performed, monitored, recorded, archived and reported.
<i>Good manufacturing practice (GMP)</i>	That part of the pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and a required by the marketing authorization. In these guidelines, GMP refers to the current GMP guidelines published by WHO.
<i>Immunogenicity</i>	Capacity of a vaccine to induce humoral (specific antibody mediated) and/or cell-mediated immunity and/or immunological memory.
<i>Incidence</i>	The number of persons who fall ill with a certain disease during a defined time period.
<i>Independent Ethics Committee (IEC)</i>	An independent body (a review board or an institutional, regional or national committee), constituted of medical professionals and non-medical members, whose responsibility it is to verify that the safety, integrity and human rights of the subjects participating in a particular clinical trials are protected, and to consider the general ethics of the trial, thereby providing public reassurance. Ethics committees should be constituted and operated so that their tasks can be executed free from bias and from any influence of those who are conducting the trial. (see also Institutional Review Board, IRB)
<i>Informed consent</i>	A subject's voluntary confirmation of willingness to participate in a particular trial, and the documentation thereof. This consent should be sought after appropriate information has been given about the trial, including an explanation of its status as research, its objectives, potential benefits, risks and inconveniences, alternative treatment that may be available, and of the subject's rights and responsibilities in accordance with the current revision of the Declaration of Helsinki.

---

<i>Inspection</i>	An officially conducted examination (i.e. review of the conduct of the clinical trial, including quality assurance, personnel involved, any delegation of authority and audit) by relevant authorities at the site of the trial and/or the site of the sponsor in order to verify adherence to Good Clinical practice as set out in these guidelines.
<i>Institutional Review Board (IRB)</i>	(see Independent Ethics Committee IEC)
<i>Intent to treat (ITT)</i>	A clinical trial where the data from all subjects that are enrolled in the trial are assessed for safety and efficacy of the treatment. This is contrasted with “as per protocol” where the data from only those subjects completing the full protocol treatment are assessed.
<i>Internal control</i>	An additional control arm, usually a placebo, which may be required when the efficacy of the active comparator is not adequately established or is known to give inconsistent results.
<i>International Conference on Harmonisation (ICH)</i>	(Complete name: International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.) The ICH was established in 1990 as a joint regulatory/industry project to improve, through harmonization, the efficiency of the process for developing and registering new medicinal products in Europe, Japan and the United States, in order to make these products available to patients with a minimum delay. Participants are the European Commission, EFPIA, Japan, JPMA, the FDA, and PhRMA. The ICH process has been based on scientific consensus developed between industry and regulatory experts, and with the commitment of the regulatory parties of the three regions (European Union countries, Japan and the United States) to implement the ICH tripartite, harmonized guidelines and recommendations.
<i>Investigator</i>	A person responsible for the clinical trial and for the rights, health and welfare of the subjects participating in the trial. The investigator should have qualifications and competence in accordance with the local laws and regulations as evidenced by an up-to-date curriculum vitae and other credentials. Decisions relating to the provision of medical or dental care must always be the responsibility of a clinically competent person legally allowed to practice medicine or dentistry.
<i>Investigator’s brochure (IB)</i>	A compilation of the clinical and non-clinical data on the investigational product that are relevant to the study of the product in humans.

---

<i>Minimal risk</i>	A level of risk similar to the risk encountered in an individual's usual daily activity. Minimal risk would include activities such as physical examination, venepuncture or urine sample collection.
<i>Non-clinical study</i>	An in vitro laboratory study or animal study performed under specified conditions (see GLP) that supports an application for a proposed clinical investigation in humans.
<i>Non-inferiority trial</i>	A trial with the primary objective of showing that the response to the investigational product is not clinically inferior to a comparative agent. (= equivalence trial)
<i>Observational studies</i>	Observational studies focus on events, exposures and diseases occurring in the population during the course of routine living conditions, not subject to experimental interventions.
<i>Outbreak</i>	The occurrence of two or more linked cases of a communicable disease.
<i>Placebo control</i>	A comparator in a vaccine trial that does not include the antigen under study. In monovalent vaccine studies this may imply an inert placebo (e.g. saline solution, vehicle of the vaccine), or an antigenically different vaccine. In combined vaccines, this may imply a control arm in which the test vaccine is lacking.
<i>Post-marketing surveillance (PMS)</i>	A system intended to monitor adverse events following licensure. Post-marketing surveillance can be passive or active. The objective of post-marketing surveillance include, but are not limited to the following: <ul style="list-style-type: none"> <li>i) to identify rare adverse reactions not detected during pre-licensure studies; and</li> <li>ii) to identify risk factors or pre-existing conditions that may promote reactions</li> </ul>
<i>Potency</i>	The quantitative measure of the specific ability or capacity of the product to achieve a defined biological effect.
<i>Pre-clinical study</i>	See non-clinical study.
<i>Pre-exposure trial</i>	Prospective trial in a population expected to be exposed to the pathogen under study within a predefined, relatively short, period.
<i>Prevalence</i>	The number of persons who have a disease at a specific time.
<i>Primary vaccination</i>	First vaccination or series of vaccinations given within a predefined period, with an interval of less than 6 months between doses, to induce clinical protection.
<i>Protective titre</i>	Antibody titre assumed to correlate to clinical protection.

---

<i>Protocol</i>	A document that states the background, rationale and objectives of a study (pre-clinical or clinical), the name of the investigator(s), and describes the design, methodology, analytical and statistical considerations, and the conditions under which it is to be performed and managed
<i>Randomization</i>	<p>To assure that subject populations for clinical trials are similar in test and control groups, a single sample population is randomly divided into groups that receive the test or control treatments.</p> <p>Randomization is a process by which <math>N</math> individuals are assigned to a test (<math>n_T</math>) or control (<math>n_C</math>) treatment so that all possible groups of size <math>N=n_T+n_C</math> have equal probability of occurring. Thus randomization avoids systematic bias in the assignment of treatment. It also promotes balance with respect to known and unknown prognostic factors that could affect the outcome of interest. While it does not guarantee that treatment groups will be exactly equal with respect to these factors, it does guarantee that any imbalance that occurs arises purely by chance. The process of randomization guarantees the validity of statistical analyses of treatment effect, and (with adequate sample size) allows the detection or ruling out of small or moderate treatment differences.</p> <p>In vaccine trials the unit for randomization may be either an individual or a larger group of persons (e.g. household, school).</p>
<i>Reactogenicity</i>	Events that are considered to have occurred in causal relationship to the vaccination. These reactions may be either local or systemic.
<i>Reproductive rate</i>	The average number of secondary cases of an infection arising from one single primary case. The measure is inherent to the potential (infectiousness, susceptibility, measures of protection) of a micro-organism to spread from person to person in a population.
<i>Secondary attack rate study</i>	An outbreak investigation in a defined susceptible population. The population to be studied is either a cluster (in an urban or semi-urban setting) or a household (or family). Outbreak investigations may be observational or experimental. The unit of randomization may be the individual, a household or a cluster.
<i>Sensitivity</i>	(statistical) The probability that a test turns out positive when it is used on an individual who truly has the disease. It is estimated in a study as the proportion of individuals classified as diseases by a “gold standard” who test positive for the disease.

---

---

<i>Serious adverse event</i>	An event that is associated with death, admission to hospital, prolongation of a hospital stay, persistent disability or incapacity, or is otherwise life-threatening in connection with the clinical trial.
<i>Seroconversion</i>	Predefined increase in antibody concentration, considered to correlate with the transition of seronegative to seropositive, providing information on the immunogenicity of a vaccine. If there are pre-existing antibodies, seroconversion is defined by a transition from a clinical unprotected to a protected state.
<i>Serological surrogate</i>	Predefined antibody concentration correlating with clinical protection.
<i>Serosurveillance</i>	The surveillance of an infectious disease by measuring disease specific antibodies in a population or sub-population.
<i>Specificity</i>	(statistical) The probability that a test turns out negative when it is used on an individual who truly does not have the disease. It is estimated in a study as the proportion on individuals classified as disease-free by a “gold standard” that test negative for the disease.
<i>Sponsor</i>	An individual, a company, an institution or an organization, which takes responsibility for the initiation, management and/or financing of a clinical trial. When an investigator initiates and takes full responsibility for a trial, the investigator then also assumes the role of the sponsor.
<i>Standard deviation</i>	The measure of the variability of a sample of observations around the mean.
<i>Superiority trial</i>	A trial with the primary objective of showing that the response to the investigational product is superior to a comparative agent (active or placebo).
<i>Surveillance</i>	The systematic collection, collation and analysis of data and the dissemination of information to those who need to know in order that action may be taken.
<i>Survey</i>	An investigation in which information is systematically collected in a sample of a predefined population group and in a defined time period. Unlike surveillance it is not ongoing though it may be repeated. If repeated regularly, surveys can form the basis of a surveillance system.

---

***Vaccine (protective) efficacy*** The reduction in the chance or odds of developing clinical disease after vaccination relative to the chance or odds when unvaccinated. Vaccine efficacy measures direct protection (i.e. protection induced by vaccination in the vaccinated population sample). Vaccine efficacy is calculated according to the following formula:

$$VE = \frac{l_u - l_v}{l_u} \times 100\% = \left(1 - \frac{l_v}{l_u}\right) \times 100\% = (1 - RR) \times 100\%$$

Where:  $l_u$ =incidence in unvaccinated population,  $l_v$ =incidence in vaccinated population, RR=relative risk (in case control studies or other studies when the incidence of target disease or adverse event is low, to be replaced by odds ratio's (OR)).

***Vaccine effectiveness*** The protection rate conferred by vaccination in a certain population. Vaccine effectiveness measures direct and indirect protection (i.e. protection to non-vaccinated persons by the vaccinated population). Vaccine effectiveness is also determined by vaccination coverage, correlation of vaccine strains with circulating strains and selection of strains not included in the vaccine following introduction of the vaccine in that population.

***Vaccine failure*** The onset of infection or disease, biologically confirmed, in a subject who is supposed to be protected, following completion of age-appropriate immunization recommended by the manufacturer.

***Vaccines*** A heterogeneous class of anti-infective medicinal products containing antigenic substances capable of inducing specific and active immunity against the infecting agent or the toxin or other important antigenic substances produced by this agent. Vaccines for human use may contain: organisms inactivated by chemical or physical means that maintain adequate immunogenic properties; living organisms that are naturally avirulent or that have been treated to attenuate their virulence whilst retaining adequate immunogenic properties; antigens extracted from the organisms secreted by them or produced by recombinant DNA technology. The antigens may be used in their native state or may be inactivated or detoxified by chemical or physical means and may be aggregated, polymerised or conjugated to a carrier to increase their immunogenicity (1).

***Validation*** The action of proving, in accordance with the principles of GLP, GMP or GCP, that any procedure, process, equipment (including the software or hardware used), material, activity or system actually leads to the expected results.

---

***Vector***

A vector is a carrier of an infectious agent, most often an animal or arthropod, which picks up the pathogen from an infected person(s) or animal and transmits it to a susceptible individual.

---

# Introduction

It is the responsibility of each country to provide safe and effective medications including vaccines. Many developing countries are now taking on the responsibility for procuring their own vaccines and their national regulatory authorities (NRA) are now performing vaccine evaluations for licensing and lot release procedures as recommended by the World Health Organization (WHO). WHO has been assisting many countries by providing guidelines and offering training courses for NRAs, covering all aspects of regulatory control of vaccines.

The Department of Vaccine and Biologicals (V&B) of WHO has developed an assessment tool for identifying the status of existing regulatory functions and the training needs of NRAs. The system identifies the need for a legal system and for six critical functions to provide quality vaccines. WHO's acronym for the six critical functions is "ASSURE", namely:

**A** published set of clear requirements for licensing (of products and manufacturers)

**S**urveillance of vaccine performance in the field (safety and efficacy)

**S**ystem of lot release

**U**se of a laboratory when needed

**R**egular inspections of manufacturers for GMP compliance

**E**valuation of clinical performance through authorized clinical trials.

Vaccines of "assured" quality are those manufactured to international standards with effective NRA oversight. These six critical control functions were established in several consultations with regulatory authorities from many different countries (WHO/V&B/99.10). Each of these functions is expanded by a list of indicators that define the scope of the tasks involved in the performance of that function.

---

This manual is concerned with the last of these functions: evaluation of clinical performance through authorized clinical trials. This function ensures that vaccines cannot be investigated in humans, marketed, or introduced into immunization programmes without first meeting the regulatory requirements of the country. The indicators for this function are:

- policy of GMP, GLP, GCP, ethical oversight of trials;
- written guidelines for the conditions under which clinical trials will be needed: consideration given to the application of clinical data to the local use of vaccines;
- published guidelines on the format for submission of clinical data;
- access to expertise in epidemiology and statistics to advise on the set up and analysis of trials;
- access to experts in the product being tested (including experts in test methods).

Each one of these indicators will be discussed in detail in this manual.

The indicators have two purposes: to enable an NRA to perform a self-assessment of its performance and to identify where improvements and training are needed, and to assist WHO regional staff responsible for vaccine quality to identify countries for priority training.

This manual provides more details on the indicators for the evaluation of clinical performance through authorized clinical trials. It offers practical suggestions, references to useful publications for NRAs, and is a resource for trainers delivering courses for WHO on Clinical Evaluation.

WHO has been working for several years on providing guidance on the subject of evaluation of clinical trials and clinical trial data. In 1998, WHO commissioned a paper entitled “Review of Existing Documents on Planning, Performance and Assessment of Clinical Trials”. And in January 1999, WHO held an informal consultation meeting in Geneva of experts in national regulation of vaccines which, among other subjects, discussed the commissioned paper and the presentation of a matrix to identify gaps in the guidance documents available. The meeting report was published *Informal consultation of experts on national regulation of vaccines* (WHO/V&B/99.08). There was general agreement that a “points to consider” document should be prepared to give guidance on the special issues of clinical evaluations of vaccines to less experienced NRAs, including some ethical issues for vaccine trials.

Following this meeting and in response to requests from NRAs for assistance in the evaluation of clinical trials for vaccines, a new guideline document has been prepared, and reviewed and accepted by a WHO Expert Committee on Biological Standardization (WHO Technical Report Series: WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations, in press). The document provides guidance to NRAs and to vaccine manufacturers, and is expected to be useful also to clinical researchers and investigators. It is the basis and the main background document for this manual on training in clinical evaluation for vaccines.

---

The subject of clinical trials and clinical evaluation of those trials, either prior to trial authorization or afterwards for marketing authorization, is a complex subject. Not only are there different considerations for each product – the disease, the product (here vaccines), the mode of action of the product, the disease incidence and prevalence, the clinical symptoms – but clinical trials come at the end of a long period of research and development which must be evaluated to ensure that the product is safe for human trials.

In the product development stage, the production and purification methods are tried and refined, scaled-up, and validated; the manufacturing facility is constructed, validated and operated to appropriate standards; and analytical testing and specifications are established and validated. In the pre-clinical stage, in vitro studies in cell cultures or immunological assays are designed to measure the product bioactivity, animal studies are designed and performed to assess as much as possible the potential side effects, toxicity, activity and pharmacology of the product, to evaluate the dose, route of inoculation, and, in the case of a vaccine, to assess immunogenicity. In addition, if there is an animal model of the disease, protective efficacy can be determined in animals. The correlates of protection are studied at this pre-clinical stage, for example by developing immunological assays that measure functional antibody. Such specific antibodies may correlate more with protection than does total antibody in certain diseases. All of this must be done in compliance with regulations before clinical trials are reviewed by the NRA for authorization. Much of the above is done before any consultation is held with the regulatory authorities.

In these developmental and pre-clinical stages, it is the manufacturer that chooses what products to develop and has the responsibility to review regulations and guidelines published by the NRA to ensure that the products will meet the regulatory requirements when they present the data to the NRA.

There are many documents describing the regulatory requirements and types of information that must be submitted to the NRA before medicinal products can be marketed for human use.

These range from legal regulations to guidance documents, notices, guidelines and “points to consider” documents. The best known of these are prepared by the two major regulatory authorities of the European Union (EU) and the USA (FDA), and by the expert committees of WHO. These can be general documents identifying, for example, the format that must be used when an application is submitted, as well as guidelines on specific topics (sterility, validation, etc) or guidance on specific types of products (e.g. rDNA products, combination vaccines, synthetic peptides) or for specific activities (reporting adverse drug reactions, toxicity testing, clinical evaluation, good manufacturing practice).

These documents are written for “industry” – instructions/guidelines for the manufacturers on general or specific requirements when developing, manufacturing or testing a product, planning/carrying out/reporting clinical trials, or preparing their documentation for submission.

---

For those newly developing national regulatory authorities that are just beginning to prepare detailed guidance for regulating vaccines, and who may not have had much experience with the in-depth evaluation of clinical trials, many of these documents can be very useful although they are prepared for manufacturers. The information provided to industry is the accepted thinking of well-respected regulatory authorities with a great deal of experience and expertise, and it can be used to train NRA staff on these topics and for them to in turn apply these principles to the review of documents and data submitted to them.

---

# Notes for trainers

(For trainers of Global Training Network (GTN) courses, or for NRA staff assigned to deliver internal courses).

1. Each section references a comprehensive list of resource materials for each indicator. The trainer should choose the most appropriate resources for the course given, and should provide printed copies to the trainees who may have trouble obtaining the references. WHO can be contacted to provide copies to the trainer or to an NRA.
2. The concept of validity should be discussed and stressed during the course. This includes:
  - a) the degree to which an instrument measures what it intends to measure;
  - b) the degree to which a research design allows for reasonable interpretations from the data based on:
    - controls (internal validity);
    - appropriate definitions (construct validity);
    - appropriate analysis procedures (statistical conclusion validity);
    - generalization (external validity or the extent to which the results of a study can be generalized beyond the internal specifications of the study sample).

(Ref.: Portney LG, Watkins MP. Foundations of Clinical Research. Applications to Practice. 2nd ed. New Jersey, Prentice-Hall Health, 2000: 79–110; 172–174.)
3. The trainer should emphasize throughout that the NRA should have a system of recording and monitoring all the actions taken with regard to all the critical functions. The credibility of an NRA and of their judgement in making decisions on information submitted for review and approval will depend on recorded evidence of how they carried out their duties, and how they arrived at each judgement.
4. It is recommended that the trainer propose or request from trainees examples of potential challenging situations for the NRA on clinical evaluation and discuss how to proceed in those cases.
5. Some of the practical approaches in each section can be used for exercises.
6. The training course should include a follow-up exercise for the trainees to draw up a plan and milestones for implementing the lessons learned.

---

# Indicator 1:

## Policy of GMP, GLP, GCP, ethical oversight of trials

### A. Background

“A clinical trial is any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s) and/or to identify any adverse reactions to one or more investigational product(s), and/or to study absorption, distribution, metabolism and excretion of one or more investigational product(s) with the object of ascertaining its (their) safety and/or efficacy” (European Parliament Directive 2001/20/EC).

Clinical trials are a complex operation, generally lasting one or more years, usually involving numerous participants and at least several trial sites. Applications for authorization of clinical trials by the major well-known regulatory authorities and international public health organizations require the submission of data on the quality of the product (production, testing, stability), pharmaco-toxicological and clinical standards, and protocols.

“The accepted basis for the conduct of human trials in humans is founded in the protection of human rights and the dignity of the human being with regard to the application of biology and medicine, as for instance reflected in the Helsinki Declaration (most recent version 2000). The clinical trials subject’s protection is safeguarded through risk assessment based on the results of toxicological experiments prior to any clinical trial, screening by ethics committees and by regulatory authorities” (European Parliament Directive 2001/20/EC). This protection especially applies to children who are a vulnerable population.

There are several issues therefore that an NRA will face regarding clinical trials that are not directly linked to the evaluation of proposed plans for studying the vaccine or to the assessment and decision on the adequacy of the clinical data collected. Specifically, these are an assessment of the quality of the vaccine that is going to be studied, and the laboratory and animal studies performed prior to the trials to obtain preliminary data on the safety, immunogenicity, and where possible, the efficacy of the vaccine. The NRA must also ensure that the trials meet ethical and scientific quality requirements for designing, conducting, recording and reporting clinical trials in human subjects. Compliance with this good practice provides assurance that the rights, safety and well-being of trial subjects are protected, and that the results of the clinical trials will be credible.

---

NRA's are responsible at two stages for the critical evaluation of the documentation supporting clinical studies: when clinical trials are being proposed for authorization and when the results of the trials are submitted in an application for marketing authorization. The review by the NRA of the product quality and of the pre-clinical data is made at the time the product is first proposed for authorization for investigational use in humans. Throughout the clinical studies, if there are changes to the manufacturing or testing procedures, and if different doses or formulations of the vaccine are developed, there will be an additional requirement for the NRA to assess any new pre-clinical study results to determine again if they are sufficient to support the changes.

In order to meet international standards of evaluation, the NRA must have a suitable policy in place that the product must be made according to appropriate GMP standards, that supporting studies must be performed according to GLP, and that the clinical investigators enrol subjects, collect data and appropriately monitor their activities and data according to GCP and ethical principles.

In this regard it is essential that the NRA have a good basic understanding of "good practice" standards in order to determine, or appropriately seek advice on, whether the product, supporting studies, clinical study performance criteria, and the protection of trial subjects meet these standards.

### *GMP*

GMP is a set of principles that ensures the quality of a medicinal product. It covers the effective control of all aspects of manufacture, including validation and documentation of the operations of facilities, production processes, in-process controls, quality control assays, and the storage, labelling and handling of the final product. The principles of GMP should be applied to all medicinal products, from clinical study lots up to the final commercial production lots. For clinical trials, any placebo or comparator products should also be produced according to GMP.

The NRA of a country where clinical trials of a product are being proposed should require that the manufacture of the investigational product meet GMP standards appropriate to the phase of the clinical trial.

Although routine well-established tests such as sterility, pyrogens, protein concentration, measurement of preservatives and stabilizers should be in place, product-specific tests and specifications such as potency and purity tests may not be finalized in the early phases. The manufacturing is often at a pilot scale in the early clinical trials and, often too, the experience from the first clinical lots provides information on production consistency, testing and setting of specifications for the final product. In addition, although short-term stability of small clinical lots is necessary to permit the use of vaccine lots in early trials over a short time period, the long-term stability of a product is not determined until several full scale lots have been produced according to the final production method and been shown over time to meet the final specifications for shelf life.

---

Although in most cases GMP audits are not performed for clinical lots for clinical studies, information indicating that GMP is being followed is required in the application for trial authorization as for marketing authorization (see licensing section in *Training manual: licensing, lot release, laboratory access* (WHO/V&B/01.16)). Depending where the trial is held, one country may require samples and test results for the clinical lots to be submitted to the national control laboratory before being used in the clinical study, while another country may only require the results of the quality control tests on each clinical lot, and others that the data be available only on request.

Although the main guidelines for GMP are for marketed products (pharmaceuticals and biologicals), supplementary guidelines and several other articles discussing the appropriate levels of GMP for clinical trial products have been published. WHO has published a guideline entitled “Good manufacturing practices: supplementary guidelines for the manufacture of investigational pharmaceutical products for clinical trials in humans”, and in volume 4 of the EU Regulations, the GMP guidelines include a specific annex (#13) on “Manufacture of Investigational Medicinal Products”. Several “Points to Consider” documents from the FDA indicate the tests that should be in place for the early clinical lots of products such as those produced by recombinant DNA technology and those made in cell substrates.

### **GLP:**

Non-clinical studies supporting an application for clinical trials or marketing are to be performed according to GLP standards. These set out the requirements for the planning, performance, documentation, and control of all non-clinical studies to support the use of a medicinal product in humans.

There are two official publications on GLP: the US 21 CFR (Code of Federal Regulations) and the European OECD (Organization of Economic Cooperation and Development) series of guidance documents on GLP.

For vaccines, many, if not most, of these non-clinical vaccine studies are animal studies investigating the safety and efficacy of the vaccine in animal models before its first use in humans. The study protocols are as detailed and specific as clinical study protocols. They must be planned and performed in compliance with national guidelines on animal research, and are subject to review by animal care committees before being performed. The safety studies cover the investigations on toxicology (local and systemic), pharmacokinetics, metabolism, biodistribution, reproductive toxicology, or tumorigenicity, as appropriate to the product being tested. For efficacy of vaccines, there are immunogenicity studies and, if there are animal models, studies of disease protection efficacy.

Non-clinical laboratory studies could also include the development of cell-based or in vitro studies of the potency of the clinical lots to be later related to the clinical efficacy, stability studies to determine the shelf life of the early clinical lots for storage, and the validation of shipping and storage conditions.

---

Generally, the NRA does not assess plans for non-clinical studies prior to their implementation, but does so when such studies are presented by the manufacturer/sponsor or an application for clinical trials is submitted. These same studies are included in the full dossier application for marketing authorizations even though they may have been reviewed and accepted as adequate to support the clinical trials at the time of the original application for trial. An NRA that receives an application for marketing authorization for a vaccine but was not involved in the approval of clinical trials of the vaccine must still ensure during the review that pre-clinical studies were appropriate and properly performed and documented.

### *GCP*

GCP is a set of general principles outlining the conduct and responsibilities of those involved in performing clinical trials of all investigational medicinal products in humans.

The conduct of clinical trials by clinical investigators, monitors and sponsors and the responsibilities of each have been detailed in the GCP regulations and guidelines of many countries and international organizations. The International Conference on Harmonisation (ICH) harmonized GCP document replaces the individual documents from Japan, the USA and the EU, and has been adopted by many other countries (Canada, Australia) in lieu of their own GCP documents. WHO has also published guidelines on GCP.

GCP guidelines cover every aspect of the requirements for the performance and recording of clinical trials: prerequisites; justification; written protocol; ethics committee approval; informed consent; regulatory approval; confidentiality of patient data; responsibilities of the sponsor, the investigators and the monitors; record keeping; accountability of the product.

The WHO GCP and the ICH-harmonized GCP guidelines are the appropriate documents to study to understand the principles involved. All NRA staff involved in licensing and clinical trial evaluation should do so. Where national standards for GCP exist, the NRA can refer to them and compare the national standards with international ones.

The two documents cover the same principles but the WHO document provides additional information on the role and responsibilities of the regulatory authorities, while the ICH guidelines include a section on the investigator's brochure (IB). The IB document is an important trials document which summarizes for the clinical investigator information on the quality of the product, pre-clinical safety and efficacy studies, and any previous human studies. The IB needs to be updated throughout clinical development. The ICH also includes a very useful appendix listing the documents needed throughout a clinical trial and indicating how they should be recorded and managed.

Another aid to NRAs consists of the guidelines for FDA staff on Bioresearch Monitoring (BIMO) published by the FDA Office of Regulatory Affairs (ORA).

---

### *Ethical oversight.*

Clinical studies are designed and written into detailed protocols by the manufacturers and their clinical investigators, and then reviewed and authorized by the NRA. The research is governed by internationally agreed upon ethical principles. But research in humans is also reviewed and approved by independent committees that look at the suitability of all research in humans taking place at their respective institutions. These committees are called institutional review boards (IRB) or independent ethics committees (IEC). This ethical review takes place at each trial site(s). (Some countries may have a central IRB.) The requirement for IRBs is included in the GCP guidelines as well as in many independent ethics guidelines (see C below).

In most countries, these review boards have a required number of members and a defined membership profile. Unlike the NRA, these are not all scientists and doctors, but must include a number of lay people, and sometimes lawyers and other professionals. This type of committee, composed of a wider spectrum of individuals and based at the institution where the research is to take place, appraises the proposed study from a different perspective.

Many documents, both national and international, provide guidance on, or regulate, the ethical considerations on research in humans. The definitive document in this regard is the current version of the Declaration of Helsinki, a guideline of ethical principles first defined by the World Medical Association General Assembly, adopted in 1964 and amended in 1975, 1983, 1989, 1996 and 2000. It provides guidance to physicians and those participants in medical research in humans. While acknowledging that medical progress is based partly on experimentation in humans, the document states that the well-being of the subject should take precedence over the interests of science and society. All GCP guidance documents refer to the Declaration of Helsinki in the sections on ethical principles and ethics committees.

Ethical oversight by the committee is not confined only to the initial approvals of the protocol and consent form but also reviews all amendments to these documents, performs trial data audits, reviews annual updates, has the right to monitor the progress of trials and obliges the investigator to report monitoring information, especially adverse events. The committee must also investigate any potential conflict of interests for the study principals.

---

## B. Practical approaches

1. Draw up a reference list of guidelines that should be available in the NRA library/office (see C: Resource materials, below). Obtain at least one internationally accepted document on GMP, GLP, GCP and Ethical Guidelines for Research in Human Subjects. The WHO and ICH-harmonized documents are recommended. The ICH documents can be downloaded from the internet from the ICH, FDA and the European Medicines Evaluation Agency: Committee for Proprietary Medicinal Products (EMA: CPMP) web sites. The WHO GMP and GCP documents are not available electronically but can be obtained from WHO.
2. Determine if your country has a policy of requiring international norms of GMP, GLP, GCP and ethical oversight for clinical trials. Obtain the national documents or reports explaining the policies, and national guidelines for each if available. Identify the ministry responsible for regulating and enforcing these policies, and meet to determine the procedure for establishing or updating such an overarching policy. This policy should cover the review of completed clinical trials performed elsewhere, or for clinical trials proposed to be held in-country whether sponsored by a domestic or a foreign manufacturer and should, similarly, regulate the clinical trials regardless of the origin of the product or of the clinical data.
3. Compare the international requirements with the national ones and list the similarities and differences. Pay special attention to differences in the level of detail.
4. The WHO GCP document includes a section on the responsibilities of NRAs concerning GCP. Prepare a list of these responsibilities and assess your country's NRA accordingly. Train staff as appropriate.
5. Review the organization of your country's NRA and determine the department(s)/ person(s) responsible for reviewing the manufacturing and pre-clinical data in an application for clinical trials, or for marketing authorization (licensing, registration). Determine their level of knowledge of GMP and GLP and their ability to assess these practices in an application. Prepare checklists for the review of manufacturing and pre-clinical data.
6. If needed, assign and/or train staff as evaluators of: (a) vaccine manufacture and quality; (b) non-clinical laboratory studies; (c) safety, immunogenicity and efficacy studies in animal models; and (d) clinical studies that cover all types of vaccine applications. For animal and clinical data, NRAs often set up different teams of evaluators for viral vaccines, bacterial vaccines, and rDNA/peptide vaccines, as each requires different experience and/or qualifications. These teams can coordinate when dealing with combination vaccines.
7. Ensure that staff who are to review various aspects of clinical trial or marketing authorization applications are familiar with the guidelines for GLP, GMP, and GCP. Even if outside experts are used, the NRA staff responsible should have sufficient knowledge to be able to choose the expert and to review the expert report.

- 
8. These guidance documents are written by well-known and experienced international regulatory authorities for manufacturers, sponsors, monitors and investigators to follow. For each of the GMP, GLP and GCP guidelines, prepare an outline and indicate how an evaluator at the NRA would be able to decide if the requirements in each case are being met. In doing so, take into consideration applications for clinical trials as well as for marketing authorization.
  9. Prepare a list the needs of the national NRA with regard to GMP, GLP, GCP, and ethical review. What departments are responsible for each of these? Do they meet on these issues? What areas need the most training?
  10. Determine the national requirements for ethics committees for clinical investigations, the responsible ministry, the rules governing the establishment of such committees, their mandate, their responsibilities, whom they report to, and whether they meet WHO and international guidelines.
  11. Draw up a list of the ethics committee chairmen and offices at large hospitals and health centres where vaccine trials have been or are likely to be held. Obtain a list of the current chairmen, members and their terms of reference. Determine if there is any government review of these committees and their activities, or if they must report to a government office.
  12. On receiving applications for marketing authorizations from other countries, reviewers should seek information on GLP, GMP, and GCP requirements in the country of origin of the product and where the trials were held (if different from the country of origin) to ascertain if these meet WHO and/or international requirements. If the studies were performed under other standards, the reviewers must be able to assess whether the manufacturing and non-clinical data will be acceptable for clinical trials, on whether clinical practice and ethical principles meet standards, be able to make a decision on whether the clinical data report from the studies should be reviewed. (In addition to reviewing the clinical data for marketing authorization applications, the NRA is also responsible for reviewing all chemical, manufacturing, control and facility information for GMP compliance. The NRA must also ensure that GMP is verified by inspection by the NRA of the country of manufacture, and ascertain that the WHO recommendation that the product be licensed in the country of origin is met before issuing a license. These functions are covered in the WHO training manuals on GMP and on licensing, lot release and laboratory access.

---

## C. Resource materials

The following documents are appropriate background and reference materials for GMP, GLP, GCP, and ethical considerations for research in humans.

### *US FDA documents*

*Current good manufacturing practice for finished pharmaceuticals: USA Code of Federal Regulations (CFR) Chapter 21: Food and Drug Regulations. Part 211*

These regulations contain the minimum requirements for the preparation of drug products for administration to humans. They cover personnel and organization, premises, equipment, control of containers and closures, control of production and processes, packaging and labelling control, storage and distribution, laboratory control testing and records and reports.

*Good laboratory practice: USA Code of Federal Regulations, Chapter 21: Food and Drug Regulations. Part 58*

These regulations prescribe good laboratory practices for conduction non-clinical laboratory studies that support or will support applications for clinical research or marketing applications. They cover the personnel, facilities, equipment and operation of the laboratory, including animal care and handling of the test products, protocols and conduct of the studies, records and reports.

*Protection of human subjects: USA Code of Federal Regulations, Chapter 21: Food and Drug Regulations. Part 50*

This regulation applies to all clinical investigations regulated by the FDA. It provides definitions, requirements for informed consent of human subjects.

*Institutional Review Boards: USA Code of Federal Regulations, Chapter 21: Food and Drug Regulations. Part 56*

This regulation provides the standards for composition, operation and responsibility of an Institutional Review Board that review clinical investigations regulated by the FDA. It provides definitions, criteria for approval of research, records and reports that must be maintained, and FDA administrative actions for IRB non-compliance.

*Concerning use of pilot manufacturing facilities for the development and manufacturing of biological products - FDA Guidance Document: 7/11/1995 CBER*

*Considerations for reproductive toxicity studies for preventive vaccines for infectious disease indications - Draft Guidance for Industry: 9/8/2000 CBER*

*On the establishment and operation of clinical trial data monitoring committees - Draft Guidance for Clinical Trial Sponsors 11/15/2001 CBER*

---

## ***Other FDA guidance***

*FDA/ORA: Bioresearch Monitoring: Compliance Program 7348.808: Good laboratory practice.* Feb 21, 2001

*FDA/ORA: Bioresearch Monitoring :Compliance Program 7348.810: Sponsors, contract research organizations and monitors.* September 30, 2000

*FDA/ORA Bioresearch Monitoring: Compliance Program 7348.811 Chapter 48: Clinical investigators.* September 30, 2000

*FDA/OSSC: Office of Good Clinical Practice. Mandate* (FDA web site)

## ***ICH documents***

### **Safety topics**

*S3A: Guidance on the assessment of systemic exposure in toxicity studies*

*S4A: Duration of Chronic Toxicity Testing in Animals (Rodent and Nonrodent Toxicity Testing)*

*S5A: Detection of toxicity to reproduction for medicinal products.*

*S6: Preclinical safety evaluation of biotechnology-derived pharmaceuticals.*

*S7A: Safety pharmacology studies for human pharmaceuticals.*

### **Efficacy topics**

*E6: Good Clinical Practice*

### **Multidisciplinary topics**

*M3: Timing of pre-clinical studies in relation to clinical trials*

### **EU documents**

*EU: The rules governing medicinal products in the European Union.*

Vol. 2: Notice to applicants

Vol. 2B: Presentation and content of the dossier

- Part II Concerning chemical, pharmaceutical and biological documentation
- Part III Toxicopharmacological documentation
- Part IV Clinical documentation

Vol. 3: Guidelines

Vol. 3A: Quality and biotechnology

Vol. 3B: Safety, environmental guidelines and information

Vol. 4: Good manufacturing practices: Basic requirements and 18 annexes (annex 2: biological products, annex 13 investigational medicinal products.

---

*OECD principles of good laboratory practice (revised 1997)*. ENV/MC/CHEM (98)17

This guideline lays out the criteria for the performance of non-clinical health and environmental safety studies, including pharmaceutical and many other products that require licensing or registering. They cover the facility organization and personnel responsibilities, quality assurance facilities, apparatus, materials and reagents, test systems, test samples and reference items, standard operating procedures, study performance, reporting and record keeping.

The document also lists 10 other related guidance documents on specific part of the GLP principles (monitoring, inspections, quality assurance, laboratory suppliers, field studies, short term studies, study director responsibilities, inspection reports, GLP of computerized systems, and roles and responsibilities of the sponsor.

*CPMP/SWP/1042/99 Note for Guidance on repeated dose toxicity* (CPMP adopted July 2000)

*CPMP/SWP/465/95 Note for Guidance preclinical pharmacological and toxicological testing of vaccines* (CPMP adopted Dec. 97)

*CPMP/BWP/328/99 Development pharmaceuticals for biotechnological and biological products - Annex to Note for Guidance on Development Pharmaceuticals* (CPMP/QWP/155/96)

*CPMP/BWP/268/95 Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses* (CPMP adopted Feb. 96)

*CPMP/SWP/728/95 Replacement of animal studies by in vitro models* (CPMP adopted February 97)

### ***WHO and the Council of International Organizations of Medical Sciences (CIOMS) documents***

*Guidelines for ethical review committees*. Geneva, CIOMS, 1998.

*International ethical guidelines for biomedical research involving human subjects*. Geneva, CIOMS (Revised draft 2002 (updated from 1993)).

This 45-page draft document presents 21 revised guideline paragraphs and commentary on each, covering several topics: ethical justification; ethical review; informed consent; control groups in clinical trials, vulnerable groups; and women as research participants; confidentiality; compensation; capacity strengthening; and sponsor obligations.

---

*International guidelines for ethical review of epidemiological studies.* Geneva, CIOMS, 1991.

This booklet “presents the first international guidelines formulated to ensure that epidemiological investigation, particularly research conducted by scientists from developed countries in developing countries, adhere to internationally agreed rules of ethical conduct”. The guidelines concentrate on four basic principles of ethics – respect for persons, beneficence, non-maleficence, and justice – and discuss topics ranging from informed consent to conflict of interest.

*Good manufacturing practice: supplementary guidelines for the manufacture of the investigational pharmaceutical products for clinical trials in humans. Annex 7.* Geneva, World Health Organization, 1996. (WHO Technical Report Series No. 863).

*Good manufacturing practices for biological products. Annex 1.* Geneva, World Health Organization, 1992. (WHO Technical Report Series No. 822).

*Good manufacturing practices for pharmaceutical products. Annex 1.* Geneva, World Health Organization, 1992. (WHO Technical Report Series No. 823).

*Guidelines for good clinical practices (GCP) for trials on pharmaceutical products. Annex 3.* Geneva, World Health Organization, 1995. (WHO Technical Report Series No. 850).

*Guidelines for national authorities on quality assurance for biological products. Annex 2* Geneva, World Health Organization, 1992. (WHO Technical Report Series No. 822).

*Operational Guidelines for ethics committees that review biomedical research.* Geneva, World Health Organization, 2000.

Guidelines to facilitate and support ethical review in all countries of the world. It discusses setting up ethical committees, membership requirements, preparation of guidelines for the application procedure, and the procedure for review of applications, decision making, and documentation.

### ***Other regulatory documents***

*Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: convention on human rights and biomedicine.* Strasbourg, Council of Europe, 1996.

*Ethical considerations in HIV preventive vaccine research.* UNAIDS guidance document, May 2000.

Deals with ethical concerns related specifically to HIV preventive vaccines.

---

*Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects.* Original adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Most recent amendment by the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October 2000.

A document listing 32 ethical principles for medical research involving humans: background; basic principles; and additional principles for medical research where a new therapy is compared to best current therapy.

### ***Local resource materials***

Documents or policies developed by local experts on ethical issues that take into consideration prevalent cultural and social factors, should also be consulted whenever possible and available.

### ***Published journal articles and books***

Beernaert H et al. The revised principles of good laboratory practice of the Organization for Economic Cooperation and Development – Changes, chances, and controversies. *Drug Information Journal*, 2000, 34: 33–45.

Discussion paper about the revision process for the OECD GLP guidelines published in 1998.

Evans D, Evans M. *A decent proposal: ethical review of clinical research*. Chichester, England. John Wiley & Sons Ltd, 1996.

Fuccella LM, Olliaro P. *Standard operating procedure for clinical investigators*. Geneva, World Health Organization, 1995. (document WHO/TDR (see also Karbwang)).

This document was prepared for the WHO Steering Committee on Drugs for Malaria. Based on the EU and WHO GCP document, this is a detailed “how to” guide covering the responsibilities of investigators carrying out clinical studies.

Fuccella LM, Teruzzi E, F. Macchi, Olliaro P. *Standard operating procedure for monitoring of clinical studies*. Geneva: World Health Organization, 1997. (document WHO/TDR).

This document was prepared for the WHO Steering Committee on Drugs for Malaria. Based on the EU and WHO GCP document, this is a detailed “how to” guide for monitors of clinical studies, and includes checklists for all site visits.

Geigert J. Appropriate specifications at the IND stage. In: Brown F, Fernandez J, eds. Development of specifications for biotechnology pharmaceutical products. Basel, Karger, 1997:39-43. *Development of Specifications for Biotechnology Pharmaceutical Products*; Vol. 91.

A short proposal on how to set an appropriate number of tests and specifications at various stages of product development throughout early clinical trials.

---

Griffiths E. Assuring the quality of vaccines: regulatory requirements for licensing and batch release. In: Robinson A, Farrar G, Wiblin C, eds. *Vaccine protocols*. Totowa, NJ: Humana Press, 1996.

Mainly a review of the control of production of vaccines for which WHO requirements have been published in the Technical Report Series. Clinical trials are discussed only in very general terms.

Karbwang J, Pattou C. *Standard operating procedures for clinical investigators*. UNDP/World Bank/WHO. (document TDR/PRD/SOP/14/06/01.1 Rev.1).

A practical “how-to” manual giving detailed guidance and procedures to ensure that: the investigator understands his obligations and understands all study procedures; the planned study is set up, conducted, documented, and reported according to the protocol, international guidelines, and applicable regulatory requirements; subjects rights are protected; and data are accurate.

Plotkin S, Brown F, Horaud F. Preclinical and clinical development of vaccine. Basel, Karger, 1998. (Brown F, ed. *Developments in Biological Standardization*; Vol. 95).

### ***Web sites for downloading documents***

US FDA: All documents listed are available electronically from:

CFR: Code of Federal Regulations: [www.access.gpo.gov/nara/cfr/](http://www.access.gpo.gov/nara/cfr/)

CBER: Center for Biologics Evaluation and Research:  
[www.fda.gov/cber/ guidelines.htm](http://www.fda.gov/cber/guidelines.htm)

BIMO: Bioresearch Monitoring: [www.fda.gov/ora/BIMO/](http://www.fda.gov/ora/BIMO/)

ICH: All documents listed are available electronically from:

[www.ifpma.org/ich5.html](http://www.ifpma.org/ich5.html)

European Union: All documents listed are available electronically from:

CPMP: Committee for Proprietary Medicinal Products:  
[www.emea.eu.int/htms/ human/](http://www.emea.eu.int/htms/human/)

Rules Governing Medicinal Products in the European Union:  
<http://pharmacos.eudra.org/F2/eudralex/index.htm>

WHO: Some publications are available electronically.

[www.who.int/pub/en/](http://www.who.int/pub/en/)

[www.who.int/vaccines-documents/](http://www.who.int/vaccines-documents/)

---

# Indicator 2:

Written guidelines for the conditions under which clinical trials will be needed: consideration given to the application of clinical data to the local use of vaccines

## A. Background

The basic requirements for the need for clinical trials are found in the legislation of the USA, the EU and other countries.

These regulations stipulate that applications for marketing authorization (licensing) of a new drug/new medicinal product (including vaccines) must be accompanied by a dossier containing the manufacturing, control, preclinical and clinical data. They also specify that clinical trials to obtain the data required for the marketing authorization application must be performed according to GCP guidelines and international standards of ethical approval.

The sponsor/manufacturer developing a vaccine must be provided with written guidelines on those situations that require clinical trials.

Trials of a new product, or for an existing product that has undergone significant changes that make it in effect a new product, go through the established phases of clinical studies. In the case of vaccines these phases are:

Phase	Principal objectives	Subject Population
I	Safety Preliminary immunogenicity	Healthy adults, and/or adolescents and/or children (not infants) depending on vaccine.  New phase 1 for infants
II	Safety Immunogenicity Dose-response Dose schedule	Targeted population (small numbers, <i>i.e.</i> hundreds)
III	Efficacy Safety	Targeted population (large numbers, <i>i.e.</i> thousands)
IV	Large scale safety in post-marketing studies	General population

These clinical studies, carried out according to a pre-approved protocol, take place sequentially. The application for each phase is made after the clinical data from the previous authorized phase have been obtained, analysed and reported to the NRA, along with the new proposed protocol. (see indicator 3). Phase IV trials are, in general, controlled clinical studies on the product after marketing authorization has been granted. They are generally larger studies, carried out under similar conditions to phase III trials, and are mainly to collect data on low frequency adverse reactions that may not show up in phase III trials or vaccine effectiveness studies. They may not be case-controlled. Phase IV safety trials are important for vaccines because they involve very large numbers of healthy people, mainly children and infants.

There are, however, other situations where clinical trials will/may be needed. These may be partial trials or small repeat trials to establish the equivalence of a changed product, or a specific phase of a trial to show the immunogenicity via a different route of inoculation. These situations must be defined as clearly as possible for manufacturers to know when such trials will be required, and for NRA evaluators in turn to identify them and review an incoming dossier accordingly.

The following table summarizes such situations.

<b>Situations where clinical studies will/may be necessary</b>
<ul style="list-style-type: none"> <li>• Significant changes in the manufacturing process for an existing authorized vaccine</li> <li>• A new combination vaccine</li> <li>• Change in antigen source or antigen composition in an existing authorized vaccine</li> <li>• Clinical bridging studies to support extrapolation of safety, immunogenicity or efficacy data from one population to another population</li> <li>• Change in the product excipients, starting materials or intermediates</li> <li>• Vaccine made by a different manufacturer</li> <li>• New dose</li> <li>• New route of inoculation</li> <li>• New indication or target population</li> <li>• New formulation</li> <li>• New adjuvant (important to note that the product is the vaccine/adjuvant combination. A change in adjuvant would constitute a new product.)</li> <li>• No assurance in an application that clinical trials carried out elsewhere were in compliance with GCP or ethics review</li> <li>• Insufficient clinical data to support the claims</li> </ul>

Much depends on the individual case, the type of vaccine and the situation encountered.

---

With regard to changes to the vaccine itself, there are specific regulations covering changes to approved marketing authorizations/product licenses for existing vaccines. In the case of a licensed vaccine that has had significant changes introduced into the production process, the need for new trials will depend on the changes made. In many cases if the end product can be shown to produce a “comparable” final product, pre-clinical data from animal studies and comparative quality data may suffice.

The EU regulations define two types of variations to a marketing authorization. Type 1 variations refer to minor changes not affecting the product and Type 2 variations to moderate to major changes that can possibly affect the product. However, please note that many changes considered to be Type 1 for pharmaceutical drugs would be considered as Type 2 changes for vaccines and biologicals, because of the inherent variability in the production of biologicals from microorganisms. For such variations, only the parts of the application that are changed need to be updated with additional and/or comparative data to show there is no inherent change to the product. The regulations, however, also state that certain changes can fundamentally alter the terms of the marketing authorization. In such cases, therefore, it would not be considered a variation but would require a new application for a complete scientific evaluation procedure (including clinical trials) as in the granting of a market authorization. The kinds of changes relevant to human medicinal products are found in EU Regulations 541/95. They relate to:

- the active substance(s) (addition, deletion, replacement, amounts);
- the therapeutic/prophylactic/diagnostic indication (change or addition);
- the strength/pharmaceutical form/route of administration (changes or additions); and in the case of adjuvanted vaccines, a new adjuvant.

For new formulations of a vaccine, for example a new stabilizer or excipient with a known safety profile, the vaccine, although against the same disease, could require limited trials to demonstrate its safety, immunogenicity, and efficacy, and possibly to compare the new formulation against the original one and demonstrate that it is at least as safe and effective. If a new stabilizer is introduced that has not been studied for safety or used in other vaccines, then full trials could be necessary. And because new adjuvants are involved in the immunological response to the vaccine antigens. The new antigen-adjuvant combination are considered new vaccines and would need to go through the full trial process.

In the case of a new indication, provided the doses of the vaccine are the same, the original phase 1 trials will most likely have adequately proved safety and the clinical studies may only need to start at phase 2 to determine its safety and efficacy in the target population and in larger numbers.

When it comes to a new route of inoculation, at least one comparative trial would be needed to show that safety and immunogenicity with the new route are equivalent to or better than the original administration route

---

If the dose or dose regimen changes, the clinical trials needed will depend on the dose change and on whether the new schedule was studied in earlier phase II trials. If the dose is reduced, at least one study would be needed to evaluate safety and immunogenicity, and possibly also the need for a booster. If the dose is increased, the need for Phase I trials will depend on whether the safety of the higher dose had already been investigated in earlier Phase I or Phase II studies.

If the vaccine is proposed for a different target population (e.g. originally for adults and now for children), then all phases of clinical trials are usually required to show the safety profile, dose levels, immunogenicity, and efficacy. However, as most vaccines are for children, they are usually subjects in the original phased trials of the vaccine.

Most countries import vaccines that were studied in clinical trials elsewhere. Most major industrialized countries accept data from authorized clinical trials from other countries provided the regulations and control of these trials meet international standards. However, even if the trials were in compliance with international requirements, the evaluation often requires an assessment of whether or not the population studied is equivalent to the target population in the importing country. Additional clinical studies called “bridging studies” are designed to provide additional data that allow extrapolation of foreign data to the local target population. The NRA must decide what data from the original vaccine trial need to be repeated, or whether additional “bridging studies” are needed for a vaccine that has been studied in another country on a different dose schedule. The NRA may, similarly, decide on the need for an assessment when a foreign clinical protocol is proposed for clinical studies in the country and the proposal is not appropriate to the country’s needs or population, or immunization programme. Proposed trials may therefore need to be revised to be relevant to the local population or schedule.

Occasionally, adverse event reports during trials may result in a temporary suspension and revision of the trials.

In all the cases needing clinical trials, the NRA guidelines offer only general guidance. The vaccine manufacturer/sponsor of an application will need to evaluate his own product according to such general guidance and then make decisions based on knowledge of the vaccine and the disease, plan appropriate studies and file an application accordingly. Many NRAs have a policy of meeting with manufacturers to discuss specific product issues.

---

## B. Practical approaches

1. Determine if the law of your country stipulates that evidence from authorized clinical studies is required before licensure of a new drug or vaccine. Review the national guidelines to find out what written criteria specify requirements for clinical trials.
2. Determine if the law or policy also stipulates that significant changes in a vaccine require approval and, possibly, additional clinical trials.
3. Review the EU criteria for Type II variations to a biological product and to product changes that require a new application (NA). Compare with the national requirements.
4. Review the FDA and EU documents concerning changes (variations) to vaccines and compare with the same details in your country's regulations. Is the definition of what constitutes significant changes equivalent? Which is more rigorous? Determine if your national guideline needs to be updated.
5. Determine if the existing national requirements for trials include an assessment of the applicability of foreign clinical data to the domestic target population.
6. Review the ICH document E5: "Ethnic Factors in the Acceptability of Foreign Clinical Data" to understand the types of factors that need to be considered when evaluating foreign data and the need for bridging studies.
7. Compare the national criteria for accepting foreign data with international criteria.

## C. Resource materials

### *USA FDA documents*

*USA Code of Federal Regulations (CFR) Chapter 21: Food and Drug Regulations. Investigational New Drug Application: Part 312.*

These regulations identify the requirements for an investigational New Drug application, the phases of trials, application contents and format, amendments, safety reports, annual reports, administrative actions, responsibilities of the sponsor and investigators, and miscellaneous items such as import/export requirements and reference to FDA guidelines.

*Changes to an approved application for specified biotechnology and specified synthetic biological products – Guidance for industry – 7/24/1997 (CBER)*

*Changes to an approved application: biological products – Guidance for industry – 7/24/1997 (CBER)*

*Concerning demonstration of comparability of human biological products, including therapeutic biotechnology-derived products – FDA Guidance: 4/1996 (CBER)*

*Evaluation of combination vaccines for preventable diseases: production, testing and clinical studies – Guidance for industry: 4/10/1997 (CBER)*

*General considerations for pediatric pharmacokinetic studies for drugs and biological products – Draft guidance for industry: 11/30/1998 (CBER)*

---

## **ICH documents**

### **Efficacy topics**

*E11: Clinical investigation of medicinal products in the pediatric population*

### **EU documents**

*EU: The rules governing medicinal products in the European Union*

Vol. 2: Notice to Applicants

Vol. 2A: Procedures for Marketing Authorization

- Chapter 1: Marketing authorization
- Chapter 5: Variations

Vol. 3: Guidelines.

Vol. 3C: Efficacy. Clinical guidelines (general and therapeutic class)

CPMP/EWP/463/97 Note for guidance on clinical evaluation of new vaccines

*CPMP/BWP/3207/00 Note for guidance on comparability of medicinal products containing biotechnology-derived proteins as drug substance* (CPMP adopted Sept. 01)

*CPMP/BWP/6622/02 Notice for guidance on requirements for the evaluation of new adjuvants in vaccines* (Concept paper)

*CPMP/BWP/2517/00 Points to consider on the reduction, elimination or substitution of thiomersal in vaccines* (Adopted, April 2001)

### **WHO documents**

*Regulation and licensing of biological products in countries with newly developing regulatory authorities. Annex 1. Geneva, World Health Organization, 1995.* (WHO Technical Report Series No. 858).

*Review of existing documents on planning, performance and assessment of clinical studies on vaccines. Geneva, World Health Organization, 1999.* (document WHO/V&B/99.09).

*A review of the documents available before 1999 that were specific to vaccine clinical studies.*

### **Other regulatory documents**

UK Medicines Control Agency: MCA: Guidance notes on applications for clinical trial exemptions and clinical trial certificates.

Criteria and requirements for application for clinical trial authorization via the UK Exemption or Certificate procedure: application, documentation format; notifiable changes; renewal; variation application form; information required to support application; pharmaceutical and biological data; experimental and biological studies; adverse drug reaction reporting.

---

## Web sites for downloading documents

US FDA: All documents listed are available electronically from:

CFR: Code of Federal Regulations: [www.access.gpo.gov/nara/cfr/](http://www.access.gpo.gov/nara/cfr/)

CBER: Center for Biologics Evaluation and Research:  
[www.fda.gov/cber/guidelines.htm](http://www.fda.gov/cber/guidelines.htm)

BIMO: Bioresearch Monitoring: [www.fda.gov/ora/BIMO/](http://www.fda.gov/ora/BIMO/)

ICH: All documents listed are available electronically from:

[www.ifpma.org/ich5.html](http://www.ifpma.org/ich5.html)

European Union: All documents listed are available electronically from:

CPMP: Committee for Proprietary Medicinal Products:  
[www.emea.eu.int/htms/human/](http://www.emea.eu.int/htms/human/)

Rules Governing Medicinal Products in the European Union:  
<http://pharmacos.eudra.org/F2/eudralex/index.htm>

WHO: Some publications are available electronically.

[www.who.int/pub/en/](http://www.who.int/pub/en/)

[www.who.int/vaccines-documents/](http://www.who.int/vaccines-documents/)

---

# Indicator 3:

## Published guidelines on the format for submission of clinical data

### A. Background

In addition to providing a general format for the submission of an application for a clinical trial or marketing authorization, the NRA of each country must provide manufacturers of medicinal products with concise instructions on the specific formats for presenting the plans for clinical trials (study protocols) and for presenting data collected during clinical trials (clinical study reports). Instructions for submitting annual reports and adverse reaction reports are also needed to ensure that NRAs remain informed on clinical safety and to ensure that relevant and accurate clinical and safety information is provided to physicians prescribing or administering a licensed product.

1. Format for the clinical section of an application for phase II, III, or IV clinical trials or for market authorization.
2. Adverse reaction reporting during clinical studies or after marketing (see bibliography 112 for AEFI: adverse reactions following immunization)
3. Annual updates of clinical trial progress, or safety updates.
4. Format for clinical information on package labelling (information leaflet).

In order to ensure that NRA resources are effectively used and that the merits of each product are evaluated in a consistent and timely manner, major regulatory authorities require that applications for clinical trials or marketing authorization be submitted in a specified format and they have published various guidance documents outlining these requirements. This makes it possible for the NRA to first screen applications in order to ensure that all the relevant data sections have been submitted as required, to accept them for a detailed review and to distribute different complete parts of the dossier to evaluators of the different sections of the data, or if insufficient, to reject them.

Equally detailed guidance documents have been published on the format and content of clinical information of various reports.

For NRAs with limited detailed national regulations or guidelines, and those with small numbers of staff and experience, the preparation of guidelines for industry is a huge task. To help prepare and/or train NRA staff, the available guidance documents from the USA and the EU as well as the harmonized documents from the ICH (from Japan, USA, EU and several other countries) can be used to compare national guidelines and standards against international guideline, to assist in updating national requirements, or to adopt or accept the ICH or other guidelines as national guidelines.

---

In some cases, a small or developing NRA may choose to accept the formats of one or more well-recognized NRAs when screening applications received from manufacturers from these countries.

In general, available guidelines on the format for clinical data and other information to be submitted in an application for a clinical trial or marketing authorization are not specific for any particular product. However, they do provide detailed instructions for the kind of information required.

Relevant published guidelines on various formats and structures are listed in C below. These are written for industry and the manufacturer or sponsor of a vaccine for clinical trial or market authorization is responsible for the preparation and submission of their data in the format required by the country where trials or market authorization are sought. Although written for industry, these guidance documents provide smaller, less experienced NRA's, with the expertise of major well-recognized regulatory opinion, and they can be used as a checklist to assess the data submitted.

Over the last several years, the members of the ICH have been working on the preparation of a Common Technical Document (CTD) so that the same application format will be accepted by the three major NRAs (USA, EU and Japan) and adopted by other countries. The CTD is divided into 5 modules covering all the information required for a market authorization review. They are: Module 1: Administrative and Prescribing Information; Module 2: CTD Summaries (containing the Clinical Overview and Clinical Summary); Module 3: Quality; Module 4: Non-clinical Study Report; Module 5: Clinical Study Reports. Of relevance to this section on format for submission of clinical data are the two clinical parts in Module 2 and Module 5. The ICH guidance document titled "M4E: Efficacy" provides a harmonized format for organization of clinical summaries in Module 2 and the clinical study reports section. M4E outlines the organization of the clinical section of a full application and gives the order of placement of individual reports. The objective of the CTD modules is to simplify both the preparation of the reports and the review by the NRA and to ensure completeness. (Please note that guidance document "M4S: Safety" is concerned with pre-clinical safety studies in animals, and that "M4E: Efficacy" deals with all human clinical studies: pharmacokinetic, pharmacology, safety and efficacy studies).

A second ICH document gives more specific information on the content of the individual clinical reports to be submitted in an application. This is summarized in the following table.

**ICH: E3 guideline: structure and content of clinical study reports  
(applies to individual study reports,  
not to an integrated summary of all studies)**

<b>Section</b>	<b>Description</b>	<b>Comment</b>
Title page	Describes items to be included on this page.	Statement that study was performed in compliance with GCP required here
Synopsis	Three (3) page summary of the study including numerical data	Example for Europe given in Annex 1 of this guideline
Table of contents for the individual study report	Includes page numbers and other location information for all sections, graphs, tables, summary tables, appendices, and case report forms	
List of abbreviations and definition of terms		Instructions to include the full term for abbreviations with the abbreviations in () in the first instance in the text
Ethics	Statements confirming IRB approvals, ethical conduct and patient consent	List of IRB and name of chair if required by NRA given in appendix  Statement that conduct is according to principles originating in the Declaration of Helsinki  Copy of patient information sheet and consent form given in appendix
Investigators and study administrative structure	Description of the administrative structure including, investigator(s), administration, monitors, statisticians, lab facilities, clinical trial supply management	List of investigators with their qualifications and CV in appendix. Also for any immediate participants in conducting the study (nurse, pharmacist etc).  Author of the report including statisticians.  Required signatures in an appendix
Introduction	One page description of the study as it relates to the development of the test product: rationale, aims, target population, treatment, and primary endpoints. It should list regulatory guidelines followed and relevant meetings/agreements with the NRA	
Study objectives	Statement of overall purpose	
Investigational plan	Details of the study design and plan, control groups, inclusion and exclusion criteria for study population, treatment for each group, identity of test product(s), assignment of subjects to groups, blinding, efficacy and safety measurements, quality assurance of measurements, statistical methods and sample size. Also any changes that were made to the conduct or planned analyses (deviations to protocol)	Can be compared to the protocol that was authorized and any amendment to check that the protocol was followed
Study patients	Full accounting of all subjects, including those discontinued, demographic data, protocol deviations to subject enrolment criteria	Example of flow chart of subject enrolment given in Annex

Section	Description	Comment
Efficacy evaluation	Details of data sets analysed, tabular lists of all patients analysed for each data set and also those not analysed, demographics and baseline data, treatment compliance, analysis of efficacy, statistical analyses, tables of individual patient data, tables of individual patient doses, efficacy conclusions	Detailed documentation of statistical methods in an appendix
Safety evaluation	Three analyses: extent of exposure (dose, duration, # patients), adverse events/lab test changes, serious and unexpected adverse events. Analyses and listings of each category of adverse events	Summary data, individual data and narratives of any significant adverse events should be presented
Discussion and overall conclusions	Efficacy and safety results, relationship of risks and benefits summarized and discussed. conclusions based on the study objectives	Not repeat of description of analyses in the efficacy and safety evaluation sections
Tables, figures and graphs referred to but not included in the text	Large or supporting tables and figures that are cross-referenced in the text	
Reference list	List of pertinent published articles	Copies of important articles included in an appendix
Appendices	Protocol, amendments, list of IRBs and copies of patient information and blank consent forms, list of investigators and qualifications, investigator(s) signatures, listing of patients and lot numbers received, randomization scheme, audit certificates, statistical methods, laboratory standardization methods, publications based on the study, other important publication.	

Regulations require that all adverse events occurring during clinical studies and post-marketing must be reported to the NRA. Several guidelines are available from regulatory authorities on the requirements for reporting adverse reactions and annual safety updates. The following guidance documents reflect current requirements and opinions of well respected regulatory authorities, and ICH-harmonized guidelines. The ICH E2 Clinical safety documents: Definitions and Standards for Expedited Reporting (E2A), Data Elements for Transmission of ADR Reports (E2B), and Periodic Safety Update Reports (E2C). E2A provides standard terminology and also guidance on mechanisms for rapid reporting of adverse reaction in the investigational phase (clinical trials). E2B standardizes the data elements of all types of reports. E2C gives the content and format of safety updates required by NRAs after marketing.

The US FDA also provides guidance and forms for adverse reaction reporting. Two that specifically include vaccines are: “Guidance for industry: how to complete the vaccine adverse events reporting form (VAERS-1) Sep 1998”; and “Draft guidance for industry: postmarketing safety reporting for human drugs and biological products including vaccines, March 2001”.

---

Clinical information is also provided in the package leaflet (labelling), and is subject to NRA review and approval. The objective in labelling is to provide information to the prescribers and users of the product. There are several specific content and format guidelines for labelling available from the US FDA: “Guidance for industry: the content and format of pediatric use supplements, May 1996” (supplements here meaning supplementary submissions of clinical data and information); “Draft guidance for industry: content and format of the adverse reactions section of labelling for human prescription drugs and biologics”; and “Draft guidance for industry: clinical studies sections of labelling for prescription drugs and biologics”. During the evaluation of an application, the NRA is responsible for reviewing the contents of information leaflets and ensuring that they accurately reflect the information from the clinical study reports and safety reports. These FDA documents provide a format for this information.

## **B. Practical approaches**

1. Review the ICH guideline M4E: “The common technical document: efficacy” with the staff responsible for screening the clinical sections of incoming applications for marketing authorization. Have them prepare a checklist based on the requirements to use for screening applications.
2. Similarly, review the ICH document E3 “Structure and content of clinical study reports” with the staff screening clinical reports to use as a guide for assessing the completeness of incoming applications containing clinical study reports.
3. If there is a nationally specified format for clinical study reports, compare it to the above and determine if the national guidelines should be revised to meet international standards.
4. Review adverse reaction reporting and annual safety update guides, prepare checklists of the format for screening of incoming reports and preparing trend analyses for each vaccine.
5. Prepare checklists of the content required for clinical data and information and of documents to be submitted for second level screening of the application. This checklist should be based on the structure and contents requirements and should cover all the items expected to be submitted

---

## C: Resource material:

The following list includes regulatory publications relevant to clinical reports.

### *US FDA documents*

*Investigational new drug application. CFR. Chapter 21 Part 312.*

These regulations identify the requirements for an investigational new drug application, the phases of trials, application contents and format, amendments, safety reports, annual reports, administrative actions, responsibilities of the sponsor and investigators, and miscellaneous items such as import/export requirements and reference to FDA guidelines.

*Biologics. CFR. Chapter 21 subchapter F, Parts 600–680.*

*Part 600: Biological products, general*

Part 601: Licensing

Part 610: General biological products

Part 620: Additional standards for bacterial products

Part 630: Additional standards for viral vaccines

These regulations describe the requirements for obtaining a license for a biological product.

*Clinical studies section of labeling for prescription drugs and biologics – content and format–draft guidance for industry: 7/9/2001 (CBER)*

*Content and format of chemistry, manufacturing and controls information and establishment description information for a vaccine or related product – guidance for industry: 1/5/1999 (CBER)*

*Content and format investigational new drug applications (INDs) for phase 1 studies of drugs, including well-characterized, therapeutic, biotechnology-derived products – guidance for industry: 11/1995 (CBER)*

*Content and format of the adverse reactions section of labeling for human prescription drugs and biologics – draft guidance for industry: 6/21/2000 (CBER)*

*How to complete the vaccine adverse reporting system form (VAERS-1) - guidance for industry: 9/8/1998 (CBER)*

*Postmarketing safety reporting for human drug and biological products including vaccines - draft guidance for industry: 3/12/2001 (CBER)*

---

## **ICH documents**

### **Efficacy topics**

*E1: The extent of population exposure to assess clinical safety:*

*E2A: Clinical safety data management: Definitions and standards for expedited reporting*

*E2B: Clinical safety data management: Data elements for transmission of ADR reports*

*E2C: Periodic safety update reports*

*E3: Structure and content of clinical study reports*

### **Multidisciplinary topics**

*M4: The Common Technical Document: CTD*

*M4: Organization of the CTD*

*M4E: The CTD – Efficacy*

*M4Q: The CTD – Quality*

*M4S: The CTD – Safety*

*M4S: The CTD – Safety Appendices*

## **EU documents**

*EU: The rules governing medicinal products in the European Union*

Vol.2: Notice to applicants

Vol. 2A: Procedures for marketing authorization

- Chapter 1: Marketing authorization
- Chapter 5: Variations

Vol. 2B: Presentation and content of the dossier

- Part II Concerning chemical, pharmaceutical and biological documentation
- Part III Toxicopharmacological documentation
- Part IV Clinical documentation

Vol. 2C: Regulatory Guidelines (categories (new vs. variation) renewals, labelling packaging, product characteristics summary, classifications, forms)

*CPMP/EWP/2747/00 Note for guidance on co-ordinating investigator signature of clinical study reports (Adopted October 2001)*

*CPMP/PhVWP/108/99: Notice to marketing authorization holders. Pharmacovigilance guidelines. Draft version, January 1999.*

---

## ***WHO and CIOMS (Council of International Organizations of Medical Sciences) documents***

*International reporting of adverse drug reactions. Final report of the CIOMS Working group.* Geneva, CIOMS, 1990.

*Surveillance of adverse events following immunization. Field Guide for managers of immunization programmes.* Geneva, World Health Organization, 1997. (document WHO/EPI/TRAM/93.02 Rev.1).

Specific guide for managers at the central, regional and district levels in disease surveillance: planning; detecting; reporting; investigating; analysing; taking action; and evaluating surveillance

## ***Other regulatory documents***

*UK Medicines Control Agency: MCA: Guidance Notes on Applications for Clinical Trial Exemptions and Clinical Trial Certificates.*

Criteria and requirements for application for clinical trial authorization via the UK Exemption or Certificate procedure: application, documentation format; notifiable changes; renewal; variation application form; information required to support application; pharmaceutical and biological data; experimental and biological studies; adverse drug reaction reporting.

## ***Web sites for downloading documents***

US FDA: All documents listed are available electronically from:

CFR: Code of Federal Regulations: [www.access.gpo.gov/nara/cfr/](http://www.access.gpo.gov/nara/cfr/)

CBER: Center for Biologics Evaluation and Research:  
[www.fda.gov/cber/guidelines.htm](http://www.fda.gov/cber/guidelines.htm)

BIMO: Bioresearch Monitoring: [www.fda.gov/ora/BIMO/](http://www.fda.gov/ora/BIMO/)

ICH: All documents listed are available electronically from:

[www.ifpma.org/ich5.html](http://www.ifpma.org/ich5.html)

European Union: All documents listed are available electronically from:

CPMP: Committee for Proprietary Medicinal Products:  
[www.emea.eu.int/htms/human/](http://www.emea.eu.int/htms/human/)

Rules Governing Medicinal Products in the European Union:  
<http://pharmacos.eudra.org/F2/eudralex/index.htm>

WHO: Some publications are available electronically.

[www.who.int/pub/en/](http://www.who.int/pub/en/)

[www.who.int/vaccines-documents/](http://www.who.int/vaccines-documents/)

---

# Indicator 4:

## Access to expertise in epidemiology and statistics to advise on set up and analysis of trials

In the development of new vaccines against infectious diseases, a manufacturer must employ experts on the disease and its epidemiology and bio-statisticians to design the most appropriate trial for demonstrating the safety and efficacy of the vaccine. These experts will have very specific expertise and will spend years investigating the vaccine from product development through production, testing, supporting animal studies, and designing the sequential phases of clinical trials. The manufacturer spends great amounts of time and money in the vaccine development process to obtain approval for a vaccine that is commercially viable.

Even well-established NRAs may not necessarily have sufficient expertise in epidemiology or bio-statistics in-house to carry out an expert review of each vaccine application, especially in the case of new vaccines. A small or newly developing NRA may not have any staff with specific expertise in epidemiology and bio-statistics to be able to critically evaluate every vaccine that is submitted for trials or licensing.

The trial design and numbers of patients in the trial all need to be well defined by the sponsor but the NRA must not just take this at face value and approve a trial because all the elements required in the dossier are present. Experts in the disease, epidemiology, as well as diagnostics of the disease, vaccinology, immunology, and biostatistics are needed to review both the design and statistical aspects of the studies.

Most NRAs will need to contract experts in the disease being studied, experts in vaccines trial design and in biostatistics to: (a) advise on proposed clinical trials that have been submitted for approval in the country, (b) review and evaluate trials performed in the country at each phase to authorize the next phase, and (c) evaluate the data and claims of clinical study reports of completed clinical trials, domestic or foreign, in applications for market authorization. The NRA may need different experts for different vaccines, especially in epidemiology. A bio-statistician, however, should be able to assess if the statistical plan and methods are appropriate for the proposed vaccine study design. The statistical plan should include details of how the collected trial data will eventually be analysed.

Apart from experts in trial design and biostatistics, the NRA may also require experts to advise on database design to capture trial data and on management of data. A well-designed trial could be ruined without a carefully designed database and data management plans.

---

However, each NRA should have at least a basic level of understanding of these topics so as to be able to appropriately choose their experts and to understand and discuss details of the reports prepared by them. When outside experts are contracted to act as reviewers, this does not absolve the NRA of the responsibility for making the final informed decision on the acceptability of the application data and information. What is needed is a collaborative effort between the experts and the NRA.

When an application is received, the NRA should do a preliminary screening of the incoming documents (see WHO *Training manual: licensing, lot release, laboratory access* (WHO/V&B/01.16)). For the clinical sections this will include checking the basic contents of the protocol or study reports to determine if the required information has been submitted and is in the correct format (see section 2). The NRA would then recruit the appropriate expert(s), preferably from a clinical advisory committee of experts, plan how the confidential data in the report will be transmitted to the expert reviewer, agree on the review timeframe, and plan the meetings to discuss the experts' findings.

Before recruiting outside researchers or clinicians as expert reviewers, the NRA should confirm that all information remains confidential by signing a confidentiality agreement (see example in WHO/VSQ/97.06). The NRA should also ascertain that potential experts have no connections with the manufacturer of the vaccine or a competing manufacturer or vaccine that could be considered a real or perceived conflict of interest.

It is important that the expert is given guidance on the evaluation to be done. The NRA should provide a framework of the information needed from the expert – checklist of important items to be assessed and the conclusions to be made), and provide the expert with a summary of the vaccine quality and the results of pre-clinical studies from the review of the other parts of the dossier, as well as any literature on the vaccine or disease that was submitted with the application. In cases where more than one expert is evaluating different parts of the dossier (e.g. clinical results or statistics), the NRA should hold interim meetings with all the experts for them to discuss and relate their findings as they review the individual sections. The NRA should be present at all these meetings.

To ensure that NRA staff can perform these activities adequately, the NRA should obtain general literature on the subject of epidemiology of vaccine-preventable infectious diseases and biostatistics to be available for reference. The NRA staff involved with clinical studies and reports should become familiar with the terminology of various types of trials as well as, when appropriate, on population estimates and basic bio-statistics.

For proposed trial designs or clinical study report analyses for specific vaccines, publications on clinical trials of the same or similar vaccines can be consulted for information on specific procedures for these diseases. Generally, in clinical study reports the manufacturer/sponsor of the clinical trials is required to submit relevant publications and a scientific rationale for their choice of trial design. The NRA or their experts should review these in conjunction with the clinical proposals and data analyses.

There are several different trial designs that can be used to study a vaccine at different stages of development (see bibliography No. 51 and 67) (also see glossary for definitions):

Study types	Situation
Pharmacological studies (Phase I-II) Pharmacokinetic studies	Kinetic properties not normally needed except for: <ul style="list-style-type: none"> <li>• Oral vaccines</li> <li>• Novel adjuvants or excipients</li> </ul>
Pharmacological studies (Phase I-II) Pharmacodynamic studies	Characteristics of the immune response Immunological interference in combined vaccines Immunological interference between new vaccines and other vaccines Dose response
Immunogenicity studies (Phase I-III)	Nature of the immune response and correlation with efficacy
Pivotal efficacy studies (Phase II-III)	Randomized controlled trials (RCT) to establish efficacy Community-based prospective studies Pre-exposure studies
Experimental studies (Phase III)	Choice of study depends on indication, strategy and type of prophylaxis Use of appropriate controls, placebo or active comparator Choice of endpoint, disease incidence or immunological surrogate marker values
Secondary attack rate studies	Infections with high secondary attack rate and outbreaks Do not provide conclusive information on efficacy
Other studies (Phase III-IV) Case control studies	Retrospective study Use when prospective controlled trials not feasible Provide supportive data for efficacy
Other studies (Phase III-IV) Observational cohort studies	Retrospective or prospective studies Use when randomized controlled trials not ethically justified Provide effectiveness data
Other studies (Phase III-IV) Bridging studies	Use to support: <ul style="list-style-type: none"> <li>• a different immunization schedule</li> <li>• ethnic differences in target population</li> <li>• safety concerns in new target population</li> </ul>

The design chosen by the manufacturer/sponsor and the numbers of subjects will be dependent on the type of vaccine, the disease, the prevalence in the population and the infectiousness of the disease. Several publications on various types of trials are found in section C below.

When assessing applications for a trial of a vaccine for which there is existing information, the NRA may only need limited advice from outside experts. This could be for a changed or modified vaccine; for an existing vaccine manufactured by a new method or by a different manufacturer; or for a combined vaccine. The epidemiology of the disease would be well understood, the safety profile of the existing vaccine and the statistical requirements could also be known. The clinical trial requirements will depend on the situation. Full phase 1-3 trials could be needed if a new and different adjuvant has been added to a vaccine; or limited bridging studies could be required to show comparable immunogenicity in a new or different target population. Similarly the application could be for a vaccine studied in early trial stages which have already been reviewed by the NRA and for which a later stage of trials is now proposed. In such cases, those expert epidemiologists and statisticians who were consulted on the original evaluations should be requested to evaluate the results of the new trials and reports.

---

For the initial (phase 1) study of a new vaccine in country, or a marketing application for a new vaccine for which clinical studies were performed outside the country, the NRA may need in-depth reviews by experts. For a completely new vaccine for a disease not previously evaluated by the NRA, it will be essential to involve experts on the disease – possibly from an existing national disease surveillance programme or diagnostic laboratory – to advise the NRA on the appropriateness of proposed trials, and statisticians to advise on the statistical methods and the adequacy of the number of subjects proposed to be enrolled.

## **B. Practical approaches**

1. Prepare a training session for staff involved in the evaluation of clinical data in applications on the general principles of estimations of sample size, type 1 and type 2 errors, and power calculations, to give them a general understanding of the elements that will be submitted in the proposals for clinical trials and that will be discussed by the expert reviewers in their assessments. A good place to start is with an easily understood basic explanation provided (although not for vaccines) on an online web site: Medical Statistic Online Help: Sample size and power for clinical trials. Oxford/ Radcliffe National Health Service, UK. Nov 29, 2001 ([www.oxfordradcliffe.nhs.uk](http://www.oxfordradcliffe.nhs.uk))”.
2. Provide each expert with a list of the information the NRA wishes to be covered and of the type of conclusions the NRA wants in the report.
3. Prepare a checklist for the review of a clinical protocol and of the clinical study report.
4. Using the ICH guidelines E8, E9 and E10 (see C below) on clinical trial design, prepare a list of questions and steps for the experts to answer and/or consider regarding the study:
  - is the protocol included? CRFs?
  - prepare a succinct summary of the study protocol;
  - were there any amendments to the protocol?
  - explain the changes for each amendment; how did they affect the study?
  - if the protocol was not previously evaluated by the NRA for authorization of clinical trials, was the protocol appropriate?
  - was the protocol followed? Including following any amendments?
  - how were patients identified who were enrolled after the amendment?
  - was there a provision for interim analysis included in the protocol?
  - are data described in the text and shown graphically in tables?
  - are the comparisons appropriate?
  - what were the inclusion and exclusion criteria? were they appropriate?
  - did the recruitment follow these criteria?
  - were there recorded deviations to the protocol?
  - other than recorded deviations, does the study report match the protocol?
  - for an efficacy trial, was the primary endpoint designated prior to trial initiation? If not, was the change made prior to study unblinding?
  - were the analyses appropriate? Did they match the proposed analyses at trial approval?

- 
- did the data on safety support the sponsors' claims?
  - did the data on efficacy support the sponsors' claims?
  - are any additional trials or repeat trials necessary?
5. Does the IB for phase 1 trials accurately summarize the quality and pre-clinical safety and efficacy studies? For later phase trials, the expert reviewer should assess the clinical sections and adverse reactions sections of the IB for accuracy.

### **C. Resource materials**

The following list is long, but it gives many options to the to obtain background information on epidemiology, biostatistics, vaccine trial design, and some general texts.

#### ***US FDA documents (CBER)***

*Clinical studies section of labeling for prescription drugs and biologics – content and format – draft guidance for industry: 7/9/2001*

*Concerning demonstration of comparability of human biological products, including therapeutic biotechnology-derived products - FDA Guidance: 4/1996*

*Content and format of the adverse reactions section of labeling for human prescription drugs and biologics – draft guidance for industry: 6/21/2000*

*Evaluation of combination vaccines for preventable diseases: production, testing and clinical studies – guidance for industry: 4/10/1997*

*General considerations for pediatric pharmacokinetic studies for drugs and biological products – (12 pages) – draft guidance for industry: 11/30/1998*

*Plasmid DNA vaccines for preventive infectious disease indications. (Points to consider): –12/27/1996*

*Providing clinical evidence of effectiveness for human drugs and biological products – guidance for industry: 5/15/1998*

#### ***ICH documents***

##### **Efficacy topics**

*E1: The extent of population exposure to assess clinical safety:*

*E3: Structure and content of clinical study reports*

*E4: Dose response information to support drug registration.*

*E5: Ethnic factors in the acceptability of foreign data.*

*E8: Clinical trial design: general considerations.*

*E9: Clinical trial design: statistical principles for clinical trials.*

*E10: Clinical trial design: choice of control group.*

*E11: Clinical investigation of medicinal products in the pediatric population.*

---

## Multidisciplinary topics

*M1: Medical terminology (MedDRA)*

## *European Union documents*

*EU: Causality classification in the European Community (Directive III/3445/91).*

*EU: The rules governing medicinal products in the European Union*

Vol. 3: Guidelines.

Vol. 3C: Efficacy. Clinical guidelines (general and therapeutic class)

Vol. 9: Pharmacovigilance

CPMP/EWP/463/97 Note for guidance on clinical evaluation of new vaccines

*CPMP/EWP/462/95 Note for guidance on clinical investigation of medicinal products in children (CPMP adopted March 97)*

*CPMP/BWP/6622/02 Notice for guidance on requirements for the evaluation of new adjuvants in vaccines (Concept paper).*

*CPMP/PhVWP/108/99: Notice to marketing authorization holders. Pharmacovigilance guidelines. Draft version, January 1999.*

*CPMP/BWP/2490/00 Note for Guidance on cell culture inactivated influenza vaccines (Adopted by CPMP January 2002) – Annex to note for guidance on harmonisation of requirements for influenza vaccines CPMP/BWP/214/96*

*CPMP/BWP/477/97 Note for guidance on pharmaceutical and biological aspects of combined vaccines, (CPMP adopted Jul. 98).*

*CPMP/BWP/214/96 Note for guidance on harmonisation of requirements for influenza vaccines (CPMP adopted March 97)*

*CPMP/BWP/2289/01 Points to consider on the development of live attenuated influenza vaccines (Released for Consultation, Sept. 01)*

## **WHO and CIOMS (Council of International Organizations of Medical Sciences) documents**

*International reporting of adverse drug reactions. Final report of the CIOMS Working group. Geneva, CIOMS, 1990.*

*Effect of vaccine formulation and other factors on the immunogenicity of oral poliovirus vaccine: results of a randomised trial in Brazil and the Gambia. Geneva, World Health Organization, 199. (document WHO/EPI)*

*Guidelines for the evaluation of dengue vaccines in populations exposed to natural infection. Geneva, World Health Organization, 2001 (document WHO TDR/IVR/DEN/01).*

A guideline for national health authorities and researchers for planning and designing protocols and making decisions about early clinical trials and field trials of vaccines against dengue virus.

---

*Guidelines for the evaluation of Plasmodium falciparum vaccines in the population exposed to natural infection.* Geneva, World Health Organization, 1997 (document WHO/TDR/VAC/97).

A guideline for national health authorities and researchers for planning and designing protocols and making decisions about early clinical trials and field trials of vaccines against malaria.

*Guidelines on Clinical Evaluation of Vaccines: Regulatory Considerations. Annex 1.* Geneva, World Health Organization, WHO TRS (in press)

This draft (soon to be published) document reviews all the regulatory documents available and provides a complete background on clinical trials, specifically for vaccines. It is the background document for this manual.

*Informal Consultation of experts on national regulation of vaccines.* Geneva, World Health Organization, 1999. (document WHO/V&B/99.08).

One session of this meeting discussed the available guidelines for planning and performing clinical studies and for assessing the resulting data. It concluded that a “points to consider” type document should be prepared (see WHO/V&B/99.09)

*Review of existing documents on planning, performance and assessment of clinical studies on vaccines.* Geneva, World Health Organization, 1999 (document WHO/V&B/99.09).

A review of the documents available before 1999 that are specific to vaccine clinical studies.

WHO recommended surveillance standards. Geneva, World Health Organization, 1997. (document WHO/EMC/DIS/97.1).

This manual is a reference for key elements and contacts at WHO for 50 communicable diseases in current WHO disease control programmes. An information sheet for each of the 50 diseases includes the recommended case definition, types of surveillance, data elements and references.

*Protocols for the evaluation of epidemiological surveillance systems.* Geneva, World Health Organization, 1997. (document WHO/EMC/DIS/97.2)

A tool for assessing an existing surveillance system and identifying areas that can be improved.

*Vaccine trial registry directory.* Geneva: World Health Organization, 1999 (document WHO/V&B/00.07)

List of all vaccine trials registered at WHO to 1999.

---

### ***Dictionaries and textbooks***

Bland, Martin. *An introduction to Medical Statistics*. Third edition, Aug 2000 Oxford University Press Inc. NY.

Griffin JP, O'Grady J, D'Arcy PF, eds. *The textbook of pharmaceutical medicine*. Belfast, United Kingdom. The Queen's University of Belfast, 1998.

Horne AD. *Statistics, use in immunology*. In *Encyclopaedia of Immunology*. London: Academic Press; 1998.

Last JM, ed. *A dictionary of epidemiology*. Third Edition ed. Oxford: Oxford University Press, 1995.

Laurence D, Carpenter J. *A dictionary of pharmacology and clinical drug evaluation*. London: UCL Press Ltd., 1994.

Mann RD, Rawlins MD, Auty RM, eds. *Textbook of pharmaceutical medicine*. Carnforth: The Parthenon Publishing Group Ltd, 1993.

*Medical Statistic Online Help: Sample size and power for clinical trials*. Oxford/Radcliffe National Health Service, UK. Nov 29, 2001 ([www.oxfordradcliffe.nhs.uk](http://www.oxfordradcliffe.nhs.uk))

This web site explains and gives examples and formulas for calculating the sample size needed for several types of clinical trial designs.

### ***Published journal articles and books***

Anderson RM, Donnelly CA, Gupta S. Vaccine design, evaluation and community based use for antigenically variable infectious agents. *Lancet* 1997, 350:1466–70.

Good short (4 page) article on general aspects of vaccine design, but mainly discussing the problems of developing vaccines against antigenically diverse pathogens.

Armitage, P, Berry G, Matthews JNS. *Statistical Methods in Medical Research*. Oxford Blackwell Science, Williston Vt.

The fourth edition of a textbook on all aspects of medical statistics with a chapter on clinical trials and one on statistical methods in epidemiology.

Aylward B, Kane M, Batson A, McNair R. A framework for the evaluation of vaccines for use in the expanded programme on immunization. *Vaccine* 1994,12;13:1155–9.

The paper looks at the importance of controlling the disease and the appropriateness of immunization as the primary control. The vaccine is then evaluated for safety and efficacy and for compatibility with current EPI antigens, and then for its impact on the existing EPI programme and delivery system and whether there is a guaranteed global supply.

---

Blackwelder WC. Sample size and power for prospective analysis of relative risk. *Stat Med* 1993, 15:12;691–698.

Gives three mathematical models for estimating relative risk in a placebo-controlled efficacy or equivalency trial, and the required sample size and power needed..

Blackwelder WC. Similarity/ equivalence trials for combination vaccines. *Annals of the New York Academy of Sciences*. 1995, 754:321–328

Combination vaccines need to be shown in clinical trials to be sufficiently similar to the individual components given separately. (i.e. we need to rule out superiority of the separate vaccines). This paper addresses the designs of such trials, covering estimation versus hypothesis testing, the choice of the clinical important difference to be ruled out, one sided and two sided confidence limits, and the type 1 and 2 error values.

Brown F et al. *Vaccine design*. Chichester: John Wiley & Sons Ltd., 1993. (James K, Morris A, eds. Molecular Medical Science Series.

A book on the design of synthetic peptide vaccines.

Brown F et al., eds. *Pertussis vaccine trials*. In Brown F, ed. *Developments in Biological Standardization*, Vol. 89. Basel: Karger, 1997

Chen RT, Orenstein WA. Epidemiologic methods in immunization programmes. *Epidemiology Review*. 1996,18;2:99–117.

A long article (14 pages, 173 references) discussing briefly the pre-licensure issues of vaccine trials, but mostly concentrating on the post-licensure activities on immunization programmes and vaccine surveillance systems (safety, serological, disease, coverage), outbreak and case study investigations, and calculations of vaccine efficacy and effectiveness.

Chow S, Liu J. *Design and analysis of clinical trials: concepts and methodologies*. In (Barnett V, Bradley RA, Fisher NI, eds. Wiley Series in Probability and Statistics. New York. John Wiley & Sons, Inc., 1998.

Clemens J et al. *Evaluating new vaccines for developing countries. Efficacy or effectiveness?* *Journal of the American Medical Association*, 1996, 275;5:390–7.

Discusses the differences between highly controlled efficacy trials under ideal conditions and large field trials of vaccine performance (effectiveness) that would be more similar to the ordinary conditions of a public health programme. Suggests a revised sequence of proceeding through the phases of clinical trials to determine the effectiveness of vaccines that may accelerate the entry of new vaccines into developing countries.

Davenport L. *Regulatory considerations in vaccine design*. In: Powell MF, Newman MJ, eds. *Vaccine design: the subunit and adjuvant approach*. New York: Plenum Press, 1995: 81–96.

---

Durham KL et al. Estimation of vaccine efficacy in the presence of waning: application to cholera vaccines. *American Journal of Epidemiology*, 1998, 147:948–59.

This article describes a non-parametric mathematical re-evaluation of data from a 4.5 year placebo controlled double blind clinical trial of cholera vaccine in Bangladesh. A subset of the participants who received the full course of vaccine or placebo was re-evaluated for vaccine efficacy using the method developed by the authors. This re-evaluation was developed to account for vaccine efficacy changes over time (waning).

Elwood M. *Critical appraisal of epidemiological studies and clinical trials*. (Second edition ed.) Oxford, England. Oxford University Press, 1998.

Ewell M. Comparing methods for calculating confidence intervals for vaccine efficacy. *Statistics in Medicine* 1996, 2379–92.

Based on a HIV vaccine intermediate trial, this highly mathematical paper looks at power calculations and the # expected infections to determine sample size. It includes a review of methods for constructing exact and large sample intervals for vaccine efficacy as a framework for comparison of their estimations.

Falk LA et al. *Testing and licensure of combination vaccines for the prevention of infectious diseases*. In: Combination vaccines: Development, clinical research and approval. RW Ellis, ed. Humana Press Inc. Totowa, NJ. Chapter 11, 1999, 233–48.

Short general review article on the manufacturing and controls on combination vaccines and with sections on clinical evaluation of safety, immunogenicity, and efficacy. Recommendations are made to include the simultaneous use of other vaccines in the immunization schedule if they will routinely be given at the same time. This is needed during the phase 2 and 3 trials to show acceptable immune responses to the combination vaccine under study and to the simultaneously administered licensed vaccines.

Fedson DS. Measuring protection: efficacy versus effectiveness. In Brown F, Plotkin S, eds. *Preclinical and clinical development of vaccines*. Basel, Karger, 1998, 95:195–201.

This article presents the advantages of prospective vaccine effectiveness trials, especially for upcoming vaccines to replace existing vaccines. Generally, effectiveness trials have been retrospective case-control or cohort studies which can require rigorous risk adjustment to ensure the comparability of the populations studied.

Folb P. In Grady JO, Joubert PH. *Handbook of phase I/II clinical drug trials*. CRC Publishers, 1997.

Giesecke J. *Modern infectious disease epidemiology*. Arnold, Oxford University Press. 1994. (1995 reprint).

A book on infectious disease epidemiology with chapters on case control studies, cohort studies, and the epidemiology of vaccination.

---

Goldenthal KL et al. Safety evaluation of vaccine adjuvants: national cooperative vaccine development meeting working group. *AIDS Research and Human Retroviruses*. 1993, 9: supplement 1: S47-S51

This is the report of a workshop that considered safety issues for adjuvants, requirements for preclinical toxicology studies, and any additional studies on investigational adjuvants that would be required to initiate clinical studies.

Halloran ME, Longini IM, Struchiner CJ. Design and interpretation of vaccine field studies. *Epidemiological Review*, 1999, 21:73–88.

In this article, the authors present a review of different measures of the effect of vaccination and vaccination programmes. They focus on field studies (phase III and IV) and consider various study designs for estimating the different measures of effect based on the choice of comparison groups, unit of observation, choice of parameter and amount of information about the transmission system required for estimation.

Halloran ME, Struchiner CJ. Causal inference of infectious diseases. *Epidemiology*, 1995;6:142–51

This article explains how clinical studies to show efficacy outcomes for a treatment for infectious diseases are complicated by the fact that not all subjects receiving the treatment are exposed to exactly the same effects. For instance, individuals may have different susceptibility to the disease, or may be exposed to a different level of infectiousness. These direct and indirect effects of differential exposure to infection are discussed.

Halloran ME, Struchiner CJ, Longini IM. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. *American Journal of Epidemiology*, 1997,146;10:789–803.

Similar discussions to Halloran et al 1999

Hayes RJ et al. Design and analysis issues in cluster-randomized trials of interventions against infectious diseases. *Statistical Methods in Medical Research*, 2000, 9:95–116.

A review article about clinical trials studied at the population level (where communities or large groupings of subjects (clusters) are randomized) to evaluate the effectiveness of interventions against infectious diseases, measured by infectious disease incidence or mortality. They discuss size of the cluster, matching, and direct and indirect effects of the intervention.

Horne AD et al. Analysis of studies to evaluate immune response to combination vaccines. *Clinical Infectious Diseases*, 2001, S4; S306-311.

Non-inferiority trials (to show one vaccine is at least as good as another) are usually held for new combination vaccines. The concept of non-inferiority is discussed as are the statistical challenges in evaluating these vaccines. Topics cover end points, hypotheses, analyses for comparing GMTs, and other important issues.

---

Plotkin S, Brown F, Hovav F, eds. In Brown F, ed. *Developments in Biological Standardization*; vol. 95. Preclinical and clinical development of vaccines. Basel: Karger, 1998.

Pocock SJ. *Clinical trials: a practical approach*. Chichester: John Wiley & Sons Ltd., 1995.

A 15-chapter book (257 pages) covering all aspects of clinical trials: rationale, history, planning, randomization, blinding; placebos; ethical issues; crossover trials; trial size; monitoring trial progress; forms and data management; protocol deviations; data analysis and interpretation.

Horne AD, Lachenbruch PA, Goldenthal KL. Intent-to-treat analysis and preventive vaccine efficacy. *Vaccine* 2000, 19:319–6.

Intent to treat (ITT) is an analysis of all the data from subjects entered into a trial, whether they finished the treatment or not. “As per protocol” is an analysis of those subjects completing the protocol. For therapeutic trials and trials for therapeutic vaccine (eg HIV) the ITT design has been used. This article discusses the difference of these two approaches to evaluate preventive vaccine efficacy trial data. Data from published trials and from a simple mathematical model are presented. The authors show that the two approaches are similar for efficacy of preventive vaccines when compliance and efficacy are high, but can be very different if compliance is low.

Horne AD. The statistical analysis of immunogenicity data in vaccine trials: a review of methodologies and issues. *Annals of the New York Academy of Sciences*.1995,754:329–46.

This paper reviews the variety of statistical techniques for analysing immunogenicity data, and comments on the appropriateness of the methods. Both single treatment trials (where all subjects receive the vaccine) and comparative trials (two or more treatment groups - placebo, different lots of vaccine, or alternative vaccine) are discussed. Suggestions are made that authors should be more specific in detailing the statistical methods used and the assumptions made, and recommends the inclusion of confidence intervals.

Jefferson T. Vaccination and its adverse effects: real or perceived. *British Medical Journal*, 1998, 317:159–60.

A brief article discusses the problems of recent vaccine scares on unproven links between vaccines and rare adverse reactions, especially other long-term diseases.

Jones B et al. Trials to assess equivalence: the importance of rigorous methods. *British Medical Journal*, 1996, 313:36–9.

In this article (not specifically about vaccines), the authors present a detailed discussion of equivalence trials (trials to show a new product equivalent to and existing treatment). They discuss why the trials need to be larger than placebo-controlled trials, and why they are different from “detection of difference” trials. They present a minimal set of criteria against which to judge reports of clinical trials where equivalence of two treatments is claimed. It is recommended that confidence intervals be determined and that analysis of both ITT and “as per protocol” data be made. Examples of sample size calculations and assessment of equivalence are given.

---

Lachenbruch PA. Sensitivity, specificity, and vaccine efficacy. *Controlled Clinical Trials* 1998; 19:569-74.

Lemeshow S et al. *Adequacy of sample size in health studies*. Chichester: John Wiley & Sons Ltd., 1990.

This WHO sponsored book has two parts. The first (application sections) gives solutions to typical problems and tables of minimal sample sizes for various survey and study designs, with the corresponding formulae. The second part (theoretical section) gives a concise explanation of the theory behind the process of determining sample size.

McFadden E. Management of data in clinical trials. New York: John Wiley & Sons, Inc., 1998. (Barnett V, Bradley RA, Fisher NI, eds. Wiley Series in Probability and Statistics; 62.

Meinert CL. *Clinical trials: design, conduct, and analysis*. New York: Oxford University Press, 1986. (Lilienfeld AM, ed. Monographs in Epidemiology and Biostatistics; vol. 8).

Nossal GJV. Host immunobiology and vaccine development. *Lancet* 1997; 350:1316-19.

This article discusses the advance of immunobiology and the scientific development of new vaccines. Although the author concentrates on host immunobiology, he concludes also that preclinical and clinical studies must keep pace with the development of new vaccines (DNA vaccines, recombinant vaccines, new adjuvants, microencapsulation, etc) so as not to delay the use of possibly superior vaccines.

Olin P et al. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. *Lancet* 1997;350:1569-77.

Orenstein WA et al. Field evaluation of vaccine efficacy. *Bulletin of the World Health Organization*. 1985,63;6:1055-68.

An older paper that describes the epidemiological techniques available for measuring vaccine efficacy and recommends a practical approach to their use. Many of the examples relate to measles vaccine which was tested by the methods described but the methods are also applicable to other vaccines. The main advantages and disadvantages of the techniques are discussed and also presented in a summary table of the 6 techniques (screening; outbreak investigations; secondary attack rates in families; secondary attack rates in clusters; vaccine efficacy using coverage in endemic areas; and case controlled studies).

Piantadosi S. *Clinical trials: a methodologic perspective*. In Barnett V, Bradley RA, Fisher NI, eds. Wiley series in probability and statistics. New York: John Wiley & Sons, 1997.

---

Powell MF, Newman MJ, Burdmann JR, eds. *Vaccine design: the subunit and adjuvant approach*. New York: Plenum Press, 1995. (Borchardt RT, ed. *Pharmaceutical Biotechnology*; vol. 6).

This 957 page, 41-chapter book contains in-depth articles about novel adjuvants and new vaccine delivery systems.

Reed GF, Meade BD, Steinhoff MC. The reverse cumulative distribution plot: a graphic method for exploratory analysis of antibody data. *Pediatrics*, 1995, 96:600–3.

The authors explain the Reverse Cumulative Distribution curve (RCD) method for visually plotting the complete distribution of the antibody data from comparative clinical trials of vaccines. They state that the curves give a better comparison of data sets as compared to the usual numerical summaries, statistical means and medians, or histograms.

Rodrigues LC, Smith PG. The use of case control approach in vaccine evaluation: Efficacy and adverse effects. *Epidemiologic Reviews*, 21: 56–72, 1999.

In this paper, the use of case control studies to measure vaccine efficacy in an area where the vaccine is in use is described, examples given, and compared to other clinical study designs. Case control studies are observational studies where the proportion of exposed cases and control subjects are compared. Cases = subjects who have the disease the vaccine is designed to prevent. Controls = matched cross section of population where the cases occurred. Vaccination histories are obtained from the cases and control groups and information is collected to avoid bias. The case control approach is also discussed for the evaluation of adverse events following immunization.

Senn S. *Statistical issues in drug development*. In Barnett V, ed. *Statistics in practice*. Chichester: John Wiley & Sons, 1997.

Siber GR. Methods for estimating serological correlates of protection. *Development of Biological. Standardization*. Basel, Karger, 1997, Vol. 89, pp 283-296.

Smith PG, Morrow RH, eds. *Field trials of health interventions in developing countries: a toolbox*. World Health Organization, 2nd ed., 1996.

This book covers much of the same material as others on study design, size, ethical considerations, randomization, data recording and methods of analysis. However, it also provides information on other aspects of field trials: community involvement, census and mapping, questionnaires, qualitative research in field trials, field organization, field laboratory methods, and in preparing grant applications to carry out the studies.

---

Smith PG, Rodrigues LC, Fine PEM. Assessment of the protective efficacy of vaccines against common diseases using case control and cohort studies. *International Journal of Epidemiology*, 1984,13:87–93.

When evidence that vaccines in use may be protective, it is difficult to justify ethically to carry out randomized controlled trials. This older paper discusses alternative approaches of cohort studies and case control studies for measuring vaccine efficacy. The authors also present two models of the results of immunization: 1) instantaneous reduction of the disease rate, or 2) making a constant proportion of individuals completely immune. They look at the effect these models have on vaccine efficacy as determined by cohort studies or case control studies.

Taylor B. et al. Autism and measles, mumps and rubella vaccine: no epidemiological evidence for a causal relationship. *Lancet*, 1999, 353: 2026–9.

An epidemiological study to investigate the postulated link between vaccination with MMR and autism. The results of this case series analysis study of 489 autistic children and controls from the same area of the UK showed no causal link, and supported earlier studies in Sweden

Vaughan JP, Morrow RH, eds. *Manual of epidemiology for district health management*. Geneva, World Health Organization,1993.

Williams et al (eds) Combined Vaccines and Simultaneous Administration. Current Issues and Perspectives. *Annals of the New York Academy of Sciences* , 1995, 754.

Part V and VI of this book present 20 papers on clinical trial design and evaluation of combined vaccine.

### ***Web sites for downloading documents***

US FDA: All documents listed are available electronically from:

CFR: Code of Federal Regulations: [www.access.gpo.gov/nara/cfr/](http://www.access.gpo.gov/nara/cfr/)

CBER: Center for Biologics Evaluation and Research:  
[www.fda.gov/cber/ guidelines.htm](http://www.fda.gov/cber/guidelines.htm)

BIMO: Bioresearch Monitoring: [www.fda.gov/ora/BIMO/](http://www.fda.gov/ora/BIMO/)

ICH: All documents listed are available electronically from:

[www.ifpma.org/ich5.html](http://www.ifpma.org/ich5.html)

European Union: All documents listed are available electronically from:

CPMP: Committee for Proprietary Medicinal Products:  
[www.emea.eu.int/htms/ human/](http://www.emea.eu.int/htms/human/)

Rules Governing Medicinal Products in the European Union:  
<http://pharmacos.eudra.org/F2/eudralex/index.htm>

WHO: Some publications are available electronically.

[www.who.int/pub/en/](http://www.who.int/pub/en/)

[www.who.int/vaccines-documents/](http://www.who.int/vaccines-documents/)

---

# Indicator 5:

## Access to experts in the product being tested (including experts in test methods)

### A. Background

There are two types of products involved in clinical trials: the vaccine product to be administered and the samples (eg blood, serum, urine, stool, etc.) that are collected from subjects during the clinical trial and tested to determine either safety parameters or efficacy endpoints.

Although for vaccines generally, safety parameters are usually local and systemic reactions, some clinical studies involve blood sampling depending on the expected reactions of the product. Assessing immunogenicity involves taking blood or serum samples, and assessing efficacy may involve testing of the stools to measure virus shedding.

#### 1. *Trial vaccine product*

For the product administered, it is clearly important, as discussed under indicator #1, that the vaccine product be produced according to the required standards for the phase of trial being carried out. The information and data should be provided that prove the quality of the vaccine in the application for clinical trial approval.

If a placebo is to be used in the trial it, too, must be manufactured according to the same quality standards, and it should be ascertained that the vials were properly filled and tested. The placebo and vaccine vials should be coded (usually by the vaccine manufacturer) and, if the trial is a double blind trial, the placebo should be indistinguishable from the test vaccine.

If a comparator product (the same vaccine from a different manufacturer or the same vaccine with different characteristics) is being used in the trial, it will be necessary to know whether it is licensed in the country where the trial is held and can be administered according to the approved instructions, or whether there is a need to approve the comparator vaccine. This can be somewhat more complicated if the study is a multi-country trial and the comparator products are not identical. Trials of combination vaccines usually compare the combined vaccine against the individual vaccine components and all the individual comparator products must be approved for the trial. In some cases, the comparator vaccine itself is a licensed combinations vaccine.

Another important characteristic to evaluate is the stability of the vaccine(s), and placebo if relevant.

---

Also to be considered are the shipping, distribution, storage of the product, on its way to the clinical trial sites, as well as the storage and handling by the clinical investigators and those administering the vaccine. It is important to ascertain that every lot used in the trial met all specifications and that all product vials (vaccine, comparator vaccine, placebo) were handled appropriately.

The results of potency or immunogenicity testing of each lot of the vaccine used in the clinical trials, and the cold chain monitoring devices for recording temperature during shipping and distribution, should be available for review by competent NRA staff or agents.

Someone with expertise in the vaccine or the type of vaccine to be administered, if such expertise is not available in the NRA, should be contacted to advise on whether the storage of the vaccine is appropriate.

## **2. *Patient samples (samples from each participant in the trial).***

The results of testing of patient samples collected during the trial are the basic data that will be used to make the final judgements on the safety, immunogenicity and, in some cases, efficacy of the vaccine. It is important, especially in multi-centre trials, to review carefully to ensure that patient samples have been collected according to the approved schedule, that any requirement for sample preparation or extraction have been done uniformly, and that tests on the samples have been done according to the approved methods by a qualified laboratory using validated methods and calibrated equipment.

If a central laboratory has not been used for a clinical trial (i.e. all samples from all sites sent to a common laboratory for testing) then there must be evidence that the tests used are equivalent and the data can be evaluated together.

For proposed trials or completed trials, the following are important:

1. Review of application for a clinical trial:
  - a) The protocol clearly indicates the samples to be taken, the schedule of sampling, the acceptable timeframe for each sample, the methods for taking each type of sample, the containers to be used, the labelling of the samples (information to be affixed, coding if any), the preparation of the sample (if any), the storage conditions, and the time limits for testing. The protocol also includes an SOP for the safe collection, transport and processing of clinical trial specimens (samples) and appropriate disposal methods.
  - b) Normal laboratory values are indicated.
  - c) Sufficient detail should also be provided about each clinical parameter to be measured on the patient, eg temperature (oral, axillary, rectal, duration, thermometer type), vital signs, height, weight, blood chemistry etc.).
  - d) The methods for testing patient samples are specified.
  - e) Determine if a central laboratory or individual site laboratories will be testing the product and if efforts are made to ensure the results are equivalent. Specify which tests are performed by which laboratory.

- 
- f) Give the credentials or accreditation of the laboratory(ies) chosen to perform the tests.
  - g) If different test methods are used at different sites, determine how the results will be compared.
  - h) Ensure that the Case Report Forms (CRF) that the clinician or nurse will fill out clearly indicate the instructions for sample taking, storage, etc.
  - i) Review the tests proposed for the patient samples and ensure that these are appropriate for the parameters to be measured.
  - j) Access experts in the disease and in the types of samples taken to ensure that the test methods are appropriate to the patient sample to be taken.
  - k) In comparative trials, and depending on the trial design, the tests on patient samples must have sufficient sensitivity to distinguish superiority and non-inferiority of the vaccines being prepared.
  - l) For laboratory analysis, quality control and quality assurance systems that have been set up to validate test results should be reviewed.
2. Review of completed clinical trial study reports (either in relation to a completed phase 1 or 2 trial in an application for the next phase of clinical trials or in an application for marketing authorization).
- a) The study report shows that the study followed the protocol or any amendments and discusses any deviations in obtaining or testing of samples.
  - b) The records show that the labelling of the sample, the sample preparation, the storage conditions, and time limits for testing complied with the protocol.
  - c) The normal laboratory values are indicated and any abnormal values in patients are highlighted. (Details of each clinical parameter to be measured on the patient should also be provided, e.g. temperature (oral, axillary, rectal, duration, type of thermometer) vital signs, height, weight etc.).
  - d) The laboratories doing the testing are specified for each patient.
  - e) If different test methods were used at different sites, an explanation is provided of how the results are compared.
  - f) Case Report Form (CRF) records include all the data on sample taking, storage, etc.
  - g) Review the tests proposed for the patient samples and ensure these are appropriate for the parameters to be measured.
  - h) Access experts in the disease and in the types of samples taken to ensure the methods are appropriate to the patient sample to be taken.
  - i) In comparative trials, and depending on the trial design, the tests on patient samples must have sufficient sensitivity to distinguish superiority and non-inferiority of the vaccines being compared.
  - j) For laboratory analysis, quality control and quality assurance systems that have been set up to validate test results should be reviewed.

---

## B. Practical approaches

### *Vaccine on trial*

1. Prepare a confidential trial registry of each vaccine proposed for, or presently in, clinical trials. Include the manufacturer, sponsor, investigator, study site(s), a list of the final quality control release tests, shelf life, storage conditions, shipping conditions, handling precautions, and preparation (eg reconstitution, mixing), the codes for the trials vaccine if the trial is blinded, a copy of the investigational label, and a copy of the label of any comparator product.
2. Upgrade the registry with any additional product data or amendments to the clinical study protocol that affect the vaccine or comparator product such as extended shelf life data, or changes in the formulation that affect the tests, handling, storage etc.
3. Do the stability data support the shelf life? Is the shelf life long enough to allow shipping, distribution and administration of the vaccine according to the proposed schedules?
4. Contact the national control laboratory or contract laboratory used by the NRA to determine if the tests for the vaccine can be performed if needed. Ensure the laboratory maintains confidentiality of information and data. The NRA should also ensure that outside laboratories have no conflict of interest through an independent relationship with the sponsor/manufacturer or with a competitor's vaccine.
5. Review the clinical study protocol and Investigator's Brochure during the authorization evaluation to ensure that vaccine storage, handling and administration are adequately described for the investigator and clinical study staff. If the product needs specific preparation techniques, ensure that an SOP with adequate instructions is included in the protocol.
6. Prepare a checklist for the review of the proposed labels in the application for clinical trial. The NRA must ensure that the vaccine and any comparator product are properly labelled with the study protocol number, vaccine name or code (if blinded), name of investigator if required, and "for Investigational Use only" or "to be Used by Qualified Investigators only" depending on the national requirements.
7. Review the Case Report Forms (CRFs) proposed for the trial to ensure that the product data to be recorded will adequately identify the individual lot or code numbers, give instructions for preparing the vaccine, vaccine combinations, or the comparator, and include the date for each administration to each subject in the trial.
8. Prepare a checklist for the eventuality that an inspection of the product at the clinical study sites may need to be made. The NRA should be able to determine from the study records and the storage facilities if the vaccine is appropriately stored and handled and used within the accepted expiry date. Use codes only for blinded trials and do not perform an inspection of the study site with any information that would jeopardize the blinding of the trial.
9. Obtain the WHO *Manual of laboratory methods – for testing vaccines used in the WHO Expanded Programme on Immunization* (WHO/VSQ/97.04) and the WHO TRS volumes that include test requirements for the vaccine under review.

---

### *Patient samples*

1. For each vaccine, prepare a list of the samples proposed to be taken for testing. Indicate the sample timing and base level samples.
2. Contact local experts on diagnostics of infectious diseases and on clinical samples (blood, serum or plasma preparation, urine, stool samples, etc) to confirm correct handling and storage of each type of sample.
3. Ensure that the instructions in the clinical study protocol and Investigator's Brochure provide adequate information to enable the investigator and study staff to take, store and label the samples correctly.
4. Review the CRFs in the application for patient sampling and sample handling to ensure the required data will be recorded.
5. Check the clinical study protocol for the plans for testing the samples. Will the samples be tested at one central laboratory, or will they be tested at the laboratories at each study site?
6. If the latter is the case, look for instructions for evaluating the combined data. Are normal values for any general clinical tests provided?
7. Do the patient samples need preparation or treatment before testing? Are there records of the preparation? Are there adequate instructions to ensure they will be prepared in the same way at each study site?
8. Are the tests performed in the same way at each site? Does the method specify the testing equipment to be used? If yes, is there an indication of how the results will be compared?
9. Are there adequate SOP instructions for the measurement of the specific antibodies?
10. Is the sponsor required to provide equipment, supplies, reagents or references for the testing of patient samples? Are there instructions for shipping or handling of reference materials? Are they coded properly if the study is blinded?
11. Are laboratories testing patient samples required to sign confidentiality agreements?
12. The NRA should check that the laboratories chosen to perform the testing of patient samples have no conflict of interest through an independent relationship with the sponsor/manufacturer or with a competitor's vaccine.
13. How are the patient samples shipped to the testing laboratory(ies)? Are there adequate instructions for storing and handling?
14. Determine if the testing of the samples is as stated in the consent form. If samples will be tested for other parameters, has the additional consent been obtained?

---

## C. Resource materials

### *US FDA documents*

*Investigational new drug application: code of Federal Regulations (CFR) Chapter 21: Food and drug regulations Part 312.*

These regulations identify the requirements for an investigational New Drug application, the phases of trials, application contents and format, amendments, safety reports, annual reports, administrative actions, responsibilities of the sponsor and investigators, and miscellaneous items such as import/export requirements and reference to FDA guidelines.

*Biologics: Chapter 21 subchapter F, Parts 600–680*

*Part 600: Biological products, general*

*Part 601: Licensing*

*Part 610: General biological products*

*Part 620: Additional standards for bacterial products*

*Part 630: Additional standards for viral vaccines*

*Analytical procedures and methods validation - chemistry, manufacturing, and controls documentation – draft guidance for industry: 8/30/2000 (CBER)*

*Content and format of chemistry, manufacturing and controls information and establishment description information for a vaccine or related product – guidance for industry: 1/5/1999 (CBER)*

*Content and format of investigational new drug applications (INDs) for Phase 1 studies of drugs, including well-characterized, therapeutic, biotechnology-derived products – guidance for industry: 11/1995 (CBER)*

*INDs for phase 2 and 3 studies of drugs, including specified therapeutic biotechnology-derived products, chemistry manufacturing and controls content and format – draft guidance for industry: 4/20/1999 (CBER)*

*Submission of chemistry, manufacturing, and controls information for synthetic peptide substance – guidance for industry: 1/16/1998. (CBER)*

---

## **ICH documents**

### **Quality topics**

Q2A: *Text on validations of analytical procedures*

Q2B: *Methodology*

Q5A: *Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin – 9/24/1998*

Q5C: *Stability testing of biotechnological / biological products – 7/10/1996*

Q5D: *Derivation and characterization of cell substrates used for production of biotechnological /biological products – 9/21/1998*

Q6B: *Test procedures and acceptance criteria for biotechnological/biological products*

### **EU documents**

*EU: The rules governing medicinal products in the European Union*

Vol. 2: Notice to applicants

Vol. 2B: Presentation and content of the dossier

- Part II Concerning chemical, pharmaceutical and biological documentation

Vol. 2C: Regulatory guidelines (categories (new vs. variation) renewals, labelling packaging, product characteristics summary, classifications, forms)

Vol. 3: Guidelines

Vol. 3A: Quality and biotechnology

Vol. 4: Good manufacturing practices: basic requirements and 18 Annexes (annex 2: biological products, annex 13 investigational medicinal products)

*CPMP/QWP/848/96 (EMEA/CVMP/598/99) Note for Guidance on Process Validation* (CPMP/CVMP Adopted Feb. 01)

## **WHO documents**

*General requirements for the sterility of biological substances.* Geneva, World Health Organization. (revised 1973, WHO Technical Report Series No. 530, 1973; amendment 1995, WHO Technical Report Series No. 872,1998).

*Good manufacturing practice: supplementary guidelines for the manufacture of the investigational pharmaceutical products for clinical trials in humans. Annex 7.* Geneva, World Health Organization, 1996. (WHO Technical Report Series No. 863).

*Guidelines for assuring quality of DNA vaccines. Annex 3.* Geneva, World Health Organization, 1998. (WHO Technical Report Series No. 878).

*Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology. Annex 3.* Geneva, World Health Organization, 1991. (WHO Technical Report Series No. 814).

---

*Guidelines for national authorities on quality assurance for biological products. Annex 2.* Geneva, World Health Organization, 1992. (WHO Technical Report Series No. 822).

*Guidelines for the production and quality control of synthetic peptide vaccines. Annex 1.* Geneva, World Health Organization, 1999. (WHO Technical Report Series No. 889).

*Immunization in practice.* Geneva, 1998. Expanded Programme on Immunization. Geneva, World Health Organization, 1998. (document WHO/EPI/TRAM/98.01-11 REV.1)

A practical training and reference manual for health care workers who deliver immunization services for EPI diseases. Some relevant sections are: cold chain; registering clients; preparing vaccines; and giving immunizations.

*Recommendations and guidelines for biological substances used in medicine and other documents. Annex 3.* Geneva, World Health Organization, 2000. (WHO Technical Report Series No. 897).

*Recommendations for the production and control of Haemophilus influenzae type b conjugate vaccines. Annex 1.* Geneva, World Health Organization, 2000. (WHO Technical Report Series No. 897).

*Regulation of vaccines: building on existing drug regulatory authorities.* Geneva, World Health Organization, 1999. (document WHO/V&B/99.10).

*Report of a WHO Consultation on Medicinal and other Products in Relation to Human and Animal Transmissible Spongiform Encephalopathies.* Geneva, World Health Organization, 1997. (document WHO/EMC/ZOO/97.3).

*Requirements for poliomyelitis vaccine (oral) (Addendum 1998). Annex 2.* Geneva, World Health Organization, 1998. (WHO Technical Report Series No. 897).

*Requirements for the Use of Animal Cells as in vitro Substrates for the production of Biologicals. Annex 1.* Geneva, World Health Organization, 1998. (WHO Technical Report Series No. 878).

### ***Published journal articles and books***

Aylward B et al. A framework for the evaluation of vaccines for use in the expanded programme on immunization. *Vaccine*, 1994,12;13:1155–9.

The paper looks at the importance of controlling the disease and the appropriateness of immunization as the primary control. The vaccine is then evaluated for safety and efficacy and for compatibility with current EPI antigens, and for its impact on the existing EPI immunization programme and delivery system and whether there is a guaranteed global supply.

Davis GC, Riggin RM. Characterization and establishment of specifications for biopharmaceuticals. In: Brown F, Fernandez J, (eds). Development of specifications for biotechnology pharmaceutical products. Basel: Karger, 1997:49–54.

---

Falk LA et al. *Testing and licensure of combination vaccines for the prevention of infectious diseases*. In: *Combination vaccines: Development, clinical research and approval*. RW Ellis (ed.). Humana Press Inc. Totowa, NJ. Chapter 11, 233–48 1999.

Short general review article on the manufacturing and controls on combination vaccines, with sections on clinical evaluation of safety, immunogenicity, and efficacy. Recommendations are made to include the simultaneous use of other vaccines in the immunization schedule if they will routinely be given at the same time. This is needed during the phase 2 and 3 trials to show acceptable immune responses to the combination vaccine under study and to the simultaneously administered licensed vaccines.

Geigert J. Appropriate specifications at the IND stage. In: Brown F, Fernandez J, eds. *Development of specifications for biotechnology pharmaceutical products*. Basel: Karger, 1997:39-43

A short proposal on how to set an appropriate number of tests and specifications at various stages of product development throughout early clinical trials.

Griffiths E. Assuring the quality of vaccines: regulatory requirements for licensing and batch release. Chapter 20 in: *Methods in Molecular Medicine: Vaccine protocols*. Robinson A, Farrar G, Wiblin C, eds., Totowa, NJ: Humana Press, 1996: pp 269-288

Mainly a review of the control of production of vaccines that have WHO requirements published in the Technical Report Series, it discusses clinical trials in only very general terms.

Patterson S, Lin L, Elchico J, et al. Global regulatory considerations for unified assay specifications. In: Brown F, Fernandez J, eds. *Development of specifications for biotechnology pharmaceutical products*. Basel: Karger, 1997:45–8. *Developments in Biological Standardization*.

---

# Bibliography

(Note: Documents identified as “draft” are not yet official, but have useful and relevant information.)

## **USA Code of Federal Regulations (CFR) Chapter 21: Food and Drug Regulations**

1. Investigational new drug application: Part 312.
2. Current good manufacturing practice for finished pharmaceuticals: Part 211
3. Good Laboratory Practice: Part 58
4. Biologics: subchapter F, Parts 600-680  
Part 600: Biological products, general  
Part 601: Licensing  
Part 610: General biological products  
Part 620: Additional standards for bacterial products  
Part 630: Additional standards for viral vaccines
5. Protection of human subjects: Part 50
6. Institutional review boards: Part 56

## **USA FDA/CBER (Center for Biologics Evaluation and Research) Guidance, Guidelines and Points to Consider) (ICH documents adopted by the US are not listed here- see list of ICH documents)**

7. Analytical procedures and methods validation – chemistry, manufacturing, and controls documentation – draft guidance for industry: 8/30/2000
8. Changes to an approved application for specified biotechnology and specified synthetic biological products – guidance for industry - 7/24/1997
9. Changes to an approved application: biological products – guidance for industry - 7/24/1997
10. Clinical studies section of labeling for prescription drugs and biologics – content and format – draft guidance for industry: 7/9/2001
11. Concerning demonstration of comparability of human biological products, including therapeutic biotechnology-derived products – FDA guidance: 4/1996
12. Concerning use of pilot manufacturing facilities for the development and manufacturing of biological products – FDA guidance document: 7/11/1995
13. Considerations for reproductive toxicity studies for preventive vaccines for infectious disease indications – draft guidance for industry: 9/8/2000

- 
14. Content and format of chemistry, manufacturing and controls information and establishment description information for a vaccine or related product – guidance for industry: 1/5/1999
  15. Content and format of investigational new drug applications (INDs) for phase 1 studies of drugs, including well-characterized, therapeutic, biotechnology-derived products - guidance for industry: 11/1995
  16. Content and format of the adverse reactions section of labeling for human prescription drugs and biologics - draft guidance for industry: 6/21/2000
  17. Evaluation of combination vaccines for preventable diseases: production, testing and clinical studies - guidance for industry for the: 4/10/1997
  18. Financial disclosure by clinical investigators - guidance for industry: 3/28/2001
  19. General considerations for pediatric pharmacokinetic studies for drugs and biological products - (12 pages) - Draft Guidance for Industry: 11/30/1998
  20. How to complete the vaccine adverse reporting system form (VAERS-1) - guidance for industry: 9/8/1998
  21. INDs for phase 2 and 3 studies of drugs, including specified therapeutic biotechnology-derived products, chemistry manufacturing and controls content and format - draft guidance for industry: 4/20/1999
  22. On the establishment and operation of clinical trial data monitoring committees - draft guidance for clinical trial sponsors 11/15/2001
  23. Plasmid DNA vaccines for preventive infectious disease indications. Points to consider. 12/27/1996
  24. Postmarketing safety reporting for human drug and biological products including vaccines - draft guidance for industry: 3/12/2001
  25. Providing clinical evidence of effectiveness for human drugs and biological products - guidance for industry: 5/15/1998
  26. Q & A content and format of INDs for phase 1 studies of drugs, including well-characterized, therapeutic, biotechnology-derived products - guidance for industry: 10/3/2000
  27. Submission of chemistry, manufacturing, and controls information for synthetic peptide substance – guidance for industry. 1/16/1998

### **Other FDA guidance**

28. FDA/ORA: Bioresearch monitoring: compliance program 7348.808: good laboratory practice. Feb 21, 2001
29. FDA/ORA: Bioresearch monitoring :compliance program 7348.810: sponsors, contract research organizations and monitors. September 30, 2000
30. FDA/ORA Bioresearch monitoring: compliance program 7348.811: chapter 48: clinical investigators. September 30, 2000
31. FDA/OSSC: Office of good clinical practice. Mandate (FDA web site)

---

**ICH documents** (also published by EU-CPMP, US-FDA and Japan's MHLW)

*Safety topics*

32. S3A: Guidance on the assessment of systemic exposure in toxicity studies.
33. S4A: Duration of chronic toxicity testing in animals (Rodent and Nonrodent Toxicity Testing)
34. S5A: Detection of toxicity to reproduction for medicinal products.
35. S6: Preclinical safety evaluation of biotechnology-derived pharmaceuticals.
36. S7A: Safety pharmacology studies for human pharmaceuticals.

*Quality topics*

37. Q2A: Text on validations of analytical procedures
38. Q2B: Methodology
39. Q5A: Viral safety evaluation of biotechnology products derived from cell lines of human or animal origin - 9/24/1998
40. Q5C: Stability testing of biotechnological / biological products - 7/10/1996
41. Q5D: Derivation and characterization of cell substrates used for production of biotechnological /biological products - 9/21/1998
42. Q6B: Test procedures and acceptance criteria for biotechnological/biological products

*Efficacy topics*

43. E1: The extent of population exposure to assess clinical safety:
44. E2A: Clinical safety data management: definitions and standards for expedited reporting.
45. E2B: Clinical safety data management: data elements for transmission of ADR reports
46. E2C: Periodic safety update reports
47. E3: Structure and content of clinical study reports
48. E4: Dose response information to support drug registration.
49. E5: Ethnic factors in the acceptability of foreign data.
50. E6: Good clinical practice
51. E8: Clinical trial design: general considerations.
52. E9: Clinical trial design: statistical principles for clinical trials.
53. E10: Clinical trial design: choice of control group.
54. E11: Clinical investigation of medicinal products in the pediatric population.

---

### *Multidisciplinary topics*

- 55. M1: Medical terminology (MedDRA)
- 56. M2: Electronic standards for transmission of regulatory information.
- 57. M3: Timing of pre-clinical studies in relation to clinical trials.
- 58. M4: The Common Technical Document: CTD
  - M4: Organization of the CTD
  - M4E: The CTD - Efficacy
  - M4Q: The CTD - Quality
  - M4S: The CTD - Safety
  - M4S: The CTD - Safety Appendices

### **European Union documents**

- 59. EU: Causality classification in the European Community (Directive III/3445/91).
- 60. EU: The rules governing medicinal products in the European Union (<http://dg3.eudra.org/F2/eudralex/>)
  - Vol. 1: Pharmaceutical Legislation: medicinal products for human use.
  - Vol. 2: Notice to applicants
    - Vol. 2A: Procedures for Marketing authorization
      - Chapter 1: Marketing authorization
      - Chapter 5: Variations
    - Vol. 2B: Presentation and content of the dossier
      - Part II Concerning chemical, pharmaceutical and biological documentation
      - Part III Toxicopharmacological documentation
      - Part IV Clinical documentation
    - Vol. 2C: Regulatory guidelines (categories (new vs. variation) renewals, labelling packaging, product characteristics summary, classifications, forms)
  - Vol. 3: Guidelines.
    - Vol. 3A: Quality and biotechnology
    - Vol. 3B: Safety, environmental guidelines and information
    - Vol. 3C: Efficacy. Clinical guidelines (general and therapeutic class)
  - Vol. 4: Good manufacturing practices: basic requirements and 18 Annexes (annex 2: biological products, annex 13 investigational medicinal products)
  - Vol. 9: Pharmacovigilance
- 61. OECD principles of good laboratory practice (revised 1997). ENV/MC/CHEM (98)17

---

## European Union: Committee for Proprietary Medicinal Products (CPMP)

Documents relevant to the clinical evaluation manual. (ICH documents adopted by the EU are not listed here – see list of ICH documents)

62. CPMP/SWP/1042/99 Note for guidance on repeated dose toxicity (CPMP adopted July 2000)
63. CPMP/SWP/465/95 Note for guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP adopted Dec. 97).
64. CPMP/SWP/728/95 Replacement of animal studies by in vitro models (CPMP adopted February 97).
65. CPMP/QWP/848/96 (EMEA/CVMP/598/99) Note for guidance on process validation (CPMP/CVMP Adopted Feb. 01)
66. CPMP/EWP/2747/00 Note for guidance on co-ordinating investigator signature of clinical study reports (Adopted October 2001)
67. CPMP/EWP/463/97 Note for guidance on clinical evaluation of new vaccines
68. CPMP/EWP/462/95 Note for guidance on clinical investigation of medicinal products in children (CPMP adopted March 97)
69. CPMP/BWP/2490/00 Note for guidance on cell culture inactivated influenza vaccines (Adopted by CPMP January 2002) - Annex to Note for guidance on harmonisation of requirements for influenza vaccines CPMP/BWP/214/96
70. CPMP/BWP/3207/00 Note for guidance on comparability of medicinal products containing biotechnology-derived proteins as drug substance (CPMP adopted Sept. 01)
71. CPMP/BWP/328/99 Development pharmaceuticals for biotechnological and biological products - Annex to note for guidance on development pharmaceuticals (CPMP/QWP/155/96)
72. CPMP/BWP/477/97 Note for guidance on pharmaceutical and biological aspects of combined vaccines, (CPMP adopted Jul. 98).
73. CPMP/BWP/214/96 Note for guidance on harmonisation of requirements for influenza vaccines (CPMP adopted March 97)
74. CPMP/BWP/268/95 Note for guidance on virus validation studies: the design, contribution and interpretation of studies validating the inactivation and removal of viruses (CPMP adopted Feb.96).
75. CPMP/BWP/2289/01 Points to consider on the development of live attenuated influenza vaccines (Released for Consultation, Sept. 01)
76. CPMP/BWP/2517/00 Points to consider on the reduction, elimination or substitution of thiomersal in vaccines (Adopted, April 2001)
77. CPMP/BWP/6622/02 Notice for guidance on requirements for the evaluation of new adjuvants in vaccines (Concept paper).
78. CPMP/PhVWP/108/99: Notice to marketing authorization holders. Pharmacovigilance guidelines. Draft version, January 1999.

---

## WHO and CIOMS (Council for Organizations of Medical Sciences) documents

79. *Guidelines for ethical review committees*. Geneva, CIOMS, 1998.
80. *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, CIOMS, 1993. (Revised draft 2002).
81. *International Guidelines for Ethical Review of Epidemiological Studies*. Geneva, CIOMS, 1991
82. *International reporting of adverse drug reactions. Final report of the CIOMS Working group*. Geneva, CIOMS, 1990.
83. *A WHO guide to good manufacturing practice (GMP) requirements: part 1: standard operating procedures and master formulae*. Geneva, World Health Organization, 1997 (document WHO/VSQ/97.01, 1997)
84. *A WHO guide to good manufacturing practice (GMP) requirements: part 2: validation*. Geneva, World Health Organization, 1997 (document WHO/VSQ/97.02, 1997).
85. *Effect of vaccine formulation and other factors on the immunogenicity of oral poliovirus vaccine: results of a randomized trial in Brazil and the Gambia*. Geneva, World Health Organization, 1993. (document WHO/EPI, 1993).
86. *General requirements for the sterility of biological substances*. Geneva, World Health Organization. (Revised 1973, WHO Technical Report Series No. 530, 1973. Amendment 1995, WHO Technical Report Series No. 872, 1998).
87. *Good Manufacturing Practice: supplementary guidelines for the manufacture of the investigational pharmaceutical products for clinical trials in humans. Annex 7*. World Health Organization, 1996 (WHO Technical Report Series No. 863).
88. *Good manufacturing practices for biological products. Annex 1*. World Health Organization, 1992 (WHO Technical Report Series No. 822).
89. *Good manufacturing practices for pharmaceutical products. Annex 1*. Geneva, World Health Organization, 1992. (WHO Technical Report Series No. 823).
90. *Guidelines for assuring quality of DNA vaccines. Annex 3*. Geneva, World Health Organization, 1998. (WHO Technical Report Series No. 878).
91. *Guidelines for assuring the quality of pharmaceutical and biological products prepared by recombinant DNA technology. Annex 3*. Geneva, World Health Organization, 1991. (WHO Technical Report Series No. 814)
92. *Guidelines for good clinical practices (GCP) for trials on pharmaceutical products. Annex 3*. Geneva, World Health Organization, 1995. (WHO Technical Report Series No. 850).
93. *Guidelines for national authorities on quality assurance for biological products. Annex 2*. Geneva, World Health Organization, 1992. (WHO Technical Report Series No. 822)
94. *Guidelines for the evaluation of dengue vaccines in populations exposed to natural infection*. Geneva, World Health Organization, 2001. (document TDR/IVR/DEN/01).

- 
95. *Guidelines for the evaluation of Plasmodium falciparum vaccines in the population exposed to natural infection.* Geneva, World Health Organization, 1997. (document WHO/TDR).
  96. *Guidelines for the production and quality control of synthetic peptide vaccines. Annex 1.* Geneva, World Health Organization, 1999. (WHO Technical Report Series No. 889).
  97. WHO Guidelines on Clinical Evaluation of Vaccines: Regulatory Considerations (WHO TRS in press)
  98. *Immunization in practice.* Geneva, World Health Organization, 1998. Expanded Programme on Immunization. (document WHO/EPI/TRAM/98.01–11 REV.1)
  99. *Informal consultation of experts on national regulation of vaccines.* Geneva, World Health Organization, 1999 (document WHO/V&B/99.08).
  100. *Operational guidelines for ethics committees that review biomedical research.* Geneva, World Health Organization, 2000
  101. Recommendations and guidelines for biological substances used in medicine and other documents. WHO (full list in each issue of the Technical Report Series reported by the Expert Committee on Biological Standardization). Geneva, World Health Organization.
  102. *Recommendations for the production and control of Haemophilus influenzae type b conjugate vaccines. Annex 1.* Geneva, World Health Organization, 2000. (WHO Technical Report Series No. 897).
  103. *Regulation and licensing of biological products in countries with newly developing regulatory authorities. Annex 1.* Geneva, World Health Organization, 1995. (WHO Technical Report Series No. 858).
  104. *Regulation of vaccines: building on existing drug regulatory authorities.* Geneva, World Health Organization, 1999 (document WHO/V&B/99.10).
  105. *Report of a WHO consultation on medicinal and other products in relation to human and animal Transmissible Spongiform Encephalopathies.* Geneva, World Health Organization, 1997 (document WHO/EMC/ZOO/97.3).
  106. *Requirements for poliomyelitis vaccine (oral). (Addendum 1998). Annex 2.* Geneva, World Health Organization, 1998. (WHO Technical Report Series No. 897).
  107. *Requirements for the use of animal cells as in vitro substrates for the production of biologicals. Annex 1.* Geneva, World Health Organization, 1998 (WHO Technical Report Series No. 878).
  108. *Review of existing documents on planning, performance and assessment of clinical studies on vaccines.* Geneva, World Health Organization, 1999 (document WHO/V&B/99.09).
  109. *Training manual: licensing, lot release, laboratory access.* Geneva, World Health Organization, 2001 (document WHO/V&B/01.16).
  110. *WHO recommended surveillance standards.* Geneva, World Health Organization 1997. (document WHO/EMC/DIS/97.1).
  111. *Protocols for the evaluation of epidemiological surveillance systems.* Geneva, World Health Organization, 1977. (document WHO/EMC/DIS/97.2).

- 
112. *Surveillance of adverse events following immunization. Field Guide for managers of immunization programmes.* Geneva, World Health Organization, 1997. (document WHO/EPI/TRAM/93.02 Rev.1).
  113. *Vaccine trial registry directory, August 1999.* Geneva, World Health Organization, 1999 (document WHO/V&B/00.07).

**Dictionaries and textbooks (no specific recommendation to these, others equally suitable)**

114. Bland, Martin. *An introduction to Medical Statistics.* Third edition, Aug 2000 Oxford Univ Press Inc. NY
115. Griffin JP, O'Grady J, D'Arcy PF, eds. *The textbook of pharmaceutical medicine.* Belfast, United Kingdom: The Queen's University of Belfast, 1998.
116. Horne AD. *Statistics, use in immunology.* In *Encyclopaedia of Immunology.* London: Academic Press; 1998.
117. Last JM, ed. *A dictionary of epidemiology.* Third Edition ed. Oxford: Oxford University Press, 1995.
118. Laurence D, Carpenter J. *A dictionary of pharmacology and clinical drug evaluation.* London: UCL Press Ltd., 1994.
119. Mann RD, Rawlins MD, Auty RM, eds. *Textbook of pharmaceutical medicine.* Carnforth: The Parthenon Publishing Group Ltd, 1993.
120. *Medical Statistic Online Help: Sample size and power for clinical trials.* Oxford/Radcliffe National Health Service, United Kingdom, 29 November 2001 ([www.oxfordradcliffe.nhs.uk](http://www.oxfordradcliffe.nhs.uk))
121. Nahler G. *Dictionary of pharmaceutical medicine.* Vienna: Springer-Verlag, 1994.

**Other regulatory documents**

122. Council of Europe: *Convention for the protection of human rights and dignity of the human being with regard to the application of biology and medicine: convention on human rights and biomedicine.* Strasbourg. Council of Europe, 1996.
123. UK Medicines Control Agency: MCA: *Guidance notes on applications for clinical trial exemptions and clinical trial certificates.*
124. *Ethical considerations in HIV preventive vaccine research.* UNAIDS guidance document. Geneva, UNAIDS, May 2000.
125. World Medical Association: *Declaration of Helsinki: Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects.* Original adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Most recent amendment by the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000.

---

## Journal publications and books

126. Anderson RM, Donnelly CA, Gupta S. Vaccine design, evaluation and community based use for antigenically variable infectious agents. *Lancet* 1997, 350:1466–70.
127. Armitage, P, Berry G, Matthews, JNS. *Statistical Methods in Medical Research*. Oxford Blackwell Science, Williston Vt.
128. Aylward B, Kane M, Batson A, McNair R. A framework for the evaluation of vaccines for use in the expanded programme on immunization. *Vaccine* 1994, 13:1155–9.
129. Beernaert H et al. The revised principles of good laboratory practice of the organization for Economic Cooperation and Development – changes, chances, and controversies. *Drug Information Journal*, 34:33–45, 2000.
130. Blackwelder WC. Sample size and power for prospective analysis of relative risk. *Stat Med* 1993, 12; 691–698.
131. Blackwelder WC. Similarity/equivalence trials for combination vaccines. *Annal of the New York Academy of Sciences*, 1995, 754:321–328
132. Brown F et al. Vaccine design. In James K, Morris A, (eds). *Molecular Medical Science Series*. Chichester: John Wiley & Sons, 1993.
133. Brown F, Greco D, Mastrantonio P, Salmaso S, Wassilak S, eds. *Pertussis vaccine trials*. In Brown F, (ed) *Developments in Biological Standardization*, Vol. 89. Basel: Karger, 1997.
134. Chen RT, Orenstein WA. Epidemiologic methods in immunization programmes. *Epidemiology Review*, 1996, 2:99–117.
135. Chow S, Liu J. *Design and analysis of clinical trials: concepts and methodologies*. In Barnett V, Bradley RA, Fisher NI, (eds.) *Wiley Series in Probability and Statistics*. New York: John Wiley & Sons, 1998.
136. Cemens J, Brenner R, Rao M, Tafari N, Lowe C. Evaluating new vaccines for developing countries. Efficacy or effectiveness? *Journal of the American Medical Association* , 1996, 5:390–7.
137. Cutts FT, Smith PG, eds. *Vaccination and world health*. Chichester: John Wiley & Sons, 1994.
138. Davenport L. *Regulatory considerations in vaccine design*. In: Powell MF, Newman MJ, eds. *Vaccine design: the subunit and adjuvant approach*. New York: Plenum Press, 1995:81–96.
139. Davis GC, Riggin RM. Characterization and establishment of specifications for biopharmaceuticals. In: Brown F, Fernandez J, eds. *Development of specifications for biotechnology pharmaceutical products*. Basel: Karger, 1997:49-54. Brown F, ed. *Developments in Biological Standardization*
140. Durham KL et al. Estimation of vaccine efficacy in the presence of waning: application to cholera vaccines. *American Journal of Epidemiology*, 1998, 47:948–59.
141. Elwood M. *Critical appraisal of epidemiological studies and clinical trials*. (Second edition ed.) Oxford, Oxford University Press, 1998.

- 
142. Evans D, Evans M. *A decent proposal: ethical review of clinical research*. Chichester: John Wiley & Sons, 1996.
  143. Ewell M. Comparing methods for calculating confidence intervals for vaccine efficacy. *Statistics in Medicine* 1996, 2379–92.
  144. Falk LA et al. Testing and licensure of combination vaccines for the prevention of infectious diseases. In: Combination vaccines: development, clinical research and approval. RW Ellis, ed. Humana Press Inc. Totowa, NJ. Chapter 11, 1999, 233–48.
  145. Fedson DS. Measuring protection: efficacy versus effectiveness. In Brown F, Plotkin S, eds. Preclinical and clinical development of vaccines. *Developments in Biological Standardization*, Basel, Karger, 1998, 95:195–201.
  146. Folb P in Grady JO, Joubert PH. *Handbook of phase I/II clinical drug trials*, CRC Publishers, 1997.
  147. Fuccella LM, Olliaro P. *Standard operating procedure for clinical investigators*. Geneva, World Health Organization, 1995 (document WHO/TDR, 1995: see also Karbwang).
  148. Fuccella LM, Teruzzi E, F. M, Olliaro P. *Standard operating procedure for monitoring of clinical studies*. Geneva, World Health Organization. 1997 (document WHO/TDR, 1997).
  149. Geigert J. Appropriate specifications at the IND stage. In: Brown F, Fernandez J, eds. Development of specifications for biotechnology pharmaceutical products. Basel: Karger, 1997:39-43. *Developments in Biological Standardization*; Vol. 91.
  150. Giesecke J. *Modern infectious disease epidemiology*. Arnold/Oxford University Press. 1994. 1995 reprint.
  151. Goldenthal KL et al. *Safety evaluation of vaccine adjuvants: National Cooperative vaccine Development Meeting Working Group*. AIDS Research and Human Retroviruses. 1993, 9, supplement 1: S47-S51
  152. Griffiths E. Assuring the quality of vaccines: regulatory requirements for licensing and batch release. In: Robinson A, Farrar G, Wiblin C, eds. *Vaccine protocols*. Totowa, NJ. Humana Press, 1996:x + 317. (Walker JM, ed. Methods in Molecular Medicine.)
  153. Halloran ME, Longini IM, Struchiner CJ. Design and interpretation of vaccine field studies. *Epidemiol. Review*, 1999, 21: 73-88.
  154. Halloran ME, Struchiner CJ. Causal inference of infectious diseases. *Epidemiology*, 1995;6:142–51
  155. Halloran ME, Struchiner CJ, Longini IM. Study designs for evaluating different efficacy and effectiveness aspects of vaccines. *American Journal of Epidemiology*, 1997,146;10:789–803.
  156. Hayes R et al. Design and analysis issues in cluster-randomized trials of interventions against infectious diseases. Tropical Epidemiology Group. *Statistical Methods in Medical Research*, 2000, 9:95–116.
  157. Horne AD et al. Analysis of studies to evaluate immune response to combination vaccines. *Clinical Infectious Diseases*, 2001, S4; S306-311.

- 
158. Horne AD, Lachenbruch PA, Goldenthal KL. Intent-to-treat analysis and preventive vaccine efficacy. *Vaccine*, 2000, 19:319–26.
  159. Horne AD. The statistical analysis of immunogenicity data in vaccine trials: a review of methodologies and issues. *Annals of the New York Academy of Sciences*. 1995, 754:329-46.
  160. Jefferson T. Vaccination and its adverse effects: real or perceived. *British Medical Journal*, 1998, 317:159–60.
  161. Jones B et al. Trials to assess equivalence: the importance of rigorous methods. *British Medical Journal*, 1996, 313:36–9.
  162. Karbwang J, Pattou C. *Standard Operating Procedures for Clinical Investigators*. UNDP/World Bank/WHO (document WHO TDR/PRD/SOP/14/06/01.1 Rev 1).
  163. Lachenbruch PA. Sensitivity, specificity, and vaccine efficacy. *Controlled Clinical Trials*, 1998; 19:569–74.
  164. Lemeshow S et al. *Adequacy of sample size in health studies*. Chichester: John Wiley & Sons Ltd., 1990.
  165. 165 McFadden E. Management of data in clinical trials. New York: John Wiley & Sons, Inc., 1998. (Barnett V, Bradley RA, Fisher NI, eds. Wiley Series in *Probability and Statistics*; 62).
  166. Nossal GJV. Host immunobiology and vaccine development. *Lancet*, 1997, 350:1316–19.
  167. Olin P et al. Randomised controlled trial of two-component, three-component, and five-component acellular pertussis vaccines compared with whole-cell pertussis vaccine. *Lancet* 1997, 350:1569–77.
  168. Orenstein WA et al. Field evaluation of vaccine efficacy. *Bulletin of the World Health Organization*, 1985, 6:1055–68
  169. 169 Patterson S, Lin L, Elchico J, et al. Global regulatory considerations for unified assay specifications. In: Brown F, Fernandez J, eds. Development of specifications for biotechnology pharmaceutical products. Basel: Karger, 1997:45-8. *Developments in Biological Standardization*
  170. Piantadosi S. *Clinical trials: a methodologic perspective*. In Barnett V, Bradley RA, Fisher NI, eds. Wiley series in *Probability and Statistics*. New York: John Wiley & Sons, Inc., 1997.
  171. Plotkin S, Brown F, Horaud F, eds. Preclinical and clinical development of vaccines. In Brown F, ed. *Developments in Biological Standardization*, Vol. 95. Basel: Karger, 1998.
  172. Pocock SJ. *Clinical trials: a practical approach*. Chichester: John Wiley & Sons, 1995.
  173. Powell MF, Newman MJ, Burdmann JR, eds. *Vaccine design: the subunit and adjuvant approach*. In Borchardt RT, ed. *Pharmaceutical Biotechnology*, Vol. 6. New York: Plenum Press, 1995.
  174. Reed GF, Meade BD, Steinhoff MC. The reverse cumulative distribution plot: a graphic method for exploratory analysis of antibody data. *Pediatrics*. 1995,96:600–3.

- 
175. Rodrigues LC, Smith PG. The use of case control approach in vaccine evaluation: Efficacy and adverse effects. *Epidemiologic Reviews*. 21:56-72, 1999.
  176. Senn S. *Statistical issues in drug development*. In Barnett V, ed. *Statistics in practice*. Chichester, John Wiley & Sons, 1997.
  177. Siber GR. Methods for estimating serological correlates of protection. *Developments in Biological Standardization*, Basel, Karger, 1997, Vol. 89, pp 283-296. Brown F, Greco D, Mastrantonio P, Salmaso S, Wassilak S: Pertussis Vaccine Trials
  178. Smith PG, Morrow RH, eds. *Field trials of health interventions in developing countries: a toolbox*. Second edition ed. London: Macmillan Education Ltd., 1996.
  179. Smith PG, Rodrigues LC, Fine PEM. Assessment of the protective efficacy of vaccines against common diseases using case control and cohort studies. *International Journal of Epidemiology*, 1984, 13:87-93.
  180. Taylor B. et al. Autism and measles, mumps and rubella vaccine: no epidemiological evidence for a causal relationship. *Lancet*, 1999, 353: 2026-9.
  181. Vaughan JP, Morrow RH, eds. *Manual of epidemiology for district health management*. Geneva, World Health Organization, 1993.
  182. Williams et al (eds) Combined vaccines and simultaneous administration. Current issues and perspectives. *Annals of the New York Academy of Sciences*, 1995: 754.

### **Web sites for downloading documents**

US FDA: All documents listed are available electronically from:

CFR: Code of Federal Regulations: [www.access.gpo.gov/nara/cfr/](http://www.access.gpo.gov/nara/cfr/)

CBER: Center for Biologics Evaluation and Research:  
[www.fda.gov/cber/guidelines.htm](http://www.fda.gov/cber/guidelines.htm)

BIMO: Bioresearch Monitoring: [www.fda.gov/ora/BIMO/](http://www.fda.gov/ora/BIMO/)

ICH: All documents listed are available electronically from:

[www.ifpma.org/ich5.html](http://www.ifpma.org/ich5.html)

European Union: All documents listed are available electronically from:

CPMP: Committee for Proprietary Medicinal Products:  
[www.emea.eu.int/htms/human/](http://www.emea.eu.int/htms/human/)

Rules Governing Medicinal Products in the European Union:  
<http://pharmacos.eudra.org/F2/eudralex/index.htm>

WHO: Some publications are available electronically.

[www.who.int/pub/en/](http://www.who.int/pub/en/)

[www.who.int/vaccines-documents/](http://www.who.int/vaccines-documents/)

[www.who.int/biologicals](http://www.who.int/biologicals)



The Department of Vaccines and Biologicals was established by the World Health Organization in 1998 to operate within the Cluster of Health Technologies and Pharmaceuticals. The Department's major goal is the achievement of a world in which all people at risk are protected against vaccine-preventable diseases.

Five groups implement its strategy, which starts with the establishment and maintenance of norms and standards, focusing on major vaccine and technology issues, and ends with implementation and guidance for immunization services. The work of the groups is outlined below.

The *Quality Assurance and Safety of Biologicals team* ensures the quality and safety of vaccines and other biological medicines through the development and establishment of global norms and standards.

The *Initiative for Vaccine Research* and its three teams involved in viral, bacterial and parasitic

diseases coordinate and facilitate research and development of new vaccines and immunization-related technologies.

The *Vaccine Assessment and Monitoring team* assesses strategies and activities for reducing morbidity and mortality caused by vaccine-preventable diseases.

The *Access to Technologies team* endeavours to reduce financial and technical barriers to the introduction of new and established vaccines and immunization-related technologies.

The *Expanded Programme on Immunization* develops policies and strategies for maximizing the use of vaccines of public health importance and their delivery. It supports the WHO regions and countries in acquiring the skills, competence and infrastructure needed for implementing these policies and strategies and for achieving disease control and/or elimination and eradication objectives.

## Department of Vaccines and Biologicals

Health Technology and Pharmaceuticals

World Health Organization

CH-1211 Geneva 27

Switzerland

Fax: +41 22 791 4227

Email: [vaccines@who.int](mailto:vaccines@who.int)

or visit our web site at: <http://www.who.int/vaccines-documents>

