

Review of existing documents on planning, performance and assessment of clinical studies on vaccines

This document was prepared as a background document for the informal consultation of experts on national regulation of vaccines, Geneva, 21-22 January 1999.



**DEPARTMENT OF VACCINES AND
OTHER BIOLOGICALS**



*World Health Organization
Geneva
1999*

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

This document was produced by the
Access to Technologies Team
of the Department of Vaccines and Other Biologicals
Ordering code: WHO/V&B/99.09
Printed: August 1999

This document is available on the Internet at:
www.who.int/gpv-documents/

Copies may be requested from:
World Health Organization
Vaccines and Other Biologicals
CH-1211 Geneva 27, Switzerland
• *Fax: +22 791 4193/4192* • *E-mail: vaccines@who.ch* •

© World Health Organization 1999

This document is not a formal publication of the World Health Organization (WHO), and all rights are reserved by the Organization. The document may, however, be freely reviewed, abstracted, reproduced and translated, in part or in whole, but not for sale nor for use in conjunction with commercial purposes.

The views expressed in documents by named authors are solely the responsibility of those authors.

Contents

<i>Acknowledgements</i>	<i>iv</i>
<i>Glossary</i>	<i>v</i>
1. Executive summary	1
2. Introduction	3
3. Documentation available	5
3.1 Guidelines for ethical review of clinical research	5
3.2 General documentation on clinical trials	5
3.3 Vaccine specific guidelines	7
3.4 Documentation sources	10
4. Current guidelines: applicability to vaccine trials	11
4.1 Ethical review	11
4.2 Production and quality assurance	11
4.3 Performance of clinical studies	12
4.4 Study design and protocols	12
4.5 Data management	13
4.6 Monitoring	13
4.7 Applicability of trial to public health needs	14
5. Conclusions	15
6. Recommendations	16
7. References	17
Annex 1: EMEA documents relevant for clinical research on human subjects	19
Annex 2: FDA documents relevant for clinical research on human subjects	20
Annex 3: Literature reviewed	21
Annex 4: Matrix to identify gaps in existing guidelines on clinical trials of vaccines	26

Acknowledgements

The Department of Vaccines and Other Biologicals thanks the donors whose unspecified financial support has made the production of this document possible, especially the World Bank, DFID, and the Government of Japan.

The Department thanks Dr Kari Lankinen, Finland, who drafted this document, the participants of the “Informal consultation of experts on national regulation of vaccines, Geneva, 21-22 January 1999” and the following additional experts who contributed to its review:

Mr Norman Ackland, Australia
Dr R Breiman, USA
Dr John Clemens, USA
Dr Felicity Cutts, UK
Dr Emmanuel Ehizibolo, Nigeria
Dr Susan Ellenberg, USA
Dr Karen Goldenthal, USA
Dr Jorge A Gomez, Argentina
Dr Juhana Idanpaan-Heikkila, WHO
Dr Isabel Kantor, Argentina
Dr Lei Dianliang, China
Dr Abdullah Molokhia, Egypt
Dr Febe Naguib, Egypt
Dr Peter Ndumbe, Cameroon
Dr Bradley Perkins, USA
Dr Thea Sesardic, UK
Dr Surinder Singh, India
Prof Martin Smith, South Africa
Ms B Voordouw, Netherlands

Glossary

ACT	Adisory Committee on Training
ADR	Adverse Drug Reaction: A response to a pharmaceutical product that is noxious and unintended and that occurs at doses normally used or tested in humans for prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function. In clinical trials, injuries caused by overdosing, abuse or dependence and interactions with any other product should be considered adverse reaction (30).
AE	Adverse Event: Any untoward medical occurrence in a clinical trial subject administered a pharmaceutical product; it does not necessarily have a causal relationship with the treatment (30).
Booster vaccination	Vaccination given after a certain time interval after primary vaccination in order to establish longer-term protection (1).
Bridging study	A study performed in the new region to provide pharmacodynamic or 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 (2).
Case control study	An observational study in which the exposure to a particular risk factor (the vaccine in the case of vaccine studies) is determined retrospectively, and this exposure is compared between individuals who experience an event (the disease, in vaccine studies), the cases, and the individuals who do not, the controls (1).
Case definition	A case is defined by three components. The symptoms from the infection experienced by the patient, sufficient to seek medical care or advice; the diagnosis suspected by the physician; confirmation by the laboratory. All three components should be addressed in the formulation of the case definition (1).
CIOMS	Council for International Organizations of Medical Sciences

CFR	Code of Federal Regulations
Combined vaccines	Products intended for protection against: 1) a single infectious disease complex caused by different strains or serotypes of organisms; 2) or protection against multiple infectious diseases; or 3) combinations of 1 and 2 (3).
Community investigations	Population based trials in predefined large segments of the population to investigate the impact of a treatment on a preventable infectious disease.
Cohort studies	Retrospective or prospective studies, in which the development of disease or infection is observed in a defined group of subjects observed over time (1).
Control	Any comparator suitable for validation of the trial. The comparator may be either active or a placebo (1).
CPMP	Committee for Proprietary Medicinal Products, the European Agency for the Evaluation of Medicinal Products, Human Medicines Evaluation Unit.
CRO	Contract Research Organization
Effectiveness	Therapeutic utility of a drug or treatment when used by the public at large under uncontrolled, real world conditions (4). See also vaccine effectiveness.
Efficacy	Therapeutic or pharmacological result of a drug or treatment in a controlled clinical situation; assessment of efficacy needs: 'specification of the effect parameters to be used, 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 (pharmacokinetic, laboratory, radiological, etc.)' (4). See also vaccine efficacy.
EFPIA	European Federation of Pharmaceutical Industries' Associations
EMA	The European Agency for the Evaluation of Medicinal Products
EC	European Commission
Ethics Committee	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 (30). (=Internal Review Board)

FDA	Food and Drug Administration (USA)
GCP	Good Clinical Practice in clinical trials: 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 (30).
GMP	Good Manufacturing Practice: The part of pharmaceutical quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorisation (30).
ICH	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 harmonisation, 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, and 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, harmonised guidelines and recommendations.
IND	Investigational New Drug (application)
Immunogenicity	Capacity of a vaccine to induce humoral (specific antibodies) and/or cell-mediated immunity (1).
Internal control	An additional control arm, usually a placebo, which may be required to when the efficacy of the active comparator is not adequately established or is known to give inconsistent results (1).
<u>IRB</u>	<u>Institutional Review Board (= ethics committee)</u>
WHO/V&B//99.09	
JPMA	Japan Pharmaceutical Manufacturers Association

MHW	Ministry of Health and Welfare, Japan
Observational studies	Observational studies focus on events, exposures and diseases occurring in the population during the course of routine living conditions (1).
PhRMA	Pharmaceutical Research and Manufacturers of America
Placebo control	A comparator in a vaccine trial that does not include the antigen under study. In mono-vaccine studies this may imply a true 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 (1).
Pre-exposure trial	Prospective trial in a population expected to be exposed to a pathogen under study within a predefined, relatively short, period (1).
Primary vaccination	First vaccination or series of vaccinations to induce clinical protection (1).
Protective titre	Antibody titre assumed to correlate to clinical protection (1).
Randomisation	To assure that subject populations are similar in test and control groups, a single sample population is randomly divided into groups that receive the test or control treatments. Randomisation avoids systematic differences between groups with respect to variables that could affect outcome. In vaccine trials the unit for randomisation may be either an individual or a larger group of persons (e.g. household, school), provided the confounders are well known and corrected for (1).
RCT	Randomised Controlled Trial
Reactogenicity	Events that are considered to have occurred in direct relationship to the vaccination. These events may be either local or systemic (1).
Sero-conversion	Predefined increase in antibody concentration, considered to correlate with the transition of seronegative to seropositive, providing information on the immunogenicity of a vaccine (1).
Serological surrogate	Predefined antibody concentration correlating with clinical protection (1).
SOP	Standard Operating Procedure: Standard, detailed, written instructions for the management of clinical trials.

	They provide a general framework enabling the efficient implementation and performance of all the functions and activities for a particular trial(30).
TDR	UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (now housed in WHO's Communicable Diseases cluster)
Vaccine effectiveness	the protection rate due to 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 strain selection (1). See also effectiveness.
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 detoxified by chemical or physical means and may be aggregated, polymerised or conjugated to a carrier to increase their immunogenicity (1).
WHO	World Health Organization

1. Executive summary

The knowledge of technical considerations for vaccine clinical trials is needed in various situations. National Regulatory Authorities (NRAs) need to review clinical data, obtained in and/or out of the country, for marketing approval for locally produced and imported products. The product may already have been approved for marketing in another country, or the NRA may be the first to review the clinical data. For newly developed NRAs and for those relatively new to this field, it will be useful to have concise yet comprehensive guidelines that present points to be considered in assessing clinical trials, including the special points for vaccines for international use.

Many new technologies are coming into the vaccine production field, which are being developed in developing as well as industrialised countries. Especially for vaccines for which the industrialised country market may be limited, the R&D process and clinical studies are being done in developing countries with active involvement of the public sector. While these are reasonable and logical steps, there have been occasions when the country chosen did not have sufficient infrastructure so that the design and the protocol of the clinical trial is scientifically acceptable, which is one of the preconditions for the trial to be ethically acceptable.

Therefore there are two major purposes for WHO to provide a guidance document on clinical trials of vaccines.

- 1) Support for strengthening National Regulatory Authorities in clinical data review, including serving as a manual in training courses of the Global Training Network on evaluation of clinical trials and licensing of vaccines.
- 2) Guidance on clinical trials on vaccines, which could optimise the possibility that vaccines successfully tested in such trials, would be suitable for international use.

There are guidelines on planning, designing and assessment of clinical trials for pharmaceuticals developed by several entities, including individual countries. However, although most general principles on clinical trials on pharmaceutical products can be adapted without difficulty for vaccine studies, this special group of pharmaceuticals has distinct features that should be taken into consideration in planning, performance and assessment of clinical studies. Most importantly, vaccines are usually intended for use in healthy individuals, which requires special considerations for ethical review and safety profiles. Many vaccines are intended for use in children, and clinical studies in children necessitate especially careful planning and a thorough assessment of the risk–benefit ratio. Immunogenicity of vaccines

may be variable in different populations, which underscores the importance of local studies before licensure. For practical reasons, identical immunization schedules may not be feasible, which may necessitate additional studies. Furthermore, differences in infectious disease epidemiology have important implications for vaccine development.

Currently WHO has the following guidelines that are relevant to vaccines:

- Good manufacturing practices for biological products
- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products
- Regulation and licensing of biological products in countries with newly developing regulatory authorities
- Guidelines for national authorities on quality assurance for biological products

However, unfortunately, there is no WHO document that gives guidance on planning, performance and assessment of clinical studies on vaccines with sufficient consideration to the distinct features of vaccines.

This document reviews the major guidelines currently available on clinical trials on vaccines. Main sources have been CIOMS, TDR, the EC, the Food and Drug Administration of the United States (hereafter FDA), the International Conference on Harmonisation of Technical Requirements on Pharmaceuticals for Human Use (hereafter ICH) and WHO documents.

Based on review of the existing documents, the following conclusions can be made:

- 1) Ethical review: WHO GCP guidelines are applicable to clinical trials on vaccines. More detailed and in depth discussions are presented in CIOMS guidelines and TDR Tool Box.
- 2) Production and quality assurance: all clinical supplies should be produced following the principles of GMP. However, more guidance is needed on the appropriate level of GMP to each phase, demonstration of consistency and standardisation of biological assays used for case definition.
- 3) Performance of clinical studies: WHO GCP guidelines are applicable to clinical trials on vaccines.
- 4) Study design and protocols: points to consider are presented mainly by documents reviewed in varying depth, by different terminology and under different headings. A document that presents all these points will be useful.
- 5) Data management: data management should be arranged following the principles of GCP and the guidelines for safety data management.
- 6) Monitoring: studies should be monitored following the principles of GCP.
- 7) Applicability of trial to public health needs: no guidelines available. More information on when bridging studies are needed, what should be considered in designing is needed.

2. Introduction

The knowledge of technical considerations for vaccine clinical trials is needed in various situations. National Regulatory Authorities (NRAs) need to review clinical data, obtained in and/or out of the country, for marketing approval for locally produced and imported products. The product may already have been approved for marketing in another country, or the NRA may be the first to review the clinical data. For newly developed NRAs and for those relatively new to this field, it will be useful to have concise yet comprehensive guidelines that presents points to be considered in assessing clinical trials, including the special points for vaccines for international use.

Many new technologies are coming into the vaccine production field, which are being developed in developing as well as industrialised countries. Especially for vaccines for which the industrialised country market may be limited, the R&D process and clinical studies are being done in developing countries with active involvement of the public sector. While these are reasonable and logical steps, there have been occasions when the country chosen did not have sufficient infrastructure that the design and the protocol of the clinical trial is scientifically acceptable, which is one of the preconditions for the trial to be ethically acceptable.

Therefore there are two major purposes for WHO to provide a guidance document on clinical trials of vaccines.

- 1) Support for strengthening National Regulatory Authorities in clinical data review, including serving as a manual in training courses of the Global Training Network on evaluation of clinical trials and licensing of vaccines.
- 2) Guidance on clinical trials on vaccines, which could optimise the possibility that vaccines successfully tested in such trials, would be suitable for international use.

There are guidelines on planning, designing and assessment of clinical trials on pharmaceuticals developed by several entities, including individual countries. However, although most general regulations and guidelines on clinical trials on pharmaceutical products can be adapted without difficulty for vaccine studies, this special group of pharmaceuticals has distinct features that influence both design and conduct of clinical studies. Most importantly, vaccines are usually intended for use in healthy individuals, which poses special requirements for ethical review and safety profiles. Many vaccines are intended for use in children, and clinical studies in children necessitate especially careful planning and a thorough assessment of the risk–benefit ratio. Immunogenicity of vaccines may be variable in different populations, which underscores the importance of local studies before licensure. For practical reasons,

identical immunisation schedules may not be feasible, which may necessitate additional studies. Furthermore, differences in infectious disease epidemiology have important implications for vaccine development.

Currently WHO has the following guidelines that are relevant to clinical trials on vaccines:

- Good manufacturing practices for biological products
- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products
- Regulation and licensing of biological products in countries with newly developing regulatory authorities
- Guidelines for national authorities on quality assurance for biological products

However, unfortunately, there is no WHO document that gives guidance on planning, performance and assessment of clinical studies on vaccines with sufficient consideration on such distinct features of vaccines and immunisation.

Existing documents currently available that are relevant to clinical studies on vaccines have been reviewed to identify the gaps in the knowledge of planning, performance and assessment of clinical studies on vaccines. These will be the basis of the guideline on clinical studies of vaccines to be developed. Main sources have been the European Committee, the Food and Drug Administration of the United States (hereafter FDA), the ICH and WHO documents.

3. Documentation available

Currently, the main body of regulations and guidelines on pharmaceutical products comes from four sources: 1) The European Agency for the Evaluation of Medicinal Products (EMA); 2) Food and Drug Administration (FDA); 3) the ICH and 4) the WHO.

3.1 Guidelines for ethical review of clinical research

The most important internationally adopted documents covering the ethical aspects of biomedical research on human subjects are:

- Nuremberg Code, 1947; available from <http://usafsg.satx.disa.mil>
- Declaration of Helsinki, World Medical Association, 1964 (revised 1975 and 1989, revision in progress); available from <http://www.fda.gov>.
- International ethical guidelines for biomedical research involving human subjects, CIOMS, 1993 (6)
- International guidelines for ethical review of epidemiological studies, CIOMS, 1991
- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products
- 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, Council of Europe, 1996 (7)

Among the documents of individual country for ethical aspects of biomedical research on human subject, the following was available at the time of this review:

- Title 45 Code of Federal Regulations Part 46 'Protection of Human subjects'; <http://www.nih.gov/grants.oprr>

3.2 General documentation on clinical trials

Unfortunately there are no WHO guidelines that present the criteria and procedures for the approval of human and veterinary medicines, as well as several other important aspects of pharmaceutical legislation.

European pharmaceutical legislation now covers all industrially manufactured medicines, including vaccines (8).

The provisions applicable to medicinal products to be proposed for marketing authorisation in the European Union include:

- a binding legislation (regulations and directives) (8);
- a notice to applicants for marketing authorisation describing the administrative procedures to be followed and the format of the application dossier (9, 10);
- guidelines on the conduct of the quality, safety and efficacy studies, which must be carried out in support of an application for marketing authorisation (11-13);
- a detailed guide to good manufacturing practice (14); and
- a detailed guide to drug monitoring (pharmacovigilance) (15).

These texts are brought together in a series of volumes entitled ‘The rules governing medicinal products in the European Union’ (8-15). Most relevant for clinical trials on vaccines are the following documents:

- Note for guidance on good clinical practice (5);
- Note for guidance on statistical principles for clinical trials (16);
- Note for guidance on clinical investigation of medicinal products in children (17);
- Note for guidance on clinical safety data management: definitions and standards for expedited reporting (18)
- Note for guidance on clinical safety data management: data elements for transmission of individual case safety reports (19).

In the US, three levels on rigidity exist in the application of the relevant regulations and guidance (20):

1. Regulations as promulgated in Title 21 of the US Code of Federal Regulations (21 CFR)
2. Guidelines published in the Federal Register; and
3. ‘Points to Consider’ (PTCs) documents published in the Federal Register.

The regulations governing good clinical practice and clinical trials are enforced by the FDA. The regulations pertaining to clinical investigations are published in Title 21 of the Code of Federal Regulations (CFR):

- Part 50 on informed consent,
- Part 56 on IRBs,
- Part 312 on investigational new drug (IND) applications, which include the responsibilities of sponsors, monitors and investigators,
- Part 314 on accelerated approval, and
- Part 601 on licensing.

Both EU and FDA regulations encompass the following organizations and people:

- clinical investigators,
- sponsors,
- monitors,
- contract research organizations (CROs), and
- Institutional Review Boards (IRBs, i.e. the ethics committees).

3.3 Vaccine specific guidelines

There are no WHO vaccine specific guidelines on clinical trials. Eight vaccine specific guidelines were reviewed, four issued by EMEA, one by the FDA, and three by the UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases (TDR).

3.3.1 Committee for Proprietary Medicinal Products: Note for guidance on preclinical pharmacological and toxicological testing of vaccines (Hereafter referred to as CPMP pre-clinical guideline).

The guideline reviews the conventional preclinical studies of pharmaceuticals providing guidance on the application of these principles in vaccine development (21). Single dose toxicity data is required from at least one animal species, with a dose providing adequate safety margin in relation to the human dose. Repeated dose toxicity testing is normally requested for vaccines that will be administered in multiple doses (may be appropriate also for vaccines with single dose schedules). Data on reproductive function are usually not necessary. Embryo or fetal and perinatal toxicity testing are recommended for vaccines intended for use in women of child bearing age. Genotoxicity and carcinogenicity studies are normally not needed.

Primary pharmacodynamics of vaccines refers to immunogenicity and level of protection. Primary pharmacodynamic studies with respect to the antigen-protective response should be carried out in a relevant species. The potential for undesirable pharmacological activities, e.g. on the circulatory and respiratory systems, should be considered and investigated in animal models. Pharmacokinetic studies are normally not needed.

For obvious reasons, local tolerance should be evaluated. Abnormal toxicity testing is part of quality control and does not belong to the pharmacological-toxicological development programme of a vaccine. For several vaccines, abnormal toxicity testing of the finished product is no longer required by the European Pharmacopoeia.

Vaccines may contain substances causing pyrogenic effects (e.g. endotoxins, glycoproteins, lipopolysaccharides, teichoic acid). Therefore, pyrogenicity or endotoxin tests should be performed for each product on a batch-to-batch basis.

Comprehensive toxicity testing and safety evaluation is recommended for vaccine additives (adjuvants, excipients and preservatives).

The effective date for this guideline was June 1998.

3.3.2 Committee for Proprietary Medicinal Products: Note for guidance on clinical evaluation of new vaccines (Hereafter referred to as CPMP new vaccine guideline).

The guideline provides guidance in the clinically relevant issues in the evaluation of new vaccines for human use (1). The document is still a draft, and comments from interested parties have been invited by January 1999.

The guideline underscores that before embarking on the clinical testing of a new vaccine the required preclinical safety and efficacy properties must have been explored and sufficiently established in appropriate animal challenge models (whenever possible). Careful consideration should be given in the clinical testing programme to obtain adequate data with regard to the appropriate route of administration, dose schedules and age categories of exposed subjects in relation to vaccine efficacy in targeted groups. The immunogenicity, humoral and cell-mediated response, and efficacy of the new vaccine should be appropriately studied.

Any extrapolation from the clinical efficacy data from a licensed vaccine to a new, antigenically similar vaccine must be scientifically justified. The same holds for the use of known adjuvants and preservatives in these new preparations.

Regional differences within the European Union and outside the EU area, caused by variability in infection epidemiology, vaccination strategy for other vaccines, or demographic characteristics should be explored before initiation of a trial, and should be discussed in the protocol. It is pointed out that a single clinical study may not be able to demonstrate efficacy for different populations and areas. When applicable, bridging studies may be considered to allow extrapolation of data from one target population to another. Extrapolation of these data to other populations or dose regimens needs to be scientifically justified, with conclusive results from additional trials.

The guideline further requires a well organised dossier based on staged clinical trials from phase I through phase III (to phase IV), and describes basic characteristics and requirements for each phase. Case control studies and observational cohort studies may be considered in situations where randomised controlled trials are not feasible or ethically justified.

The guideline further requires that uniform, reliable and valid definition of cases should be developed before and applied during the study. Laboratory confirmation of at least some cases is necessary to validate a clinical case definition. It is important to ensure that all efforts to detect cases among vaccinated and unvaccinated populations are equal.

Vaccine efficacy may be evaluated and assessed either on the basis of clinical (protection) endpoints and/or validated serological surrogate endpoints whenever appropriate. Special consideration for combined vaccines are also reviewed.

The protocol should include sample size calculations for each endpoint (immunogenicity, safety and efficacy whenever applicable). Guidance is provided on both study design, sample size determination and other statistical criteria for the trials.

An appropriate analysis of the relation of the observed adverse events to the vaccine using standard categories for causality assignment is warranted when possible. In addition, the current draft version of the guideline recommends that the AE analysis should additionally apply to the following categories:

- 1) vaccine induced adverse reactions following immunization: those due to intrinsic characteristics of the vaccine preparation and the individual response,
- 2) vaccine precipitated adverse reactions following immunization: those triggered due to the receipt of the vaccine, but which probably would have occurred at a later time,
- 3) programmatic errors, including GMP errors, administration errors, and
- 4) coincidental; only temporally related, not due to immunization.

The effective date for this guideline has not been set.

3.3.3 Committee for Proprietary Medicinal Products: Note for guidance on pharmaceutical and biological aspects of combined vaccines (Hereafter referred to as CPMP combined vaccines guideline).

The guideline reviews the special aspects related to the development of combined vaccines (3). Each combination must be developed and studied individually in terms of quality, stability, safety, clinical tolerability and efficacy/immunogenicity. Initially, this includes the pharmaceutical development to establish the correct formulation, the stability of and compatibility between the individual components in the combined vaccine, including preservatives, excipients and adjuvants. It is emphasised that antigenic competition, epitope specific suppression, adjuvant effects (exerted by specific components of the combined vaccine) and adverse adjuvant interactions should be considered.

The guideline further covers manufacturing and control requirements, formulations, adjuvants, use of antimicrobial agents and other ingredients, issues on stability, potency and consistency testing and immunogenicity studies of combination vaccines.

The effective date for this guideline is January 1999.

3.3.4 Food and Drug Administration: Guidance for industry for the evaluation of combination vaccines for preventable diseases: production, testing and clinical studies (Hereafter referred to as FDA guidance on combination vaccines).

FDA has also issued a guideline dealing with combination vaccines. The guideline covers essentially the same issues as the European guideline (22). It describes manufacturing issues (formulation, consistency of production, testing), and the required preclinical and clinical studies. In addition, the guideline suggests that immunogenicity and safety data should be obtained in prelicensure studies to support the simultaneous administration of a new vaccine with already licensed vaccines that would be given to the same target population using the same (or overlapping) schedule.

3.3.5 Committee for Proprietary Medicinal Products: Note for guidance on harmonisation of requirements for influenza vaccines (Hereafter referred to as CPMP influenza guideline).

The guideline describes the annual choice of influenza virus strains for the vaccines, labelling, potency and control authority batch release of influenza vaccine (23). In addition, requirements for clinical trials and criteria for assessment of vaccines are set out. Clinical trials are necessary to verify the tolerance, or incidence of adverse reactions; and the immunogenicity of the hemagglutinin of the vaccine strains, i.e. the titre and frequency of anti-hemagglutinin antibody responses. The effective date for this guideline is January 1999.

3.3.6 Other guidelines

In addition to the above guidelines TDR has published three guidelines specifically for malaria vaccine studies: Guidelines for the evaluation of *Plasmodium falciparum* vaccines in the population exposed to natural infection (24), Standard operating procedure for clinical investigators (25), and Standard operating procedure for monitoring of clinical studies (26).

3.4 Documentation sources

The above CPMP/EMEA documents are available through Internet at <http://www.eudra.org/emea.html>.

FDA documentation is available from <http://www.fda.gov> and <http://www.fda.gov/cber/guidelines.htm>.

4. Current guidelines: applicability to vaccine trials

4.1 Ethical review

Ethical review of clinical trials on vaccines should follow the general principles set out in the internationally adopted documents for biomedical research on human subjects listed above. These documents cover clinical trials on pharmaceutical products, including vaccines. The main ethical principles for clinical trials are voluntary participation, the use of (written) informed consent and an acceptable risk-benefit. As the ethical principles have wide scope, there is no direct need to create vaccine specific regulations or guidelines for ethical review of clinical research.

Ethical review of clinical trials in terms of performance is presented by the WHO GCP guidelines.

However, as most, if not all, vaccines are intended for use in healthy individuals, ethical review should pay particular attention to acceptable safety profiles. Many vaccines are also primarily intended for use in children, which requires special consideration from the ethical review committees. EMEA have published a guideline covering the special aspects of clinical trials in children (17). This guideline deals with ethical and scientific considerations and underscores the need to minimise risks and distress.

While the participation of children in clinical trials is dependent on the informed consent of the parents or guardian, it is recommended that the child is informed in understandable language and terms, and when possible, the child should also sign the consent form. The guideline states that the child should stand to obtain some direct benefit from the trial, except under very special circumstances.

4.2 Production and quality assurance

Production and quality assurance aspects of pharmaceutical products are covered by WHO guidelines on good manufacturing practice (28). Most countries have pharmacopoeia level specifications for vaccines. International specifications issued by the Expert Committee on Biological Standardization have been published by the WHO in its Technical Report Series. It is important to ensure that vaccines used in clinical trial are prepared according to these principles.

However, GMP guidelines state only the manufacturing standard for a final product that is to be filed for licensure. What level of GMP is necessary for each phase of clinical study is decided on a case by case basis by the national regulatory authority that reviews the IND. The GMP requirements for each phase of clinical studies are not mentioned in any document reviewed.

Consistency of production should be ensured for the products to be used in the trial so that the data on earlier and later trials will be comparable. Demonstration of consistency of production, especially the points that should be considered for combination vaccines, are discussed in FDA guidance on combination vaccines. However, information on how to ensure comparability of products prepared at different production levels is not discussed in the documents reviewed.

If biological assays are to be used for case definition and/or assessing endpoints, it is important that the assays are standardised. This is particularly important in multi-institutional clinical trials in more than one country, which will be conducted for vaccines. The issue of standardisation of assays is not dealt with in any document reviewed.

4.3 Performance of clinical studies

Performance of clinical trials such as informed consent in written forms, record keeping, inclusion and exclusion criteria are covered by WHO GCP guidelines. These are applicable to clinical studies on vaccines.

4.4 Study design and protocols

What needs to be demonstrated before embarking on clinical studies is written in varying depth in different documents. For instance, the CPMP new vaccines guideline mentions that pre-clinical safety properties of the vaccine should be explored and established in appropriate animal challenge models. The CPMP pre-clinical guideline discusses this topic in depth, including necessary considerations in repeated dose toxicity in relation to the intended clinical use of the vaccine. The CPMP combined vaccine guideline recommends animal protection studies.

Pharmaco-kinetic studies are generally not required (CPMP new vaccines guideline).

Information that should be provided by pharmaco-dynamic studies, including the basis for dose regimen with respect to quantity of antigen per dose, is discussed in the CPMP new vaccines guideline.

Study design (randomised, controlled study, case control study), sample size, data analysis and power calculation are discussed in varying depths under different headings in TDR field trials of health interventions in developing countries, the CPMP new vaccines guideline, and FDA Guidance on combination vaccines.

Basic knowledge and general considerations for case definition is provided in TDR field trials of health interventions in developing countries. The importance of validity of methods for diagnosis is mentioned in the CPMP new vaccine guideline, which also states that in cases where highly specific methods of diagnosis are not available or not feasible, validation and justification of the clinical criteria used in the study should be justified.

The importance of case finding in a successful study is mentioned in TDR field trials of health interventions in developing countries, and case detection is discussed from a more vaccine specific perspective in the CPMP 'guidance on new vaccine'.

The general concept of endpoint is discussed in TDR field trials of health interventions in developing countries. These are dealt with in a more vaccine specific way in the CPMP new vaccines guideline, as clinical (protection) endpoints and validated serological surrogate endpoints and in FDA guidance on combination vaccines as disease incidence and a well established correlate of protection.

The selection of the optimal dosage is also discussed in varying depth in various documents. TDR field trials of health interventions in developing countries mentions only that the dosage should be optimal. The CPMP new vaccines guideline describes that it should be decided based on the pharmaco-dynamic data as mentioned above, and the CPMP combined vaccine guideline recommends that the selection of dosage should refer to WHO recommendations whenever possible.

Duration of follow-up of the studies is given both in FDA guidance on combination vaccines and the CPMP new vaccines guideline. However, while FDA states that follow-up should continue through at least thirty days for safety, and nothing is mentioned about efficacy studies, the CPMP states that though it is dependent upon the chosen endpoints, the follow-up should be at least 6 months. These different statements may reflect the positions of FDA and CPMP, or the situations being presented.

As seen above, study design and protocol are covered mainly in three documents, FDA guidance on combination vaccines, the CPMP new vaccines guideline and TDR field trials of health interventions in developing countries. The former two are vaccine specific guidelines for industry and the third is a textbook for field investigators. They are not presented in the same depth and terminology. Therefore those who are relatively new to this field may need to consult all these documents, and may be confounded by the different terminology used in these documents. However, no major contradictory statements were found among the reviewed documents on vaccines.

4.5 Data management

There are no regulations or specific guidelines covering data management in clinical trials in general. However, the WHO GCP guidelines pose requirements for data management, and there are specific guidelines on management of safety data (18, 19). The guideline on structure and content of clinical study reports has implications for organisation of data management during the trial and in its analysis phase (29). The FDA (draft) guidelines on electronic submission of data are also relevant for data management.

4.6 Monitoring

Monitoring of clinical trials on vaccines should be carried out according to the principles of GCP and there should be no need to create vaccine specific trial monitoring protocols (5).

4.7 Applicability of trial to public health needs

As described in pharmaco-dynamic studies in 4.4 (the CPMP new vaccines guideline), dose regimen should be decided on the basis of scientific data, but at the same time, it should be practical in light of the vaccination schedule. Therefore discussion not only with the national regulatory authority but also with the national immunization programme from an early phase is encouraged.

The CPMP new vaccines guideline recognises the need to pay attention to regional differences in vaccine efficacy, which may be ethnic, socio-economic or epidemiological in origin (5). Therefore, bridging studies may be necessary, but there are currently no guidelines or regulations to assist in planning of such studies.

Guidance is needed in determining whether a full-scale clinical study is necessary, a bridging study would be sufficient, or foreign data are acceptable in marketing approval of an imported vaccine that has already been licensed in another country. These may be dependent on vaccine and the disease against which the vaccine is to protect the vaccinated, and therefore may have to be disease- or vaccine-specific. However, an outline or a list of points to be considered may be useful when a new vaccine is coming onto the market. Such information would also be useful for those developing vaccines for international use, as conducting clinical trials in many countries concurrently could speed up the regulatory aspect of introduction of new vaccines.

5. Conclusions

Eight vaccine specific documents were reviewed and the following conclusions can be drawn:

- 1) Ethical review: WHO GCP guidelines are applicable to clinical trials on vaccines. More detailed and in depth discussions are presented in CIOMS guidelines and TDR Tool Box.
- 2) Production and quality assurance: all clinical supplies should be produced following the principles of GMP. However, more guidance is needed on the appropriate level of GMP to each phase, demonstration of consistency and standardisation of biological assays used for case definition.
- 3) Performance of clinical studies: WHO GCP guidelines are applicable to clinical trials on vaccines.
- 4) Study design and protocols: points to consider are presented mainly by documents reviewed in varying depth, by different terminology and under different headings. A document that presents all these points would be useful.
- 5) Data management: data management should be arranged following the principles of GCP and the guidelines for safety data management.
- 6) Monitoring: studies should be monitored following the principles of GCP.
- 7) Applicability of trial to public health needs: no guidelines are available. More information is needed on when bridging studies are needed, and considerations for study design.

Vaccine specific guidelines are available (Item 3), but these come from several sources with inconsistent contents. For the last mentioned item (Item 7) there is a major gap, as guidelines are totally lacking. There is a need for a comprehensive guideline to assist in the regulatory review of clinical trials on vaccines, which would provide:

- 1) Support for strengthening National Regulatory Authorities in clinical data review, including serving as a manual in training courses of the Global Training Network on evaluation of clinical trials and licensing of vaccines.
- 2) Guidance on clinical trials on vaccines, which could optimise the possibility that vaccines successfully tested in such trials, would be suitable for international use.

Although the primary use of such a guideline could be in regulatory review of clinical documentation, it could be useful also for sponsors and investigators working with vaccine development.

6. Recommendations

Existing guidelines such as GMP and GCP can be applied to clinical trials on vaccines. However, there is currently no guideline for assessing the applicability of trials to public health needs, and extensive efforts will be required to collect documents in pursuit of all necessary information for clinical study design.

To fill this gap, we propose to develop a comprehensive, yet concise, guideline for points to be considered in clinical trials on vaccines, including the special points for vaccines for international use. As a tool for those involved in clinical trials on vaccines, the document will be supplemental to GMP and GCP guidelines.

This will start from collation of all information available from existing documents into one document, probably taking one of the existing documents as a starting point. The CPMP new vaccines guideline could be a good starting point as it presents most of the topics discussed in 4.4 Study design and protocol. Annexes should include a checklist of points to be considered and a list of reference materials.

We propose that a group of experts be identified to review the draft, identify the gaps and give technical input, especially in the missing points. The group should consist of experts both in regulatory aspects and infectious disease control, including representatives from countries in need of guidance in this field.

It is proposed to submit the document, after review by a group of experts, to the Expert Committee on Biological Standardization for their review and recommendations.

7. References

1. Committee for Proprietary Medicinal Products: Note for guidance on clinical evaluation of new vaccines. London: EMEA, 1998:
2. Note for guidance on ethnic factors in the acceptability of foreign clinical data. London: EMEA/CPMP, 1998:
3. Committee for Proprietary Medicinal Products: Note for guidance on pharmaceutical and biological aspects of combined vaccines. London: EMEA, 1998:
4. Nahler G. Dictionary of pharmaceutical medicine. Vienna: Springer-Verlag, 1994.
5. Note for guidance on good clinical practice. London: EMEA/CPMP, 1996:
6. International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS, 1993.
7. 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:
8. Volume 1: Pharmaceutical legislation: medical products for human use. (1998 ed.) Luxembourg: European Commission, DG III, 1998. The rules governing medicinal products in the European Union; vol 1).
9. Volume 2A: Notice to applicants: medicinal products for human use: procedures for marketing authorisation. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 2A).
10. Volume 2B: Notice to applicants: medicinal products for human use: presentation and content of the dossier. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 2B).
11. Volume 3A: Guidelines: medicinal products for human use: quality and biotechnology. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 3A).
12. Volume 3B: Guidelines: medicinal products for human use: safety, environment and information. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 3B).
13. Volume 3C: Guidelines: medicinal products for human use: efficacy. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 3C).

-
14. Volume 4: Pharmaceutical legislation: medicinal products for human and veterinary use: good manufacturing practices. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 4).
 15. Volume 9: Pharmacovigilance: medicinal products for human and veterinary use. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 9).
 16. Note for guidance on statistical principles for clinical trials. London: EMEA/CPMP, 1998:
 17. Note for guidance on clinical investigations on medicinal products in children. London: EMEA/CPMP, 1997:
 18. Note for guidance on clinical safety data management: definitions and standards for expedited reporting. London: EMEA, 1994:
 19. Note for guidance on clinical safety data management: data elements for transmission of individual case safety reports. London: EMEA, 1997:
 20. Brown KR, Douglas RG. New challenges in quality control and licensure. *Intl J Technology Assessment in Health Care* 1994;10(1):55-64.
 21. Committee for Proprietary Medicinal Products: Note for guidance on preclinical pharmacological and toxicological testing of vaccines. London: EMEA, 1997:
 22. Guidance for industry for the evaluation of combination vaccines for preventable diseases: production, testing and clinical studies. Washington, D.C.: FDA/CBER, 1997:
 23. Committee for Proprietary Medicinal Products: Note for guidance on harmonisation of requirements for influenza vaccines. London: EMEA, 1997:
 24. Guidelines for the evaluation of *Plasmodium falciparum* vaccines in the population exposed to natural infection. Geneva: WHO/TDR, 1997:
 25. Fuccella LM, Olliaro P. Standard operating procedure for clinical investigators. Geneva: WHO/TDR, 1995:
 26. Fuccella LM, Teruzzi E, F. M, Olliaro P. Standard operating procedure for monitoring of clinical studies. Geneva: WHO/TDR, 1997:
 27. A WHO guide to good manufacturing practice (GMP) requirements: part 1: standard operating procedures and master formulae. Geneva: WHO/VSQ, 1997:
 28. A WHO guide to good manufacturing practice (GMP) requirements: part 2: validation. Geneva: WHO/VSQ, 1997:
 29. Note for guidance on structure and content of clinical study reports. London: EMEA/CPMP, 1995:
 30. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products: WHO Technical Report Series, No. 850, 1995
 31. Good manufacturing practices for biological products: WHO Technical Report Series, No. 822, 1992
 32. Regulation and licensing of biological products in countries with newly developing regulatory authorities: WHO Technical Report Series, No. 858, 1995

Annex 1:

EMA documents relevant for clinical research on human subjects

The documents are available from the following web addresses:

<http://www.eudra.org/document.htm>

<http://www.eudra.org/humandocs/humans/bwp.htm>

<http://www.eudra.org/humandocs/humans/ewp.htm>

<http://www.eudra.org/humandocs/humans/ICH.htm>

<http://www.eudra.org/humandocs/humans/bwp.htm>

<http://www.eudra.org/humandocs/humans/PhV.htm>

<http://www.eudra.org/humandocs/humans/regulate.htm>

<http://www.eudra.org/humandocs/humans/SOP.htm>

<http://www.eudra.org/humandocs/humans/Tempintro.htm>

Annex 2:

FDA documents relevant for clinical research on human subjects

The documents are available from the following web addresses:

<http://www.fda.gov/cber/guidelines.htm>

Annex 3:

Literature reviewed

1. Medical Research Council. MRC guidelines for good clinical practice in clinical trials. MRC, MRC Clinical Trials Series;
2. Ethics and research on human subjects: international guidelines. In: Bankowski Z, Levine RJ, eds. XXVIth CIOMS Conference. Geneva: CIOMS, 1992:ix + 228.
3. International ethical guidelines for biomedical research involving human subjects. Geneva: CIOMS, 1993.
4. 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: WHO/EPI, 1993:
5. Note for guidance on clinical safety data management: definitions and standards for expedited reporting. London: EMEA, 1994:
6. Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. WHO Technical Report Series. Geneva: WHO, 1995:vol 850).
7. Note for guidance on structure and content of clinical study reports. London: EMEA/CPMP, 1995:
8. World Health Organization, Global Programme on Vaccines. Vaccine trial registry directory. Geneva: WHO, 1996:
9. Progress of vaccine research and development and plan of activities - 1996. Including report of the meeting of the Research and Development Technical Group (TRG), 10-11 June 1996. Geneva: WHO/GPV, 1996:
10. Code of conduct for research involving humans. Ottawa: Medical Research Council of Canada, 1996:
11. Note for guidance on general considerations for clinical trials. London: EMEA/CPMP, 1996:
12. Note for guidance on good clinical practice. London: EMEA/CPMP, 1996:
13. 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:
14. Points to consider on plasmid DNA vaccines for preventive infectious disease indications. Washington, D.C.: FDA/CBER, 1996:
15. Guidelines for the evaluation of Plasmodium falciparum vaccines in the population exposed to natural infection. Geneva: WHO/TDR, 1997:

-
16. Tropical disease research: progress 1995-96: thirteenth programme report of the UNDP/World Bank/WHO Special Programme for Research & Training in Tropical Diseases. Geneva: WHO/TDR, 1997:
 17. Derivation and characterization of cell substrates used for production of biotechnological/biological products. International Conference on Harmonization, 1997:
 18. A WHO guide to good manufacturing practice (GMP) requirements: part 1: standard operating procedures and master formulae. Geneva: WHO/VSQ, 1997:
 19. A WHO guide to good manufacturing practice (GMP) requirements: part 2: validation. Geneva: WHO/VSQ, 1997:
 20. Proceedings of the fourth international conference on harmonisation. In: D'Arcy PF, Harron DWG, eds. Fourth international conference on harmonisation. Brussels: IFPMA, 1997.
 21. Committee for Proprietary Medicinal Products: Note for guidance on preclinical pharmacological and toxicological testing of vaccines. London: EMEA, 1997:
 22. Committee for Proprietary Medicinal Products: Note for guidance on harmonisation of requirements for influenza vaccines. London: EMEA, 1997:
 23. Guidance for industry for the evaluation of combination vaccines for preventable diseases: production, testing and clinical studies. Washington, D.C.: FDA/CBER, 1997:
 24. Note for guidance on clinical investigations on medicinal products in children. London: EMEA/CPMP, 1997:
 25. Note for guidance on clinical safety data management: data elements for transmission of individual case safety reports. London: EMEA, 1997:
 26. Committee for Proprietary Medicinal Products: Note for guidance on clinical evaluation of new vaccines. London: EMEA, 1998:
 27. Committee for Proprietary Medicinal Products: Note for guidance on pharmaceutical and biological aspects of combined vaccines. London: EMEA, 1998:
 28. Note for guidance on statistical principles for clinical trials. London: EMEA/CPMP, 1998:
 29. Guidelines for ethical review committees. Geneva: CIOMS, 1998:
 30. Volume 1: Pharmaceutical legislation: medical products for human use. (1998 ed.) Luxembourg: European Commission, DG III, 1998. The rules governing medicinal products in the European Union; vol 1).
 31. Volume 2A: Notice to applicants: medicinal products for human use: procedures for marketing authorisation. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 2A).
 32. Volume 2B: Notice to applicants: medicinal products for human use: presentation and content of the dossier. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 2B).

-
33. Volume 3A: Guidelines: medicinal products for human use: quality and biotechnology. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 3A).
 34. Volume 3B: Guidelines: medicinal products for human use: safety, environment and information. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 3B).
 35. Volume 3C: Guidelines: medicinal products for human use: efficacy. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 3C).
 36. Volume 4: Pharmaceutical legislation: medicinal products for human and veterinary use: good manufacturing practices. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 4).
 37. Volume 9: Pharmacovigilance: medicinal products for human and veterinary use. (1998 ed.) Luxembourg: European Commission, 1998. The rules governing medicinal products in the European Union; vol 9).
 38. Note for guidance on ethnic factors in the acceptability of foreign clinical data. London: EMEA/CPMP, 1998:
 39. Anderson RM, Donnelly CA, Gupta S. Vaccine design, evaluation, and community-based use for antigenically variable infectious agents. *Lancet* 1997;350:1466-70.
 40. Brown F, Dougan G, Hoey EM, Martin SJ, Rima BK, Trudgett A. Vaccine design. Chichester: John Wiley & Sons Ltd., 1993. (James K, Morris A, eds. Molecular Medical Science Series;
 41. Brown KR, Douglas RG. New challenges in quality control and licensure. *Intl J Technology Assessment in Health Care* 1994;10(1):55-64.
 42. Brown F, Greco D, Mastrantonio P, Salmaso S, Wassilak S, eds. Pertussis vaccine trials. Basel: Karger, 1997. (Brown F, ed. *Developments in Biological Standardization*; vol 89).
 43. Chen RT. Special methodological issues in pharmacoepidemiology studies of vaccine safety. In: Strom BL, ed. *Pharmacoepidemiology*. Chichester: John Wiley & Sons Ltd., 1995:xix + 741.
 44. Chow S, Liu J. Design and analysis of clinical trials: concepts and methodologies. New York: John Wiley & Sons, Inc., 1998. (Barnett V, Bradley RA, Fisher NI, eds. *Wiley Series in Probability and Statistics*;
 45. Cutts FT, Smith PG, eds. *Vaccination and world health*. Chichester: John Wiley & Sons Ltd., 1994.
 46. 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.
 47. 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. *Dev Biol Stand*;

-
48. Dent NJ, ed. Good research practices: a practical guide to the implementation of GxPs. Oxford: Butterworth-Heinemann, 1997.
 49. Elwood M. Critical appraisal of epidemiological studies and clinical trials. (Second edition ed.) Oxford: Oxford University Press, 1998.
 50. Evans D, Evans M. A decent proposal: ethical review of clinical research. Chichester: John Wiley & Sons Ltd, 1996.
 51. Fuccella LM, Olliaro P. Standard operating procedure for clinical investigators. Geneva: WHO/TDR, 1995:
 52. Fuccella LM, Teruzzi E, F. M, Olliaro P. Standard operating procedure for monitoring of clinical studies. Geneva: WHO/TDR, 1997:
 53. 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. Dev Biol Stand; vol 91).
 54. Gillon R, ed. Principles of health care ethics. Chichester: John Wiley & Sons Ltd, 1994.
 55. Griffin JP, O'Grady J, D'Arcy PF, eds. The textbook of pharmaceutical medicine. Belfast, United Kingdom: The Queen's University of Belfast, 1998.
 56. Griffiths E. Assuring the quality of vaccines: regulatory requirements for licensing and barch 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.
 57. Last JM, ed. A dictionary of epidemiology. Third Edition ed. Oxford: Oxford Univeristy Press, 1995.
 58. Laurence D, Carpenter J. A dictionary of pharmacology and clinical drug evaluation. London: UCL Press Ltd., 1994.
 59. Lemeshow S, Hosmer DW, Klar J, Lwanga SK. Adequacy of sample size in health studies. Chichester: John Wiley & Sons Ltd., 1990.
 60. Mann RD, Rawlins MD, Auty RM, eds. Textbook of pharmaceutical medicine. Carnforth: The Parthenon Publishing Group Ltd, 1993.
 61. 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).
 63. Nahler G. Dictionary of pharmaceutical medicine. Vienna: Springer-Verlag, 1994.
 64. Nossal GJV. Host immunobiology and vaccine develoment. Lancet 1997;350:1316-19.
 65. Olin P, Rasmussen F, Gustafsson L, Hallander HO, Heijbel H. 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.

-
66. Ott MB, Yingling GL, eds. Guide to good clinical practice. Washington, D.C.: Thompson Publishing Group, 1997.
 67. 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. (Brown F, ed. Dev Biol Stand;
 68. Piantadosi S. Clinical trials: a methodologic perspective. New York: John Wiley & Sons, Inc., 1997. (Barnett V, Bradley RA, Fisher NI, eds. Wiley series in probability and statistics;
 69. Plotkin S, Brown F, Haraud F, eds. Preclinical and clinical development of vaccines. Basel: Karger, 1998. (Brown F, ed. Developments in Biological Standardizations; vol 95).
 70. Pocock SJ. Clinical trials: a practical approach. Chichester: John Wiley & Sons Ltd., 1995.
 71. 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).
 72. Rondel RK, Varley SA, Webb CF, eds. Clinical data management. Chichester: John Wiley & Sons Ltd., 1995.
 73. Schwartz JA. Leitfaden klinische Prüfungen: plannug, prganisation, durchführung. Aulendorf: Editio Cantor Verlag, 1995. Der Pharmazeutische Betrieb; vol 43).
 74. Senn S. Statistical issues in drug development. Chichester: John Wiley & Sons, 1997. (Barnett V, ed. Statistics in practice;
 75. Smith PG, Morrow RH, eds. Fied trials of health interventions in developing countries: a toolbox. Second edition ed. London: Macmillan Education Ltd., 1996.
 76. Strom BL, ed. Pharmacoepidemiology. Chichester: John Wiley & Sons Ltd., 1995.
 77. Trouvin JH. Development of specifications for biotechnology products - perspectives from Europe. In: Brown F, Fernandez J, eds. Development of specifications for biotechnology pharmaceutical products. Basel: Karger, 1997:25-30. Dev Biol Stand; vol 91).
 78. Vaughan JP, Morrow RH, eds. Manual of epidemiology for district health management. Geneva: WHO, 1993.
 79. Witte PU, Schenk J, Schwartz JA, Kori-Lindner C, eds. Ordnungsgemässe klinische Prüfung: good clinical practice. Berlin: E. Habrich Verlag, 1995.

Annex 4:

Matrix to identify gaps in existing guidelines on clinical trials of vaccines

Topics	Pre clinical	I	II	III	IV
Ethics		GCP, CIOMS, others			GCP, CIOMS, others
Production and Quality assurance	GLP		Appropriate GMP Consistency of lots Standardisation of bioassays		Definite GMP
Performance			GCP		GCP
Design and protocol		EU, FDA, TDR guidelines Varying depth Different terminology			EU, FDA, TDR guidelines
Data Management			GCP		GCP
Monitor			GCP		GCP
Applicability to public health needs		No specific guidance found			No specific guidance found

Covered

Covered but needs more input

Not covered