

HANDBOOK FOR GOOD CLINICAL RESEARCH PRACTICE (GCP)

GUIDANCE FOR

IMPLEMENTATION



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Contents

Preamble	1
Introduction	3
Overview of the Clinical Research Process	8
WHO Principles of GCP	21
Principle 1: Ethical Conduct	21
Principle 2: Protocol	27
Principle 3: Risk Identification	35
Principle 4: Benefit-Risk Assessment	42
Principle 5: Review by Independent Ethics Committee/ Independent Review Board	48
Principle 6: Protocol Compliance	54
Principle 7: Informed Consent	59
Principle 8: Continuing Review/Ongoing Benefit-Risk Assessment	72
Principle 9: Investigator Qualifications	82
Principle 10: Staff Qualifications	87
Principle 11: Records	92
Principle 12: Confidentiality/Privacy	103
Principle 13: Good Manufacturing Practice	110
Principle 14: Quality Systems	115
References:	121
Documents on CD	121
Other documents cited in the Handbook	122
Related documents	123
National Good Clinical Practice and Other Guidelines	124
Acknowledgements	125

Preamble

Clinical research is necessary to establish the safety and effectiveness of specific health and medical products and practices. Much of what is known today about the safety and efficacy of specific products and treatments has come from randomized controlled clinical trials¹ that are designed to answer important scientific and health care questions. Randomized controlled trials form the foundation for “evidence-based medicine”, but such research can be relied upon only if it is conducted according to principles and standards collectively referred to as “Good Clinical Research Practice” (GCP).

This handbook is issued as an adjunct to WHO’s “Guidelines for good clinical practice (GCP) for trials on pharmaceutical products” (1995), and is intended to assist national regulatory authorities, sponsors, investigators and ethics committees in implementing GCP for industry-sponsored, government-sponsored, institution-sponsored, or investigator-initiated clinical research. The handbook is based on major international guidelines, including GCP guidelines issued subsequent to 1995, such as the International Conference on Harmonization (ICH) Good Clinical Practice: Consolidated Guideline and is organized as a reference and educational tool to facilitate understanding and implementation of GCP by:

- describing the clinical research process as it relates to health and medical products, and identifying and explaining each of the activities that are common to most trials and the parties who are ordinarily responsible for carrying them out;
- linking each of these processes to one or more Principle(s) of GCP within this Handbook;

¹ These trials assign trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

- explaining each GCP Principle and providing guidance on how each Principle is routinely applied and implemented;
- directing the reader to specific international guidelines or other references that provide more detailed advice on how to comply with GCP.

Introduction

Good Clinical Research Practice (GCP) is a process that incorporates established ethical and scientific quality standards for the design, conduct, recording and reporting of clinical research involving the participation of human subjects. Compliance with GCP provides public assurance that the rights, safety, and well-being of research subjects are protected and respected, consistent with the principles enunciated in the Declaration of Helsinki and other internationally recognized ethical guidelines, and ensures the integrity of clinical research data. The conduct of clinical research is complex and this complexity is compounded by the need to involve a number of different individuals with a variety of expertise, all of who must perform their tasks skillfully and efficiently.

The responsibility for GCP is shared by all of the parties involved, including sponsors, investigators and site staff, contract research organizations (CROs), ethics committees, regulatory authorities and research subjects.

Background

For the purposes of this handbook, a general definition of human research is:

“Any proposal relating to human subjects including healthy volunteers that cannot be considered as an element of accepted clinical management or public health practice and that involves either (i) physical or psychological intervention or observation, or (ii) collection, storage and dissemination of information relating to individuals. This definition relates not only to planned trials involving human subjects but to research in which environmental factors are manipulated in a way that could incidentally expose individuals

to undue risks.” (World Health Organization, *Governance, rules and procedures*, WHO Manual XVII).

Before medical products can be introduced onto the market or into public health programmes, they must undergo a series of investigations designed to evaluate safety and efficacy within the parameters of toxicity, potency, dose finding, and field conditions. Full information must be documented on therapeutic indications, method of administration and dosage, contraindications, warnings, safety measures, precautions, interactions, effects in target populations and safety information.

During the clinical research and development process, most medical products will only have been tested for short-term safety and efficacy on a limited number of carefully selected individuals. In some cases, as few as 100, and rarely more than 5000 subjects will have received the product prior to its approval for marketing. Given these circumstances and because the decision to allow a new product on the market has such broad public health significance, the clinical trial process and data must conform to rigorous standards to ensure that decisions are based on data of the highest quality and integrity.

In the early 1960s, widespread concern about the safety and control of investigational drugs and the clinical research process developed among members of the medical profession, the scientific community, regulatory authorities, and the general public. In 1968, WHO convened a Scientific Group on Principles for Clinical Evaluation of Drugs. The Scientific Group was charged with reviewing and formulating principles for clinical evaluation of drug products, whether new or already marketed, including considerations for new indications or dosage forms for marketed products and new combination products. In 1975, another WHO Scientific Group was convened to specifically consider all aspects of the evaluation and testing of drugs and to formulate proposals and guidelines for research in the field of drug development. These reports formed the basis for WHO’s “Guidelines for good clinical practice (GCP) for trials on pharmaceutical products”, published in 1995, as well as many national and international guidelines that have subsequently been developed, including:

- International Conference on Harmonization (ICH) E6, “Good Clinical Practice: Consolidated Guideline” (1996)
- International Standards Organization (ISO), “Clinical investigation of medical devices for human subjects, Part 1 (General requirements) and Part 2 (Clinical investigation plans) (2001)
- Pan American Health Organization (PAHO). Pan American Network on Drug Regulatory Harmonization (PANDRH). “Good Clinical Practices: Document of the Americas” (2005)

The conduct of clinical research in accordance with the principles of GCP helps to ensure that clinical research participants are not exposed to undue risk, and that data generated from the research are valid and accurate. By providing a basis both for the scientific and ethical integrity of research involving human subjects and for generating valid observations and sound documentation of the findings, GCP not only serves the interests of the parties actively involved in the research process, but also protects the rights, safety and well-being of subjects and ensures that investigations are scientifically sound and advance public health goals.

Objectives of this handbook

The objectives of this current WHO Handbook for GCP include the following:

- To support and promote the achievement of a globally applicable unified standard for the conduct of **all** clinical research studies on human subjects;
- To provide an overview and practical advice on the application and implementation of internationally accepted principles for GCP and clinical research in human subjects;
- To provide an educational and reference tool for anyone interested in, or intending to become or already actively engaged in, clinical research by providing the necessary background and insight into the reasons for the requirements of GCP and their efficient application;

- To assist editors in evaluating the acceptability of reported research for publication, and regulators in evaluating the acceptability of any study that could affect the use or the terms of registration of a medical product.

This handbook can be adopted or referenced by WHO Member States. Where national regulations or requirements do not exist or require supplementation, relevant regulatory authorities may designate or adopt these GCP principles and standards. Where national or adopted international standards are more demanding than WHO GCP, the former should take precedence.

Guidance on various aspects of clinical research is also available from several other national and international bodies such as, the International Conference on Harmonization (ICH), the International Standards Organization (ISO), and the Council for International Organizations of Medical Sciences (CIOMS), the European Agency for the Evaluation of Medicinal Products (EMA), and the United States Food and Drug Administration (FDA). (See References)

Scope of this handbook

This handbook defines fourteen principles of GCP, and provides guidance and assistance in the application and implementation of these principles by all parties involved in the clinical research process. In describing each principle, the handbook articulates the research processes and systems that need to be in place, and within these, the roles and responsibilities of various stakeholders (notably sponsors, investigators, ethics committees, and regulatory authorities) involved in the conduct of health and clinical research studies.

To the extent possible, the principles of GCP should generally apply to all clinical research involving human subjects, and not just research involving pharmaceutical or other medical products. Included here are:

- studies of a physiological, biochemical, or pathological process, or of the response to a specific intervention – whether physical, chemical, or psychological – in healthy subjects or in patients;

- controlled studies of diagnostic, preventive or therapeutic measures, designed to demonstrate a specific generalizable response to these measures against a background of individual biological variation;
- studies designed to determine the consequences for individuals and communities of specific preventive or therapeutic measures;
- studies concerning human health-related behaviour in a variety of circumstances and environments;
- studies that employ either observation or physical, chemical, or psychological intervention. Such studies may generate records or make use of existing records containing biomedical or other information about individuals who may or may not be identifiable from the records or information. The use of such records and the protection of the confidentiality of data obtained from those records are discussed in the "International Guidelines for Ethical Review of Epidemiological Studies" (CIOMS, 1991, currently being updated).

Although some principles of GCP may not apply to all types of research on human subjects, consideration of these principles is strongly encouraged wherever applicable as a means of ensuring the ethical, methodologically sound and accurate conduct of human subject's research.

Overview of the clinical research process

This section outlines key activities involved in the conduct of a clinical trial. This shows one possible sequence in which these activities may occur; other sequences (e.g., simultaneous completion of one or more activities) are also acceptable. Multiple parties are responsible for the success of these activities and procedures; the individual responsibilities of investigators, sponsors, ethics committees, and regulatory authorities will be the topic of subsequent sections of this Handbook.

Key trial activities include:

1. Development of the trial protocol

Within GCP, clinical trials should be described in a clear, detailed protocol.

The sponsor, often in consultation with one or more clinical investigators, generally designs the study protocol; clinical investigators may also design and initiate clinical studies, as sponsor-investigators. Integral to protocol development are the concepts of risk identification, study design and control groups, and statistical methodology. The sponsor and clinical investigator(s) should be aware of any national/local laws or regulations pertaining to designing, initiating, and conducting the study.

See WHO GCP Principles 2: Protocol; 3: Risk Identification; 4: Benefit-Risk Assessment.

2. Development of standard operating procedures (SOPs)

All parties who oversee, conduct or support clinical research (i.e., sponsors, clinical investigators, Independent Ethics Committees/

Institutional Review Boards [IECs/IRBs] monitors, contract research organizations [CROs]) should develop and follow written standard operating procedures (SOPs) that define responsibilities, records, and methods to be used for study-related activities.

See WHO GCP Principles 6: Protocol Compliance; 7: Informed Consent; 11: Records; 12: Confidentiality/Privacy; and 14: Quality Systems.

Sponsors should consider preparing SOPs for

- developing and updating the protocol, investigator's brochure, case report forms (CRFs), and other study-related documents;
- shipping, handling, and accounting for all supplies of the investigational product;
- standardizing the activities of sponsors and study personnel (e.g., review of adverse event reports by medical experts; data analysis by statisticians);
- standardizing the activities of clinical investigators to ensure that trial data is accurately captured;
- monitoring, to ensure that processes are consistently followed and activities are consistently documented;
- auditing, to determine whether monitoring is being appropriately carried out and the systems for quality control are operational and effective.

Similarly, clinical investigators should consider developing SOPs for common trial-related procedures not addressed in the protocol. These may include but are not limited to: communicating with the IEC/IRB; obtaining and updating informed consent; reporting adverse events; preparing and maintaining adequate records; administering the investigational product; and accounting for and disposing of the investigational product.

IECs/IRBs should develop and follow written procedures for their operations, including but not limited to: membership requirements; initial and continuing review; communicating with the investigator(s) and institution; and minimizing or eliminating conflicts of interest.

Regulators should consider developing written procedures for activities pertaining to the regulation of clinical research. These may include but are not limited to: reviewing applications and safety reports; conducting GCP inspections (where applicable) and communicating findings to the inspected parties; and establishing an infrastructure for due process and imposing sanctions on parties who violate national/local law or regulations.

3. Development of support systems and tools

Appropriate support systems and tools facilitate the conduct of the study and collection of data required by the protocol. Support systems and tools include, but are not limited to, trial-related information documents (e.g., investigator's brochure, case report forms [CRFs], checklists, study flow sheets, drug accountability logs; see *Overview Process 4: Generation and approval of trial-related information documents*), computer hardware and software, electronic patient diaries, and other specialized equipment.

See WHO GCP Principles 2: Protocol; 11: Records; 14: Quality Systems.

The sponsor is generally responsible for developing, maintaining, modifying, and ensuring the availability of support systems and tools for conducting the trial and collecting and reporting required data.

For example, the sponsor may consider developing/designing/providing/designating:

- diagnostic or laboratory equipment required by the study protocol, and procedures/schedules for servicing the equipment according to the manufacturer's specifications;
- computer systems (hardware and software) to be used in the clinical trial (e.g., statistical or other software, electronic patient diaries, coding of personal data), and software validation systems, as needed;
- facsimile or other communications equipment to facilitate reporting of serious adverse events;
- information and training tools for clinical investigators and site personnel.

4. Generation and approval of trial-related documents

Development of trial-related documents may facilitate the conduct of the study, collection and reporting of study-related data, and analysis of study results.

The sponsor generally develops, designs, and provides various standardized forms and checklists to assist the clinical investigator and his/her staff in capturing and reporting data required by the protocol.

See WHO GCP Principles 2: Protocol; 7: Informed Consent; 11: Records; 14: Quality Systems.

Examples of trial information documents include, but are not limited to:

- investigator's brochure;
- checklists to identify and document the required steps for each of the various clinical trial activities (e.g., investigator selection, approvals and clearances, monitoring, adverse event reporting and evaluation, analysis of interim data);
- investigational supplies accountability forms to document the amount and source of investigational product shipped and received, the amount dispensed to subjects, and the return/destruction, as appropriate, of any unused product;
- signature logs and other forms to document by whom activities are completed, when, and the sequence in which they are carried out;
- case report forms (CRFs) for each scheduled study visit to capture all of the necessary data collected from and reported for each subject;
- informed consent documents;
- adverse event or safety reporting forms;
- administrative forms to track research funds and expenses;
- forms to disclose information about the investigator's financial, property, or other interests in the product under study, in accordance with national/local law or regulations;

- formats for reports of monitoring visits;
- formats for progress reports, annual reports, and final study reports.

5. Selection of trial sites and the selection of properly qualified, trained, and experienced investigators and study personnel

Clinical investigators must be qualified and have sufficient resources and appropriately trained staff to conduct the investigation and be knowledgeable of the national setting and circumstances of the site and study population(s). Sponsors should review the requirements of the study protocol to determine the type(s) of expertise required and identify clinical investigators who have the particular medical expertise necessary to conduct the study and who have knowledge, training and experience in the conduct of clinical trials and human subject protection.

See WHO GCP Principles 2: Protocol; 9: Investigator Qualifications; 10: Staff Qualifications.

6. Ethics committee review and approval of the protocol

Within GCP, studies must be reviewed and receive approval/favourable opinion from an Independent Ethics Committee (IEC)/ Institutional Review Board (IRB) prior to enrollment of study subjects.

The investigator generally assumes responsibility for obtaining IEC/ IRB review of the study protocol. Copies of any approval/favourable opinion are then provided to the sponsor.

See WHO GCP Principles 1: Ethical Conduct; 2: Protocol; 4: Benefit-Risk Assessment; 5: Review by IEC/IRC; 7: Informed Consent; 8: Continuing Review/Ongoing Benefit-Risk Assessment; 11: Records; 12: Confidentiality/Privacy.

7. Review by regulatory authorities

Within GCP, studies must undergo review by regulatory authority(ies) for use of the investigational product or intervention in human subjects and to ensure that the study is appropriately designed to meet its stated objectives, according to national/regional/local law and regulations. [Note: Some countries may not have systems in place for reviewing research or may depend on external review. Also, some countries may have additional requirements for the review and approval of trial sites and/or investigators.]

The sponsor is generally responsible for ensuring that the applicable regulatory authority(ies) review and provide any required authorizations for the study before the study may proceed. The sponsor should also list the trial in applicable and/or required clinical trial registry(ies).

See WHO GCP Principles 2: Protocol; 4: Benefit-Risk Assessment.

8. Enrollment of subjects into the study: recruitment, eligibility, and informed consent

The clinical investigator has primary responsibility for recruiting subjects, ensuring that only eligible subjects are enrolled in the study, and obtaining and documenting the informed consent of each subject. Within GCP, informed consent must be obtained from each study subject prior to enrollment in the study or performing any specific study procedures.

See WHO GCP Principles 2: Protocol; 6: Protocol Compliance; 7: Informed Consent; 11: Records.

9. The investigational product(s): quality, handling and accounting

Quality of the investigational product is assured by compliance with Good Manufacturing Practices (GMPs) and by handling and storing the product according to the manufacturing specifications and the study protocol. GCP requires that sponsors control access to the in-

vestigational product and also document the quantity(ies) produced, to whom the product is shipped, and disposition (e.g., return or destruction) of any unused supplies. GCP also requires investigators to control receipt, administration, and disposition of the investigational product.

See WHO GCP Principles 2: Protocol; 11: Records; 13: Good Manufacturing Practice; 14: Quality Systems

10. Trial data acquisition: conducting the trial

Research should be conducted according to the approved protocol and applicable regulatory requirements. Study records documenting each trial-related activity provide critical verification that the study has been carried out in compliance with the protocol.

See WHO GCP Principles 2: Protocol; 6: Protocol Compliance; 11: Records.

11. Safety management and reporting

All clinical trials must be managed for safety. Although all parties who oversee or conduct clinical research have a role/responsibility for the safety of the study subjects, the clinical investigator has primary responsibility for alerting the sponsor and the IEC/IRB to adverse events, particularly serious/life-threatening unanticipated events, observed during the course of the research. The sponsor, in turn, has primary responsibility for reporting of study safety to regulatory authorities and other investigators and for the ongoing global safety assessment of the investigational product. A data and safety monitoring board (DSMB) may be constituted by the sponsor to assist in overall safety management.

See WHO GCP Principles 2: Protocol; 3: Risk Identification; 6: Protocol Compliance; 8: Continuing Review/Ongoing Benefit-Risk Assessment; 11: Records; 14: Quality Systems

12. Monitoring the trial

Sponsors generally perform site monitoring of a clinical trial to assure high quality trial conduct. The sponsor may perform such monitoring directly, or may utilize the services of an outside individual or organization (e.g., contract research organization [CRO]). The sponsor determines the appropriate extent and nature of monitoring based on the objective, purpose, design, complexity, size, blinding, and endpoints of the trial, and the risks posed by the investigational product.

The “on site” monitors review individual case histories in order to verify adherence to the protocol, ensure the ongoing implementation of appropriate data entry and quality control procedures, and verify adherence to GCP. In blinded studies, these monitors remain blinded to study arm assignment.

For an investigator-initiated study, the sponsor-investigator should consider the merits of arranging independent, external monitoring of the study, particularly when the study involves novel products or potential significant risks to subjects.

See WHO GCP Principles 2: Protocol; 6: Protocol Compliance; 8: Continuing Review; 11: Records; 14: Quality Systems.

13. Managing trial data

Within GCP, managing clinical trial data appropriately assures that the data are complete, reliable and processed correctly, and that data integrity is preserved. Data management includes all processes and procedures for collecting, handling, manipulating, analysing, and storing/archiving of data from study start to completion.

The sponsor bears primary responsibility for developing appropriate data management systems. The sponsor and the investigator share responsibility for implementing such systems to ensure that the integrity of trial data is preserved.

See WHO GCP Principles 2: Protocol; 6: Protocol Compliance; 11: Records; 14: Quality Systems.

See also *Overview Processes 1: Protocol development; 2: Development of standard operating procedures; 3: Support systems and tools; 4: Trial information documents; 10: Trial data acquisition.*

Data management systems should address (as applicable):

- data acquisition;
- confidentiality of data/data privacy;
- electronic data capture (if applicable);
- data management training for investigators and staff;
- completion of CRFs and other trial-related documents, and procedures for correcting errors in such documents;
- coding/terminology for adverse events, medication, medical histories;
- safety data management and reporting;
- data entry and data processing (including laboratory and external data);
- database closure;
- database validation;
- secure, efficient, and accessible data storage;
- data quality measurement (i.e., how reliable are the data) and quality assurance;
- management of vendors (e.g., CROs, pharmacies, laboratories, software suppliers, off-site storage) that participate directly or indirectly in managing trial data.

14. Quality assurance of the trial performance and data

Quality assurance (QA) verifies through systematic, independent audits that existing quality control systems (e.g., study monitoring: see GCP Process 12, *Monitoring the trial*; data management systems: see GCP Process 13, *Managing trial data*) are working and effective. Quality assurance audits may be performed during the course of the clinical trial and/or upon trial completion.

Sponsors bear primary responsibility for establishing quality systems and conducting quality assurance audits.

See WHO GCP Principles 11: Records; 14: Quality Systems.

See also Overview Processes 2: Development of standard operating procedures; 10: Trial data acquisition: conducting the trial; 12: Monitoring the trial; and 13: Managing trial data.

15. Reporting the trial

The results of each controlled study involving an investigational product should be summarized and described in an integrated clinical study report containing clinical data and statistical descriptions, presentations, and analyses. The report should be complete, timely, well-organized, free from ambiguity, and easy to review.

The sponsor is responsible for preparing clinical study reports.

Such reports should generally include:

- a description of the ethical aspects of the study (e.g. confirmation that the study was conducted in accordance with basic ethical principles);
- a description of the administrative structure of the study (i.e. identification and qualifications of investigators/sites/other facilities);
- an introduction that explains the critical features and context of the study (e.g. rationale and aims, target population, treatment duration, primary endpoints);
- a summary of the study objectives;
- a description of the overall study design and plan;
- a description of any protocol amendments;
- an accounting of all subjects who participated in the study, including all important deviations from inclusion/exclusion criteria and a description of subjects who discontinued after enrollment;
- an accounting of protocol violations;
- a discussion of any interim analyses;

- an efficacy evaluation, including specific descriptions of subjects who were included in each efficacy analysis and listing of all subjects who were excluded from the efficacy analysis and the reasons for such exclusion;
- a safety evaluation, including extent of exposure, common adverse events and laboratory test changes, and serious or unanticipated or other significant adverse events including evaluation of subjects who left the study prematurely because of an adverse event or who died;
- a discussion and overall conclusions regarding the efficacy and safety results and the relationship of risks and benefits;
- tables, figures, and graphs that visually summarize the important results or to clarify results that are not easily understood;
- a reference list.

Where permitted, abbreviated or less detailed reports may be acceptable for uncontrolled or aborted studies.

See WHO GCP Principles 2: Protocol; 11: Records; see also ICH E3 (Structure and Content of Clinical Study Reports)

WHO Principles of GCP

Principle 1: Research involving humans should be scientifically sound and conducted in accordance with basic ethical principles, which have their origin in the Declaration of Helsinki. Three basic ethical principles of equal importance, namely respect for persons, beneficence, and justice, permeate all other GCP principles.

Principle 2: Research involving humans should be scientifically justified and described in a clear, detailed protocol.

Principle 3: Before research involving humans is initiated, foreseeable risks and discomforts and any anticipated benefit(s) for the individual trial subject and society should be identified. Research of investigational products or procedures should be supported by adequate non-clinical and, when applicable, clinical information.

Principle 4: Research involving humans should be initiated only if the anticipated benefit(s) for the individual research subject and society clearly outweigh the risks. Although the benefit of the results of the trial to science and society should be taken into account, the most important considerations are those related to the rights, safety, and well-being of the trial subjects.

Principle 5: Research involving humans should receive independent ethics committee/institutional review board (IEC/IRB) approval/favourable opinion prior to initiation.

Principle 6: Research involving humans should be conducted in compliance with the approved protocol

Principle 7: Freely given informed consent should be obtained from every subject prior to research participation in accordance with national culture(s) and requirements. When a subject is not capable of giving informed consent, the permission of a legally authorized representative should be obtained in accordance with applicable law.

Principle 8: Research involving humans should be continued only if the benefit-risk profile remains favourable.

Principle 9: Qualified and duly licensed medical personnel (i.e., physician or, when appropriate, dentist) should be responsible for the medical care of trial subjects, and for any medical decision(s) made on their behalf.

Principle 10: Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s) and currently licensed to do so, where required.

Principle 11: All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Principle 12: The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

Principle 13: Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing

Practice (GMP) and should be used in accordance with the approved protocol.

Principle 14: Systems with procedures that assure the quality of every aspect of the trial should be implemented.

WHO Principles of GCP

PRINCIPLE 1: ETHICAL CONDUCT

Research involving humans should be scientifically sound and conducted in accordance with basic ethical principles, which have their origin in the Declaration of Helsinki. Three basic ethical principles of equal importance, namely respect for persons, beneficence, and justice, permeate all other GCP principles enumerated below.

Ethical principles have been established by many national and international bodies, including:

- 1) The World Medical Association Declaration of Helsinki;
- 2) The Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines for Biomedical Research Involving Human Subjects;

and other guidelines (see References).

Application

Principle 1 is applied through

- design and approval of the protocol
- informed consent
- scientific and ethical review
- a favourable risk/benefit assessment
- fair and transparent procedures and outcomes in the selection of research subjects
- compliance with national and international laws, regulations, and standards.

Questions and Answers:

What is meant by “respect for persons” and how is it most directly implemented within GCP?

“Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection.” (The Belmont Report; CIOMS, International Ethical Guidelines)

“Respect for persons requires that subjects, to the degree that they are capable, be given the opportunity to choose what shall or shall not happen to them. This opportunity is provided when adequate standards for informed consent are satisfied.” (The Belmont Report)

In general, all individuals, including healthy volunteers, who participate as research subjects should be viewed as intrinsically vulnerable.

When some or all of the subjects, such as children, prisoners, pregnant women, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons are likely to be more vulnerable to coercion or undue influence, additional safeguards should be included in the study to protect the rights and welfare of these subjects. These safeguards may include, but are not limited to: special justification to the ethical review committee that the research could not be carried out equally well with less vulnerable subjects; seeking permission of a legal guardian or other legally authorized representative when the prospective subject is otherwise substantially unable to give informed consent; including an impartial witness to attend the informed consent process if the subject or the subject’s legally authorized representative cannot read; and/or additional monitoring of the conduct of the study.

Within GCP, the principle of “respect for persons” is most directly implemented through the process of informed consent. Included here is the provision that the subject (or subject’s legally authorized representative) will be informed in a timely manner if information becomes available that may be relevant to the subject’s willingness to continue participation in the trial. (See GCP Principle 7: *Informed Consent*)

What is meant by “beneficence” and how is it most directly implemented within GCP?

“**Beneficence** refers to the ethical obligation to maximize benefit and to minimize harm. This principle gives rise to norms requiring that the risks of research be reasonable in the light of the expected benefits, that the research design be sound, and that the investigators be competent both to conduct the research and to safeguard the welfare of the research subjects. Beneficence further proscribes the deliberate infliction of harm on persons; this aspect of beneficence is sometimes expressed as a separate principle, **nonmaleficence** “do no harm”. (CIOMS, International Ethical Guidelines)

The principle of “beneficence” bears a close relationship to the (GCP) “requirement that research be justified on the basis of a favourable risk/benefit assessment.” (The Belmont Report)

“Risks and benefits of research may affect the individual subjects, ... and society at large (or special groups of subjects in society).” “In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight.” (The Belmont Report)

Within GCP, the principle of “beneficence” is most directly implemented through risk/benefit assessment during design and review (initial review as well as continuing review) of the study protocol. (See also WHO GCP Principles 3: Risk Identification; 4: *Benefit-Risk Assessment*; 8: *Continuing Review/Ongoing Benefit-Risk Assessment*)

What is meant by “justice” and how is it most directly implemented within GCP?

“... the principle of justice gives rise to moral requirements that there be fair procedures and outcomes in the selection of research subjects.” (The Belmont Report)

Justice in the selection of research subjects requires attention in two respects: the individual and the social.

“Individual justice in the selection of subjects requires that researchers exhibit fairness; thus, they should not offer potentially beneficial research to only some patients who are in favor or select only “undesirable” persons for risky research.” (The Belmont Report)

Social justice relates to groups of subjects, including the involvement of vulnerable subjects or subject populations. “Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted” (The Belmont Report). “Equity requires that no group or class of persons should bear more than its fair share of the burdens of participation in research. Similarly, no group should be deprived of its fair share of the benefits of research, short-term or long-term... Subjects should be drawn from the qualifying population in the general geographic area of the trial without regard to race, ethnicity, economic status, or gender unless there is a sound scientific reason to do otherwise.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 12)

Within GCP, the principle of “justice” is most directly implemented by considering procedures and outcomes for subject selection during the design and review of the study protocol as well as during recruitment and enrollment of study subjects. (See also WHO GCP Principles 2: *Protocol*, and 7: *Informed Consent*)

Implementation

The basic ethical principles of biomedical research are reflected in all GCP principles and processes, impacting on the role and responsibilities of each party within GCP. Each party participating in clinical research has responsibility for ensuring that research is ethically and scientifically conducted according to the highest standards. This includes the investigator(s) and site staff, the sponsor and sponsor’s staff (including monitors and auditors), the ethics committee(s), the regulatory authority(-ies), and the individual research subjects.

For more information (including Roles and Responsibilities):

For **IECs/IRBs**, refer to:

Responsibilities (ICH E6, Section 3.1)

Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, 2000, Section 6.2)

Follow-Up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, 2000, Section 9)

Ethical review of externally sponsored research, CIOMS, International Ethical Guidelines, Guideline 3)

For **clinical investigators**, refer to:

Communications with the IRB/IEC (ICH E6, Section 4.4)

Informed Consent of Trial Subjects (ICH E6, Section 4.8)

Safety Reporting (ICH E6, Section 4.11)

For **sponsors**, refer to:

Trial Design (ICH E6, Section 5.4)

Notification/Submission to Regulatory Authority(ies) (ICH E6, Section 5.10)

Safety Information (ICH E6, Section 5.16)

For **regulatory authorities**, refer to:

WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995

See also:

Discussion of the WHO Principles of GCP

GCP Principle 2: Protocol

GCP Principle 3: Risk Identification

GCP Principle 4: Benefit-Risk Assessment

GCP Principle 7: Informed Consent

GCP Principle 8: Continuing Review/Ongoing Benefit-Risk Assessment

Definitions for:

Impartial Witness (ICH E6, 1.26)

Informed Consent (ICH E6, 1.28)

Legally Acceptable Representative (ICH E6, 1.37)

Vulnerable Subjects (ICH E6, 1.61)

Well-being [of the Trial Subjects] (ICH E6, 1.62)

Clinical Trial Protocol and Protocol Amendment(s):

Selection and Withdrawal of Subjects (ICH E6, Section 6.5)

Ethics (ICH E6, Section 6.12)

PRINCIPLE 2: PROTOCOL

Research involving humans should be scientifically justified and described in a clear, detailed protocol.

“The experiment should be such as to yield fruitful results...unprocurable by other methods or means of study, and not random and unnecessary in nature.” (The Nuremburg Code)

“The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol.” (Declaration of Helsinki)

Application

Principle 2 is applied through development of a clear, detailed, scientifically justified and ethically sound protocol that (1) complies with requirements established by national and local laws and regulations, and (2) undergoes scientific and ethical review prior to implementation.

Questions and Answers

What is meant by “scientifically justified”?

The protocol must be carefully designed to generate statistically and scientifically sound answers to the questions that are being asked and meet the objective(s) of the study. The objective(s) should also justify the risk; that is, the potential benefits (if any) of participation in the study should outweigh the risks.

“A clinical trial cannot be justified ethically unless it is capable of producing scientifically reliable results.” (CIOMS, International Ethical Guidelines, Guideline 11)

What is a clear detailed protocol?

A protocol “describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could

be provided in other protocol referenced documents.” (ICH E6, Section 1.44)

A protocol “provides the background, rationale, and objective(s) of a biomedical research project and describes its design, methodology, and organization, including ethical and statistical considerations. Some of these considerations may be provided in other documents referred to in the protocol.” (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Glossary)

What information should be included in a study protocol?

The study protocol is the core document communicating trial requirements to all parties who have responsibility for approval, conduct, oversight, and analysis of the research.

GCP recognizes that certain essential elements should be included in the study protocol. These include but are not limited to:

- general information;
- background information;
- description of the trial objectives and purpose;
- description of the trial design;
- criteria for inclusion, exclusion, and withdrawal of study subjects;
- treatment information;
- methods and timing for assessing, recording and analysing data gathered on the investigational product;
- methods for obtaining safety information, including plans for safety monitoring;
- description of the statistical methods to be employed;
- description of ethical considerations relating to the trial;
- a statement related to permitting trial-related monitoring, audits, and inspection by the sponsor, IEC/IRB, and regulators, including direct access to source data/documents;

- means for obtaining informed consent and communication of information to prospective subjects.

What is a “protocol amendment”?

“A protocol amendment is a written description of a change(s) to or formal clarification of a protocol.” (ICH E6, Section 1.45)

What types of changes may require formal amendment of the protocol?

Regional,¹ national, or local laws and regulations may require sponsors to prepare formal protocol amendments to describe any change that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study.

Examples of changes that generally require formal amendment include, but are not limited to:

- changes in drug dosage or duration of exposure of individual subjects to an investigational product beyond that described in the current protocol;
- significant increase in the number of subjects under study or in the duration of the study;
- significant change in the study design, such as adding or dropping a control group; and
- addition of a new test or procedure that is intended to improve monitoring for or reduce the risk of a side effect or adverse event, or the dropping of a test intended to monitor safety.

¹ In this document, “regional” refers to supranational laws, regulations, or requirements, such as those adopted by the European Union.

What is the “investigator’s brochure” and how does it relate to the protocol?

The investigator’s brochure is a “compilation of the clinical and non-clinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects.” (ICH E6, 1.36)

In general, the investigator’s brochure provides more complete background information on the investigational product than is provided in the protocol. The investigator’s brochure assists the investigator in interpreting and implementing the study protocol, and may be of particular importance in helping the investigator determine whether specific adverse events are unanticipated, and accordingly, when and how such events should be reported to the sponsor, IEC/IRB, and regulators.

What is meant by a well-controlled study?

A well-controlled study uses a design that permits a comparison of subjects treated with the investigational agent/intervention to a suitable control population, so that the effect of the investigational agent/intervention can be determined and distinguished from other influences, such as spontaneous change, “placebo” effects, concomitant therapy(ies)/intervention(s), or observer expectations.

What are some designs for controlled clinical studies?

Commonly used designs for controlled clinical studies include: placebo concurrent control; no-treatment concurrent control; dose-response concurrent control; active (positive) concurrent control; external control (including historical control); and combination (multiple control group) designs. (See ICH E10: Choice of Control Group and Related Issues in Clinical Trials)

“As a general rule, research subjects in the control group of a trial of a diagnostic, therapeutic, or preventive intervention should receive an established effective intervention. In some circumstances it may be ethically acceptable to use an alternative comparator, such as placebo or “no treatment”.” (CIOMS, International Ethical Guidelines, Guideline 11)

What can be done to minimize bias in a clinical investigation?

Bias implies subjective or unfair distortion of judgment in favor of or against a person or thing. The purpose of conducting a clinical trial of an investigational product is to distinguish the effect of the investigational product from other factors, such as spontaneous changes in the course of the disease, placebo effects, or biased/subjective observation. Bias can be minimized in a clinical trial by designing well-controlled studies, by using blinding, and by using procedures to randomize subjects to the various study arms.

What is meant by “blinding” or “masking”?

Blinding or masking is “[a] procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single blinding usually refers to the subject(s) being unaware, and double blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).” (ICH E6, 1.10)

When is unblinding of the trial by the investigator permissible? How should unblinding be accomplished (in those situations where it would be allowed)?

Unblinding may be necessary in the event of a medical emergency for a trial subject. Generally breaking the blind involves procedures specified in the study protocol that allow the investigator and/or sponsor to find out whether a particular subject received the investigational product, or received a comparator product or placebo, where applicable, while on the study.

“The investigator... should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).” (ICH E6, Section 4.7)

What is meant by “randomization”?

Randomization is the “process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.” (ICH E6, 1.48)

“Randomization is the preferred method for assigning subjects to the various arms of the clinical trial unless another method, such as historical or literature controls, can be justified scientifically and ethically. Assignment to treatment arms by randomization, in addition to its usual scientific superiority, offers the advantage of tending to render equivalent to all subjects the foreseeable benefits and risks of participation in a trial.” (CIOMS, International Ethical Guidelines, Guideline 11)

“The investigator should follow the trial’s randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol.” (ICH E6, Section 4.7)

How should the protocol address reporting of adverse events?

The protocol should specify procedures for eliciting reports of, and for recording and reporting, adverse event and inter-current illnesses; the type and duration of the follow-up of subjects after adverse events, and the methods to be used in, and timing for, assessing, recording, and analysing safety parameters.

The protocol and investigator’s brochure will assist the investigator and sponsor in determining whether an adverse event is “unexpected” and how it should be reported. Unexpected serious adverse drug reactions should be reported to the regulatory authority(ies) and to other investigators involved in the trial in accordance with applicable regulatory requirement(s).

Implementation

Sponsors are primarily responsible for (a) designing the clinical investigation, (b) developing the study protocol, investigator’s brochure, and related materials to describe the procedures that will be followed, study endpoints, and data collection, and other study

requirements; and (c) ensuring that the protocol complies with applicable national and local laws and regulations.

Investigators may be consulted by the sponsor during protocol design or, in some cases, may personally contribute to the design of the protocol. Investigators are responsible for familiarizing themselves with the study protocol, investigator's brochure, and related materials to ensure that they are able to carry out the study in compliance with the specifications of the protocol.

IECs/IRBs are responsible for conducting ethical review of the study protocol. This also includes arranging for a scientific review or verifying that a competent body has determined that the research is scientifically sound. (See GCP Principle 5: *Review by IEC/IRB*)

Regulators bear responsibility for allowing a protocol to proceed in accordance with applicable laws and regulations. This may include prospective review of the protocol, the investigator's brochure and other relevant information. Where the protocol or investigator's brochure is inaccurate or materially incomplete, where the protocol does not adequately provide for the protection of subject rights and safety, or where the protocol is deficient in design to meet its stated objectives, the regulatory authority may require protocol modification or take action to disallow the protocol to proceed in accordance with applicable laws and regulations.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Clinical Trial Protocol and Protocol (sic) (ICH E6, Section 6)

- Investigator's Brochure (ICH E6, Section 7)

- Documentation (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 5.3)

- Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2)

For **clinical investigators**, refer to:

- Investigator's Qualifications and Agreements (ICH E6, Section 4.1)

- Adequate Resources (ICH E6, Section 4.2)

- Compliance with Protocol (ICH E6, Section 4.5)

Randomization Procedures and Unblinding (ICH E6, Section 4.7)
Safety Reporting (ICH E6, Section 4.11)
Clinical Trial Protocol and Protocol (*sic*) (ICH E6, Section 6)
Investigator's Brochure (ICH E6, Section 7)

For **sponsors**, refer to:

Trial Design (ICH E6, Section 5.4)
Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee (ICH E6, Section 5.5)
Notification/Submission to Regulatory Authorities (ICH E6, Section 5.10)
Clinical Trial Protocol and Protocol (*sic*) (ICH E6, Section 6)
Investigator's Brochure (ICH E6, Section 7)
Items to be Included in a Protocol (or Associated Documents) for Biomedical Research Involving Human Subjects (CIOMS, International Ethical Guidelines, Appendix 1)
WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995 (Section 2)

For **regulatory authorities**, refer to:

GCP Compliance Monitoring Programs by Regulatory Authorities (Good Clinical Practices: Document of the Americas, PAHO, Chapter 7)
WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995

See also:

Discussion of the WHO Principles of GCP
GCP Principle 3: Risk Identification
GCP Principle 4: Benefit-Risk Assessment
GCP Principle 5: Review by IEC/IRB
GCP Principle 6: Protocol Compliance
GCP Principle 11: Records

Definitions for:

Investigator's Brochure (ICH E6, 1.36)
Protocol (ICH E6, 1.44)
Protocol Amendment (ICH E6, 1.45)

PRINCIPLE 3: RISK IDENTIFICATION

Before research involving humans is initiated, foreseeable risks and discomforts and any anticipated benefit(s) for the individual trial subject and society should be identified. Research of investigational products or procedures should be supported by adequate non-clinical and, when applicable, clinical information.

“The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study that the anticipated results will justify the performance of the experiment.” (The Nuremberg Code)

“Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate animal experimentation.” (Declaration of Helsinki)

“The assessment of risks and benefits requires a careful arrayal of relevant data, including, in some cases, alternative ways of obtaining the benefits sought in the research... [T]he assessment presents both an opportunity and a responsibility to gather systematic and comprehensive information about proposed research.” (The Belmont Report)

Application

Principle 3 is applied through:

- conducting a thorough search of available scientific information about the investigational product or procedure(s) (including findings from tests in laboratory animals and any previous human experience);
- developing the investigator’s brochure, the study protocol, and the informed consent document to adequately, accurately, and objectively reflect the available scientific information on foreseeable risks and anticipated benefits.

Questions and Answers:

What is meant by “risk(s)” and “benefit(s)”?

“The term “risk” refers to a possibility that harm may occur. However, when expressions such as “small risk” or “high risk” are used, they usually refer (often ambiguously) both to the chance (probability) of experiencing a harm and the severity (magnitude) of the envisioned harm. The term “benefit” is used in the research context to refer to something of positive value related to health or welfare.” (The Belmont Report)

“Many kinds of possible harms and benefits need to be taken into account. There are, for example, risks of psychological harm, physical harm, legal harm, social harm and economic harm and the corresponding benefits. While the most likely types of harms to research subjects are those of psychological or physical pain or injury, other possible kinds should not be overlooked.” (The Belmont Report)

“Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society).” “... In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight.” (The Belmont Report) (See GCP Principle 1: *Ethical Conduct*)

How is identification of risks and benefits implemented within GCP and where may information about risks and benefits be obtained?

Within GCP, the identification of risks and benefits is undertaken as part of the scientific review that accompanies protocol development.

“... [M]edical research involving humans must conform to generally accepted scientific principles, and be based on a thorough knowledge of the scientific literature, other relevant sources of information and adequate laboratory and, where indicated, animal experimentation. Scientific review must consider, inter alia, the study design,

including the provisions for avoiding or minimizing risk and for monitoring safety.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 2)

Important to any scientific review is the critical selection and evaluation of that literature accessed from available scientific publications. However, it may also be important to review relevant unpublished data, particularly where such data raise concerns for subject safety.

What is non-clinical information?

Non-clinical information is information derived from non-clinical studies, defined as “Biomedical studies not performed on human subjects.” (ICH, E6, 1.41)

The term includes in vivo (animal or plant studies) or in vitro (laboratory) experiments in which investigational products are studied in test systems under laboratory conditions to determine their safety. Regulators and others may require non-clinical studies to comply with standards for Good Laboratory Practice (GLP); such studies may be called or referred to as “GLP studies.”

What is GLP (Good Laboratory Practice) and what is the relationship between GLP and GCP Principle 3?

The purpose of GLP is to assure the quality and integrity of non-clinical (notably animal) data submitted in support of research permits or marketing applications. In accordance with national/local laws and regulations, regulators may establish GLP standards for the conduct and reporting of non-clinical studies. GLP standards include requirements for: organization and management of the testing facility, qualifications of personnel and the study director, quality assurance units, characteristics of animal care facilities, laboratory operation areas, and specimen and data storage facilities, equipment maintenance, standard operating procedures, characterization of test and control articles, protocols, study conduct, reports, and record keeping.

In accordance with national/local laws and regulations, compliance with GLP may be a requirement for the acceptance of animal toxicology studies in support of human testing. Where not required by national/local laws and regulations, GLP standards provide important guidance to the conduct of quality animal toxicology studies.

What does the term “clinical information” include?

Clinical information here refers to information derived from prior clinical study or experience. A clinical study is defined as “[a]ny investigation in human subjects intended to discover or verify the clinical, pharmacological, and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.” (ICH E6, 1.12)

What is meant by “foreseeable” and “anticipated”?

The terms “foreseeable” and “anticipated” connote knowledge that is available or predictable at the time of protocol review. Implicit in these terms is the obligation to conduct a thorough search of scientific literature contemporaneous to the time of initial protocol review and the obligation to keep apprised of significant new findings on risks and/or benefits that become available as the protocol proceeds.

Implementation

The responsibility for implementing this principle is shared by sponsors, investigators, IECs/IRBs, and regulators:

The **sponsor** generally conducts the literature review to ensure that there is sufficient information available to support the proposed clinical trial in the population to be studied and that there is sufficient safety and efficacy data to support human exposure to the product. The sponsor may need to conduct pre-clinical studies to ensure

there is sufficient safety and efficacy data to support human exposure. The sponsor should summarize available information about the procedure/product in the investigator's brochure, and accordingly set forth the design of the study in the protocol. In general, it is important that the sponsor develop a comprehensive, accurate and complete investigator's brochure, as this is a principal means of communicating vital safety and scientific information to the investigator and, in turn, to the IEC/IRB.

Review of the protocol, investigator's brochure, and other relevant information enables the **IECs/IRBs** to (1) determine whether the benefits outweigh the risks, (2) understand the study procedures or other steps that will be taken to minimize risks, and (3) ensure that the informed consent document accurately states the potential risks and benefits in a way that will facilitate comprehension by all study subjects, with particular attention to vulnerable groups.

Investigators must be knowledgeable of the protocol, investigator's brochure and other relevant information regarding potential risks and benefits, and must be able to adequately, accurately and objectively identify the potential risks and benefits to subjects. Investigators may need to do some additional literature search beyond that provided by the sponsor. Investigators should also be thoroughly familiar with the appropriate use of the trial product(s)/procedures and should take the necessary steps to remain aware of all relevant new data on the investigational product, procedure, or method that becomes available during the course of the clinical trial.

Regulators bear responsibility for allowing a protocol to proceed in accordance with existing national laws/regulations or internationally accepted standards. This may include prospective review of the protocol, the investigator's brochure and other relevant information to ensure that risk(s) and benefit(s) are accurately identified and justify allowing the protocol to proceed. As appropriate, adopted national standards should address additional national or regional racial, cultural, or religious standards/issues not otherwise covered by the international standards. In accordance with national/local laws and regulations, regulators may establish standards for the conduct of

non-clinical studies, review non-clinical and clinical data submitted in support of research permits or marketing applications, and/or inspect facilities that conduct non-clinical and clinical studies.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Responsibilities (ICH E6, Section 3.1)
- Procedures (ICH E6, Section 3.3)
- Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2)
- Follow-up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 9)

For **clinical investigators**, refer to:

- Investigator’s Brochure (ICH E6, Section 7)
- Clinical Trial Protocol, General Information (ICH E6, Section 6)

For **sponsors**, refer to:

- Investigator’s Brochure (ICH E6, Section 7)
- Clinical Trial Protocol (ICH E6, Section 6)
- UNDP/World Bank WHO Special Programme for Research and Training in Tropical Diseases (TDR) “Handbook on Good Laboratory Practice (GLP): Quality Practices for Regulated Non-Clinical Research and Development” (September 2000)
- Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (ICH M3)
- Preclinical Testing of Biotechnology-Derived Pharmaceuticals (ICH S6)
- Literature review (“Clinical Investigation of medical devices for human subjects,” ISO 14155-1, Part 1, Annex A)

For **regulatory authorities**, refer to:

- Guidelines for good clinical practice (GCP) for trials on pharmaceutical products. WHO Technical Report Series, No. 850, 1995
- UNDP/World Bank WHO Special Programme for Research and Training in Tropical Diseases (TDR) “Handbook on Good Labora-

tory Practice (GLP): Quality Practices for Regulated Non-Clinical Research and Development” (September 2000)
Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals (ICH M3)
Preclinical Testing of Biotechnology-Derived Pharmaceuticals (ICH S6)

See also:

Discussion of the WHO Principles of GCP

GCP Principle 1: Ethical Conduct

GCP Principle 2: Protocol

GCP Principle 4: Benefit-Risk Assessment

GCP Principle 7: Informed Consent

Definitions for:

Investigator’s Brochure (ICH E6, 1.36)

Nonclinical Study (ICH E6, 1.41)

Protocol (ICH E6, 1.44)

Protocol Amendment (ICH E6, 1.45)

PRINCIPLE 4: BENEFIT-RISK ASSESSMENT

Research involving humans should be initiated only if the anticipated benefit(s) for the individual research subject and society clearly outweigh the risks. Although the benefit of the results of the trial to science and society should be taken into account, the most important considerations are those related to the rights, safety, and well being of the research subjects.

“The degree of risk to be taken should never exceed that determined by the humanitarian importance of the problem to be solved by the experiment.” (The Nuremberg Code)

“Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research.” (Declaration of Helsinki)

“For all biomedical research involving human subjects, the investigator must ensure that potential benefits and risks are reasonably balanced and risks are minimized.” (CIOMS, International Ethical Guidelines, Guideline 8)

“It is commonly said that benefits and risks must be ‘balanced’ and shown to be ‘in a favourable ratio.’... Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible. The method of ascertaining risks should be explicit... It should also be determined whether ... estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies.” (The Belmont Report)

“... Risks should be reduced to those necessary to achieve the research objective. It should be determined whether it is in fact necessary to use human subjects at all. Risk can perhaps never be entirely eliminated, but it can often be reduced by careful attention to alternative procedures... .When research involves significant risk of serious impairment, review committees should be extraordinarily

insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject—or in some rare cases, to the manifest voluntariness of the participation)... ” (The Belmont Report)

“... Scientific review must consider inter alia, the study design, including the provisions for avoiding or minimizing risk and for monitoring safety.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 2)

“Risks and benefits of research may affect the individual subjects, the families of the individual subjects, and society at large (or special groups of subjects in society).” “... In balancing these different elements, the risks and benefits affecting the immediate research subject will normally carry special weight.” (The Belmont Report)

“In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.” (Declaration of Helsinki)

Application

Principle 4 is applied through appropriate study design and through ethical, scientific, and, where applicable, regulatory review of the study protocol prior to its initiation.

Questions and Answers

Who is responsible for determining that the risk/benefit profile of a study is acceptable or unacceptable?

Within GCP, the sponsor of the study, the investigator(s), IECs/IRBs, and the regulatory authority(-ies) each have responsibilities for evaluating the risk/benefit profile of a study (see Implementation, below). In accordance with applicable laws and regulations, the regulatory authority may stop a study from proceeding or require modifications to the protocol based on an unacceptable risk/benefit profile. The IEC/IRB has authority to issue an approval/favourable opinion; require modifications prior to approval/favourable opinion; issue a disapproval/negative opinion; or terminate/suspend a prior approval/favourable

opinion. An investigator may decide either to participate or not participate in a study based on his/her assessment of the risk/benefit profile. The sponsor may decide either not to initiate or to terminate/suspend a trial where the risk/benefit profile is unacceptable.

When should a risk/benefit determination be performed?

A risk/benefit determination should be performed prior to study initiation as well as periodically during the study (see also GCP Principle 8: *Continuing Review/Ongoing Benefit-Risk Assessment*).

What if the risk-benefit profile of a study appears favourable from a national, societal, institutional, or scientific standpoint but unfavourable to the participating research subjects?

The most important considerations in a study are those related to the rights, safety, and well-being of the trial subjects. "In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society." (Declaration of Helsinki)

What about financial reimbursements to research subjects?

Financial reimbursements to subjects are distinct from any benefits contributing to the risk-benefit analysis.

Where applicable laws and regulations allow, financial reimbursements may be provided to subjects for participation in a study. Where no requirements exist, fair compensation should be provided in an appropriate manner after consultation with the relevant institutions/organizations. Such reimbursements are generally viewed as part of the recruitment process rather than as benefits of the study. However, at the time of initial review, the IEC(s)/IRB(s) should review both the amount of the financial reimbursement(s) and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence. The reimbursements provided should not be so large as to unduly induce subjects to enroll in the

study or to stay in the study when they would otherwise withdraw. Any credit for payment should accrue as the study progresses and not be contingent upon the subject completing the entire study. The reimbursements should not replace adequate insurance to be provided by the sponsor against claims for any trial-related injuries.

Implementation

The responsibility for implementing this principle is shared by sponsors, investigators, IECs/IRBs, and regulators.

The **sponsor** should design research studies to ensure that risks to subjects are minimized.

The **investigator(s)** should review the investigator's brochure and other relevant risk and benefit information in making a decision to conduct the study. The investigator is also responsible for providing adequate, accurate, and objective information on risks and benefits during informed consent of study subjects.

Prior to study initiation, the IEC(s)/IRB(s) should review the protocol, investigator's brochure, and other relevant information to (1) understand the study procedures or other steps that will be taken to minimize risks, (2) understand the potential benefits (if any) and determine whether those benefits outweigh the anticipated risks, and (3) ensure that the informed consent document accurately states the potential risks and benefits in a way that will allow study subjects to understand what they are undertaking.

Regulators bear responsibility for allowing a protocol to proceed in accordance with applicable laws and regulations. This may include prospective review of the protocol, the investigator's brochure, and other relevant information to ensure that risk(s) and benefit(s) are accurately identified and justify allowing the protocol to proceed. The regulatory authority may require modification to a protocol as a condition to its proceeding and/or may suspend or terminate a protocol based on an unacceptable risk/benefit profile in accordance with applicable laws and regulations.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

Responsibilities (ICH E6, Section 3.1)

Procedures (ICH E6, Section 3.3)

Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2)

Communicating a Decision (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 8)

Follow-up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 9)

Inducement to participate in research (CIOMS International Ethical Guidelines, 2002, Guideline 7)

For **clinical investigators**, refer to:

Investigator's Qualifications and Agreements (ICH E6, Section 4.1)

Clinical Trial Protocol, General Information (ICH E6, Section 6)

Investigator's Brochure (ICH E6, Section 7)

Inducement to participate in research (CIOMS International Ethical Guidelines, 2002, Guideline 7)

For **sponsors**, refer to:

Notification/Submission to Regulatory Authority(ies) (ICH E6, Section 5.10)

Clinical Trial Protocol, General Information (ICH E6, Section 6)

Investigator's Brochure (ICH E6, Section 7)

For **regulatory authorities**, refer to:

WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995

See also:

Discussion of the WHO Principles of GCP

GCP Principle 2: Protocol

GCP Principle 3: Risk Identification

GCP Principle 7: Informed Consent

GCP Principle 8: Continuing Review/Ongoing Benefit-Risk Assessment

Definitions for:

Applicable Regulatory Requirement(s) (ICH E6, 1.4)

Approval (in relation to institutional review boards [IRBs]) (ICH E6, 1.5)

Informed Consent (ICH E6, 1.28)

Investigator's Brochure (ICH E6, 1.36)

PRINCIPLE 5: REVIEW BY IEC/IRB

Research involving humans should receive independent ethics committee/institutional review board (IEC/IRB) approval/favourable opinion prior to initiation.

The "... protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor, or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed..." (Declaration of Helsinki)

"Failure to submit a protocol to the committee should be considered a clear and serious violation of ethical standards." (CIOMS, International Ethical Guidelines, Commentary to Guideline 2)

Application

Principle 5 is applied through protocol review by an IEC/IRB that is constituted and operating in accordance with GCP and applicable national/local laws and regulations.

Questions and Answers

What is the objective of obtaining IEC/IRB review of the protocol?

It is the IEC/IRB "... whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving/providing favourable opinion on the trial protocol..." (ICH E6, 1.27)

The principal focus of the IEC/IRB is ethical review of the protocol. However, "... [s]cientific review and ethical review cannot be separated: scientifically unsound research involving humans as subjects is ipso facto unethical in that it may expose them to risk or inconvenience to no purpose; even if there is no risk of injury, wasting of

subjects' and researchers' time in unproductive activities represents loss of a valuable resource. Normally, therefore, an ethical review committee considers both the scientific and the ethical aspects of proposed research. It must either carry out or arrange for a proper scientific review or verify that a competent expert body has determined that the research is scientifically sound... " (CIOMS, International Ethical Guidelines, Commentary to Guideline 2)

Review by the IEC/IRB also helps ensure that the research is evaluated by a party that is independent of the trial. "The review committees must be independent of the research team, and any direct financial or other material benefit they may derive from the research should not be contingent on the outcome of their review." (CIOMS, International Ethical Guidelines, Guideline 2)

How does the composition and operation of the IEC/IRB within GCP promote its independence?

Within GCP, "the IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include: (a) [a]t least five members, (b) [a]t least one member whose primary area of interest is in a nonscientific area, (c) [a]t least one member who is independent of the institution/trial site." (ICH E6, Section 3.2)

In its operations, "[o]nly those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter." (ICH E6, Section 3.2).

"To maintain the review committee's independence from the investigators and sponsors and to avoid conflict of interest, any member with a special or particular, direct or indirect, interest in a proposal should not take part in its assessment if that interest could subvert the member's objective judgment. Members of ethical review committees should be held to the same standard of disclosure as scientific and medical research staff with regard to financial or other interests that could be construed as conflicts of interest. A practical

way of avoiding such conflict of interest is for the committee to insist on a declaration of possible conflict of interest by any of its members. A member who makes such a declaration should then withdraw, if to do so is clearly the appropriate action to take, either at the member's own discretion or at the request of the other members. Before withdrawing, the member should be permitted to offer comments on the protocol or to respond to questions of other members." (CIOMS, International Ethical Guidelines, Commentary to Guideline 2)

"The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC." (ICH E6, Section 3.2)

"[T]here should be a predefined method for arriving at a decision (e.g., by consensus, by vote); it is recommended that decisions be arrived at through consensus, where possible; when a consensus appears unlikely, it is recommended that the EC vote." (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 7, *Decision Making*)

Within GCP, what is meant by "prior" opinion by the IEC/IRB?

GCP requires that "[b]efore initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects." (ICH E6, Section 4.4)

"The IRB/IEC should establish, document in writing, and follow its procedures, which should include: ... [s]pecifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial." (ICH E6, Section 3.3)

What is the authority of the IEC/IRB with respect to rendering a decision/opinion on the protocol?

The IEC/IRB may render a decision/opinion that can be positive, conditional, or negative. Regardless of the nature of the decision/opinion, it should be documented and communicated in writing to the applicant.

Approval/favourable opinion. This positive decision/opinion is required prior to initiating a new protocol and prior to making changes in a protocol that has previously received an approval/favourable opinion. In communicating this decision/opinion to the applicant, the IEC/IRB should include a statement of the responsibilities of the applicant.

Modifications required prior to its approval/favourable opinion. This is a conditional decision/opinion that requires response from the applicant and consideration of the applicant's response by the IEC/IRB. Implementation of the protocol/protocol change(s) may not occur until required modifications are made and the IEC/IRB has rendered an approval/favourable opinion based on these modifications. In the case of a conditional decision/opinion, any requirements of the IEC/IRB, including clear suggestions for revision and the procedure for having the application re-reviewed should be specified in written communication to the applicant. The written communication should emphasize that no study activities requiring IEC/IRB approval/favourable opinion may take place under a conditional decision.

Disapproval/negative opinion. This negative decision/opinion can apply to the disapproval/negative opinion of a new protocol or the disapproval/negative opinion of changes to an ongoing protocol. Communication of a disapproval/negative opinion should include clearly stated reason(s) for the negative decision/opinion.

Termination/suspension of any prior approval/favourable opinion. This negative decision/opinion constitutes an action by the IEC/IRB to terminate or suspend its prior approval/favourable opinion. Written communication by the IEC/IRB should include clearly stated reason(s) for this decision/opinion.

Implementation

The responsibility for implementing this principle is shared by IEC(s)/IRB(s), investigators, sponsors, and regulators.

A properly constituted and operational **IEC/IRB** reviews the protocol (and/or any proposed changes to the protocol) and provides the investigator with a written decision/opinion. IEC/IRB written procedures should ensure that no subject be admitted to a trial and no deviations from, or changes to, the protocol be initiated before the IEC/IRB issues its approval/favourable opinion.

Investigators submit the study protocol to their IEC(s)/IRB(s) and are responsible for securing an approval/favourable opinion prior to admitting any subjects to the trial. Investigators should not implement any deviation from, or changes to, the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IEC(s)/IRB(s) of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects. (See GCP Principle 6, *Protocol Compliance*)

The **sponsor** develops the protocol, selects qualified investigators/institutions, and confirms that each investigator has had the study protocol reviewed by an IEC/IRB and received IEC/IRB approval/favourable opinion.

In accordance with applicable laws/regulations, **regulators** may inspect the investigator(s), sponsor(s), and/or IEC(s)/IRB(s) to ensure compliance with IEC/IRB review requirements. Regulators should also encourage IECs/IRBs to communicate with them directly on issues or concerns they may encounter in their review of human trials.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

Responsibilities (ICH E6, Section 3.1)

Composition, Functions, and Operations (ICH E6, Section 3.2)

Procedures (ICH E6, Section 3.3)

Records (ICH E6, Section 3.4)

Constituting an EC (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 4)
Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6)
Decision-Making (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 7)
Communicating a Decision (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 8)
Follow-Up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 9)
Documentation and Archiving (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 10)
Ethical review committees (Guideline 2) and Ethical review of externally sponsored research (Guideline 3), (CIOMS International Ethical Guidelines, 2002)

For **clinical investigators**, refer to:

Communication with IRB/IEC (ICH E6, Section 4.4)

For **sponsors**, refer to:

Confirmation of Review by IRB/IEC (ICH E6, Section 5.11)

For **regulatory authorities**, refer to:

Surveying and Evaluating Ethical Review Practices (a complementary guideline to the Operational Guidelines for Ethics Committees that Review Biomedical Research), WHO, 2002

See also:

Discussion of the WHO Principles of GCP:

GCP Principle 2: Protocol

GCP Principle 4: Benefit-Risk Assessment

GCP Principle 6: Protocol Compliance

GCP Principle 8: Continuing Review/Ongoing Benefit-Risk Assessment

Definitions for:

Approval (in relation to institutional review boards (IRBs)) (ICH E6, 1.5)

Independent Ethics Committee (IEC) (ICH E6, 1.27)

Institutional Review Board (IRB) (ICH E6, 1.31)

Opinion (in relation to Independent Ethics Committee) (ICH E6, 1.42)

PRINCIPLE 6: PROTOCOL COMPLIANCE

Research in humans should be conducted in compliance with the approved protocol.

Once the IEC/IRB gives its approval/favourable decision on the protocol, it is essential that the trial be conducted in compliance with that protocol so that the decision on the ethical acceptability of the trial remains valid.

“The investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), change of telephone number(s)).” (ICH E6, Section 4.5)

Application

Principle 6 is applied through: 1) verifiable investigator adherence to the protocol requirements; 2) submission of any protocol changes to the sponsor and to the IEC/IRB (with approval/favourable opinion) prior to their implementation; and 3) effective monitoring of the study by the sponsor.

Questions and Answers

What does conducting the trial in compliance with the protocol mean?

Compliance with the protocol means performing all of the study activities covered by the protocol (i.e. identifying, informing, selecting, treating, observing, recording, withdrawing, terminating, reporting, analysing) in the precise manner specified in the approved protocol.

It is especially important that those study activities most critical to ensuring the rights and well being of subjects and the quality and integrity of safety and efficacy data are carried out strictly according to the approved protocol, including but not limited to:

- informing subjects fully and obtaining their agreement and documented consent before enrolling them in the study;
- selecting subjects in accordance with the inclusion and exclusion criteria;
- treating subjects with the investigational product as specified in the protocol;
- observing and accurately recording key safety and efficacy endpoint data;
- reporting all serious adverse events (SAEs) to the sponsor immediately except for those SAEs that the protocol or other document (e.g. investigator's brochure) identifies as not needing immediate reporting.

How is compliance with the protocol ensured and documented within GCP?

The first step in promoting protocol compliance is the development of a well-designed, clearly written protocol. (See GCP Principle 2: *Protocol*)

To ensure and document understanding of the protocol “[t]he sponsor should obtain the investigator’s/institution’s agreement: (a) To conduct the trial in compliance with GCP, with the applicable regulatory requirement(s), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC...” (ICH E6, Section 5.6)

“... The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm their agreement” to conduct the study in compliance with the protocol. (ICH E6, Section 4.5; see also Section 5.6)

Once the study is underway, compliance with the protocol is principally ensured through the investigator’s supervision and through the sponsor’s monitoring of the study. Within GCP, the purposes of trial monitoring explicitly include verifying that “... [t]he conduct of the trial is in compliance with the currently approved protocol/amendment(s),

with GCP, and with applicable regulatory requirement(s).” (ICH E6, Section 5.18)

“The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.” (ICH E6, Section 5.18)

“Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor’s staff should lead to prompt action by the sponsor to secure compliance.” (ICH E6, Section 5.20)

“... If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator’s/institution’s participation in the trial... ” (ICH E6, Section 5.20)

The IEC/IRB may also terminate or suspend any prior approval/favourable opinion. Within GCP, this would include the authority to terminate or suspend an approval/favourable opinion when information is received that the study is not being conducted in compliance with the protocol or other requirements of the IEC/IRB.

Who is responsible for compliance with the protocol?

The investigator has direct contact with study subjects and bears primary responsibility for complying with the provisions of the protocol. The investigator also bears responsibility to personally supervise all study staff and ensure their compliance with the protocol.

The sponsor has responsibility to monitor the study and ensure the investigator and site staff comply with the protocol.

Implementation

The responsibility for implementing this principle is shared by IEC(s)/IRB(s), investigators, sponsors, and regulators.

IEC/IRB written procedures should ensure that no subject be admitted to a trial and no deviations from, or changes of, the protocol be initiated before the IEC/IRB issues its approval/favourable opinion.

Investigators should be thoroughly familiar with the protocol and are responsible for conducting the trial in compliance with the protocol. Investigators should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB(s)/IEC(s) of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects.

The **sponsor** monitors the study to ensure investigator compliance with the protocol and takes action to secure compliance or terminate the trial in the case of noncompliance. If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. All parties, including the IEC/IRB, should be notified in such cases.

In accordance with applicable laws/regulations, **regulators** may inspect the investigator(s) or sponsor to ensure compliance with protocol adherence requirements. Regulators should be promptly notified when a sponsor identifies serious and/or persistent noncompliance on the part of an investigator/institution leading to termination of the investigator's/institution's participation in a study.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

Responsibilities (ICH E6, Section 3.1)

Procedures (ICH E6, Section 3.3)

For **clinical investigators**, refer to:

Compliance with Protocol (ICH E6, Section 4.5)

For **sponsors**, refer to:

Record Access (ICH E6, Section 5.15)

Monitoring (ICH E6, Section 5.18)

Noncompliance (ICH E6, Section 5.20)

For **regulatory authorities**, refer to:

WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995

See also:

Discussion of the WHO Principles of GCP:

GCP Principle 2: Protocol

Definitions for:

Compliance (in relation to trials) (ICH E6, 1.15)

Monitoring (ICH E6, 1.38)

PRINCIPLE 7: INFORMED CONSENT

Freely given informed consent should be obtained from every subject prior to research participation in accordance with national culture(s) and requirements. When a subject is not capable of giving informed consent, the permission of a legally authorized representative should be obtained in accordance with applicable law.

“In particular, no one shall be subjected without his free consent to medical or scientific experimentation.” (United Nations International Covenant on Civil and Political Rights)

“The subjects must be volunteers and informed participants in the research project.” (Declaration of Helsinki)

“...[T]here is widespread agreement that the consent process can be analysed as containing three elements: information, comprehension, and voluntariness.” (The Belmont Report)

“For all biomedical research involving humans, the investigator must obtain the voluntary informed consent of the prospective subject or, in the case of an individual who is not capable of giving informed consent, the permission of a legally authorized representative in accordance with applicable law. Waiver of informed consent is to be regarded as uncommon and exceptional, and must in all cases be approved by an ethical review committee.” (CIOMS, International Ethical Guidelines, Guideline 4)

“Obtaining informed consent is a process that is begun when initial contact is made with a prospective subject and continues throughout the course of the study. By informing the prospective subjects, by repetition and explanation, by answering their questions as they arise, and by ensuring that each individual understands each procedure, investigators elicit their informed consent and in so doing manifest respect for their dignity and autonomy.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

Application

Principle 7 is applied through a process of informing and ensuring comprehension by study subjects (and/or their legally authorized representatives) about the research and obtaining their consent, including appropriate written informed consent.

Questions and Answers

What is meant by “freely given” consent or “voluntary” participation in an investigation? How is this implemented within GCP?

“Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research. Informed consent protects the individual’s freedom of choice and respects the individual’s autonomy.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

“An agreement to participate in research constitutes a valid consent only if voluntarily given. This element of informed consent requires conditions free of coercion and undue influence.” (The Belmont Report)

“Unjustifiable pressures usually occur when persons in positions of authority or commanding influence – especially where possible sanctions are involved – urge a course of action for a subject.” “... [U]ndue influence would include actions such as manipulating a person’s choice through the controlling influence of a close relative and threatening to withdraw health services to which an individual would otherwise be entitled.” (The Belmont Report)

“The quality of the consent of prospective subjects who are junior or subordinate members of a hierarchical group requires careful consideration, as their agreement to volunteer may be unduly influenced, whether justified or not, by the expectation of preferential treatment if they agree or by fear of disapproval or retaliation if they refuse.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 13)

“... The researcher should give no unjustifiable assurances about the benefits, risks or inconveniences of the research, for example, or induce a close relative or a community leader to influence a prospective subject’s decision.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 6)

What is meant by “in accordance with national culture(s) and requirements”?

“In some cultures, an investigator may enter a community to conduct research or approach prospective subjects for their individual consent only after obtaining permission from a community leader, a council of elders, or another designated authority. Such customs must be respected. In no case, however, may the permission of a community leader or other authority substitute for individual informed consent.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

What is meant by “informed” consent?

“Informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

Who may administer informed consent?

The person who conducts the consent interview should be knowledgeable about the study and able to answer questions. Some sponsors and some IECs/IRBs require the clinical investigator to personally conduct the consent interview. If someone other than the clinical investigator conducts the interview and obtains consent, the clinical investigator should ensure that this responsibility is formally delegat-

ed to that individual, and that the person so delegated is qualified and receives appropriate training to perform this activity.

What “information” should be given to study subjects in accordance with GCP?

GCP recognizes that certain essential elements of informed consent should be included in the informed consent discussion, the written informed consent form, and any other information to be provided to subjects who participate in the study. All information must be communicated in a comprehensive and understandable manner to the trial subject. This includes, but is not limited to:

- title of the protocol;
- identity of the sponsor;
- identity of the clinical investigator and institutional affiliation of the investigator;
- source of research funding (e.g., public, private, or both);
- that the trial involves research;
- that the subject’s participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled;
- the purpose of the trial;
- the trial treatment(s) and the probability for random assignment to each treatment;
- the trial procedures to be followed, including all invasive procedures;
- the subject’s responsibilities;
- those aspects of the trial that are experimental;
- the reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus or nursing infant;

- the reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this;
- the alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks;
- the compensation and/or treatment available to the subject in the event of trial-related injury;
- the anticipated prorated money or other forms of payment (e.g., material goods), if any, to the subject for participating in the trial;
- the anticipated expenses, if any, to the subject for participating in the trial. This may include expenses to the subject for routine medical care for conditions that are not within the scope of the research;
- that the monitor(s), the auditor(s), the IEC/IRB, and the regulatory authority(-ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally authorized representative is authorizing such access;
- that records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential;
- the potential risks should confidentiality measures be compromised (e.g., stigma, loss of reputation; potential loss of insurability);
- that the subject or the subject's legally authorized representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial;

- the person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury;
- the foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated;
- the expected duration of the subject's participation in the trial;
- the approximate number of subjects involved in the trial.

"... Information about risks should never be withheld for the purpose of eliciting the cooperation of subjects, and truthful answers should always be given to direct questions about the research. Care should be taken to distinguish cases in which disclosure would destroy or invalidate the research from cases in which disclosure would simply inconvenience the investigator." (The Belmont Report)

Due consideration should be given to obtaining consent for the collection and/or use of biological specimens, including future purposes. Guidance is developing in this area (see CIOMS International Ethical Guidelines; CIOMS Report on Pharmacogenetics – Towards improving treatment with medicines, 2005; Council of Europe [CDBI] Additional Protocols to Oviedo Convention, 2005).

What is meant by "comprehension"? That is, how do investigators ensure that subjects understand information about the study, and how is this implemented in accordance with GCP?

"The manner and context in which information is conveyed is as important as the information itself. For example, presenting information in a disorganized and rapid fashion, allowing too little time for consideration or curtailing opportunities for questioning, all may adversely affect a subject's ability to make an informed choice." (The Belmont Report)

"Informing the individual subject must not be simply a ritual recitation of the contents of a written document. Rather, the investigator must convey the information, whether orally or in writing, in language that

suits the individual's level of understanding. The investigator must bear in mind that the prospective subject's ability to understand the information necessary to give informed consent depends on that individual's maturity, intelligence, education and belief system... .. The investigator must then ensure that the prospective subject has adequately understood the information. The investigator should give each one full opportunity to ask questions and should answer them honestly, promptly and completely. In some instances the investigator may administer an oral or a written test or otherwise determine whether the information has been adequately understood." (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

What is meant by "vulnerable persons"?

In general, all individuals, including healthy volunteers, who participate as research subjects should be viewed as intrinsically vulnerable because:

- 1) during the course of the study they are (or may be) exposed to an investigational product about which the safety and efficacy is unknown or incompletely understood; and
- 2) there may be other factors – social, cultural, economic, psychological, medical – that may adversely affect the subjects' ability to make rational, objective choices that protect their own interests, but which may not be readily apparent to the researcher.

Some vulnerabilities may be readily identified because they are obvious (e.g., institutionalized subjects, individuals with diminished mental capacities) or relevant to the research (e.g., children participating in a paediatric vaccine trial). Other vulnerabilities of subjects may not be so readily identified (e.g. subjects who are homeless or economically disadvantaged). Subjects may also become more or less vulnerable throughout a study as circumstances about their health status and lives change.

"Vulnerable persons are those who are relatively (or absolutely) incapable of protecting their own interests. More formally, they may have insufficient power, intelligence, education, resources, strength,

or other needed attributes to protect their own interests.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 13)

Examples of vulnerable persons include, but are not limited to: children, individuals with diminished mental capacity, prisoners, institutionalized persons (including orphans), patients in emergency situations, the economically disadvantaged, individuals who cannot give consent.

“One special instance of injustice results from the involvement of vulnerable subjects. Certain groups, such as racial minorities, the economically disadvantaged, the very sick, and the institutionalized may continually be sought as research subjects, owing to their ready availability in settings where research is conducted. Given their dependent status and their frequently compromised capacity for free consent, they should be protected against the danger of being involved in research solely for administrative convenience, or because they are easy to manipulate as a result of their illness or socioeconomic condition.” (The Belmont Report)

What special protections are required to enable vulnerable populations to participate in research?

“For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.” (Declaration of Helsinki)

“Special provision may need to be made when comprehension is severely limited ... for example, by conditions of immaturity or mental disability. Each class of subjects that one might consider as incompetent (e.g. infants and young children, mentally disabled patients, the terminally ill and the comatose) should be considered on its own terms. Even for these persons, however, respect requires giving

them the opportunity to choose to the extent they are able, whether or not to participate in research. The objections of these subjects to involvement should be honored, unless the research entails providing them a therapy unavailable elsewhere. Respect for persons also requires seeking the permission of other parties in order to protect the subjects from harm. Such persons are thus respected both by acknowledging their own wishes and by the use of third parties to protect them from harm.” (The Belmont Report)

“The third parties chosen should be those who are most likely to understand the incompetent subject’s situation and to act in that person’s best interest. The person authorized to act on behalf of the subject should be given an opportunity to observe the research as it proceeds in order to be able to withdraw the subject from the research, if such action appears in the subject’s best interest.” (The Belmont Report)

How is informed consent documented? Is getting the subject (or the subject’s representative) to sign a consent document all that is necessary? How should the process be documented throughout the study?

“Obtaining informed consent is a process that is begun when initial contact is made with a prospective subject, and continues throughout the course of the study. By informing the prospective subjects, by repetition and explanation, by answering their questions as they arise, and by ensuring that each individual understands each procedure, investigators elicit their informed consent and in so doing manifest respect for their dignity and autonomy. Each individual must be given as much time as is needed to reach a decision, including time for consultation with family members or others. Adequate time and resources should be set aside for informed-consent procedures.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

“Consent may be indicated in a number of ways. The subject may imply consent by voluntary actions, express consent orally, or sign a consent form. As a general rule, the subject should sign a consent

form, or, in the case of incompetence, a legal guardian or other duly authorized representative should do so.When consent has been obtained orally, investigators are responsible for providing documentation or proof of consent.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

When material changes occur in the conditions or the procedures of a study, and also periodically in long-term studies, the investigator should once again seek informed consent from the subjects... ” (CIOMS, International Ethical Guidelines, Commentary on Guideline 4)

Is it ethical to include subjects who are unable to consent?

“Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee... ” (Declaration of Helsinki)

“When there is ethical and scientific justification to conduct research with individuals incapable of giving informed consent, the risk from research interventions that do not hold out the prospect of direct benefit for the individual subject should be no more likely and not greater than the risk attached to routine medical or psychological examination of such persons. Slight or minor increases above such risk may be permitted when there is an overriding scientific or medical rationale for such increases and when an ethical review committee has approved them.” (CIOMS, International Ethical Guidelines, Guideline 9)

When should informed consent be obtained? What is meant by “prior to trial participation”?

Informed consent should be obtained from each subject or the subject’s legally authorized representative prior to involving the subject

in any study-specific activities. This includes diagnostic or other tests that are administered solely for determining the subject's eligibility to participate in the research.

Implementation

The responsibility for implementing and overseeing the informed consent process is shared by sponsors, clinical investigators, IECs/IRBs, and regulatory authorities.

IECs/IRBs are responsible for:

- reviewing the informed consent document to ensure that it is accurate, complete, and written in language that will be understood by the potential study subjects and translated into other languages, as appropriate;
- requesting modifications to the informed consent document, as appropriate; and
- at their discretion, observing the consent process and the research.

Investigators are responsible for ensuring that:

- staff responsible for obtaining informed consent receive appropriate training, both in research ethics and in the requirements of the specific study protocol;
- the IEC/IRB reviews and approves the informed consent form and other written information to be used in the study prior to its use; and
- informed consent is obtained from each subject or the subject's representative prior to involving the subject in any study related activities, including diagnostic or other tests that are administered solely for determining the subject's eligibility to participate in the research.

Sponsors are responsible for monitoring the research at study sites to ensure that sites are obtaining informed consent from all study subjects prior to subjects' inclusion in the research study.

In accordance with national and local laws and regulations, **regulators** may inspect the various parties who conduct or oversee research to ensure that they are complying with applicable laws and regulations and enforcing non-compliance. For example, regulators may inspect IECs/IRBs to ensure that informed consent documents and procedures are appropriately reviewed; they may inspect clinical investigators to determine whether informed consent was obtained prior to subjects' inclusion in the study; they may inspect sponsors to ascertain whether studies are being appropriately monitored.

For more information (including Roles and Responsibilities)

For all parties:

CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, Guidelines 4, 5, 6, 13, 14, 15, and 16;
Clinical Investigation of Medicinal Products in the Pediatric Population (ICH E11)

For IECs/IRBs, refer to:

Responsibilities (ICH E6, Section 3.1)
Documentation (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 5.3)
Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2)
Communicating a Decision (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 8)
Surveying and Evaluating Ethical Review Practices (a complementary guideline to the Operational Guidelines for Ethics Committees That Review Biomedical Research), WHO, 2002

For clinical investigators, refer to:

Communication with IRB/IEC (ICH E6, Section 4.4)
Informed Consent of Trial Subjects (ICH E6, Section 4.8)

For sponsors, refer to:

Confirmation of Review by IRB/IEC (ICH E6, Section 5.11)
Monitoring (ICH E6, Section 5.18)

For **regulatory authorities**, refer to

Surveying and Evaluating Ethical Review Practices (a complementary guideline to the Operational Guidelines for Ethics Committees That Review Biomedical Research), WHO, 2002

A Guide to Clinical Investigator Inspections (Good Clinical Practices: Document of the Americas, PAHO, Annex 4)

See also:

Discussion of the WHO Principles of GCP

GCP Principle 1: Ethical Conduct

GCP Principle 4: Benefit-Risk Assessment

Definitions for:

Informed Consent (ICH E6, 1.28)

Legally Acceptable Representative (ICH E6, 1.37)

Vulnerable Subjects (ICH E6, 1.61)

Well-being (of the trial subjects) (ICH E6, 1.62)

PRINCIPLE 8: CONTINUING REVIEW/ ONGOING BENEFIT-RISK ASSESSMENT

Research involving humans should be continued only if the benefit-risk profile remains favourable.

“During the course of the experiment the scientist in charge must be prepared to terminate the experiment at any stage, if he has probable cause to believe, in the exercise of the good faith, superior skill, and careful judgment required of him that a continuation of the experiment is likely to result in injury, disability, or death to the experimental subject.” (The Nuremberg Code)

“... The ethical review committee should conduct further reviews as necessary in the course of the research, including monitoring of its progress.” (CIOMS, International Ethical Guidelines, Guideline 2)

“... The committee has the right to monitor ongoing trials... ” (Declaration of Helsinki)

“... Clinical trial sponsors should develop a process to assess, evaluate and act on safety information during drug development on a continuous basis in order to ensure the earliest possible identification of safety concerns and to take appropriate risk minimization steps. Such steps can include modification of study protocols, to incorporate strategies to ensure that clinical trial participants are not exposed to undue risk.” (Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI. *Identification and Evaluation of Risk from Clinical Trial Data*)

Application

Principle 8 is applied through development and implementation of processes for evaluating risks and benefits of the research as additional information becomes available during the course of the study. Principle 8 encompasses (1) safety monitoring of the study by investigator(s) and sponsor (including use of a data and safety monitoring board [DSMB], where appropriate); (2) reporting serious unexpected adverse events or other unanticipated risks to the sponsor, IEC/IRB, and regulators; (3) review by the IEC/IRB of any unan-

anticipated risks as they occur, or at scheduled intervals appropriate to the degree of risk; (4) revising the protocol, investigator's brochure, and/or informed consent document as needed, and suspending or terminating studies if necessary to protect the rights and welfare of study subjects.

Questions and Answers:

How are unanticipated risks identified during the course of a study?

Investigators and site staff are often the first to discover or observe unanticipated risks to subjects (e.g., serious unexpected adverse events; significant breaches of confidentiality) during the course of a study. Sponsors may also identify unanticipated risks to subjects in the course of study monitoring or from planned interim data analyses.

"The frequent review of serious and special interest adverse events, as well as overall assessment of all AEs, regardless of seriousness, causality, or expectedness, should be performed periodically: (1) *ad hoc*, for serious and special interest AEs, (2) routine, periodic general review of all data, whose frequency will vary from trial to trial and from development program to development program and depend on many factors, and (3) reviews triggered by specific milestones established for a trial or a program (e.g., numbers of completed patients, end-of-trial, end-of program, preparation of integrated summary of safety, and a marketing application." (Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI. *Frequency of Review of Safety Information*)

How should serious unexpected adverse events (SAEs) be reported and to whom?

"All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g. investigator's brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly

by detailed written reports.” “... The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.” (ICH E6, Section 4.11)

“In addition to the usual criteria for an expedited report, adverse events that are not deemed to be drug-related but are considered to be protocol related should also be reported in an expedited fashion if they are serious.” (Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI. *Regulatory Reporting and other Communication of Safety Information from Clinical Trials*)

Who is responsible for reviewing the benefit-risk profile of the investigational product(s) while the study is proceeding?

Within GCP, the sponsor has primary responsibility for the ongoing safety evaluation of the investigational product(s) and should promptly notify all concerned investigator(s), institution(s), and the regulatory authority(ies) of information that could adversely affect the safety of subjects, the conduct of the trial, or alter the IEC/IRB approval/favourable opinion to continue the trial. Such reviews may be performed by the sponsor’s staff (e.g., physicians, statisticians) or by an independent data and safety monitoring board (DSMB), if one is established (see below).

The IEC/IRB is also responsible for “... following the progress of all studies for which a positive decision has been reached, from the time the decision was taken until the termination of the research.” (See “Follow-up”, Section 9, *WHO Operational Guidelines for Ethics Committees that Review Biomedical Research*)

How are follow-up reviews carried out?

Sponsors generally monitor trials to ensure that (1) the study is being conducted according to the approved protocol, GCP, and applicable regulatory requirements, and (2) all data, including adverse event reports are accurately and completely recorded and reported. The sponsor also employs qualified individuals (e.g., physicians, statisti-

cians) as appropriate, throughout all stages of the trial process, to analyse data and prepare interim reports about the progress of the trial and the benefits and risks of the investigational product. The sponsor may also establish an independent data and safety monitoring board (DSMB, see below) to review the accumulating data. The sponsor should ensure that significant new information that arises about a clinical trial is promptly shared with all investigators, regulatory authorities and IECs/IRBs.

The IEC/IRB generally establishes procedures for (1) ensuring that new information that may adversely affect the safety of subjects or the conduct of the trial (e.g. serious/unexpected adverse events; unanticipated risks) are communicated to the IEC/IRB; (2) conducting the follow-up review; and (3) communicating decisions/opinions to the investigator.

When or how often should a benefit-risk determination be performed?

An evaluation should be carried out promptly following receipt of significant new information that may adversely affect the safety of subjects or the conduct of the trial. Generally, such new information is supplied by the clinical investigator(s), but it may also come from a DSMB or the study sponsor.

“An important principle in the evaluation of safety data from clinical trials is that while the data are designed to be analysed in a comprehensive fashion at the end of a trial or development program, they also must be evaluated in an ongoing fashion, so that important safety signals can be detected early and that trial participants are protected.” (Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI. Identification and Evaluation of Risk from Clinical Trial Data)

A sponsor may establish a schedule of interim analyses. The study protocol will generally describe this schedule and will also typically describe the statistical approach to the interim analysis of trial data. To minimize the potential for bias, these descriptions should be completed before the conduct of any interim analyses.

The IEC/IRB should conduct follow-up reviews in accordance with established procedures. In general, the IEC/IRB should conduct follow-up review of each ongoing trial at scheduled intervals appropriate to the degree of risk, but, generally, at least once per year.

What should be done if the benefit-risk profile of a study becomes unfavourable?

The sponsor should notify investigator(s), the IEC(s)/IRB(s), and in accordance with national/local laws and regulations, the national regulatory authority if the benefit-risk profile of a study becomes unfavourable. In consultation with the IEC(s)/IRB(s), investigator(s), and regulatory authority(ies), the sponsor may need to amend the study protocol and/or revise the investigator's brochure and informed consent document(s) to reflect the new information.

"If a significant safety issue is identified, either from an individual case report or review of aggregate data, then the sponsor should issue a prompt notification to all parties, namely regulatory authorities, investigators and IECs/IRBs. A significant safety issue could be defined as one that has a significant impact on the course of the clinical trial or programme (including the potential for suspension of the trial programme or amendments to protocols), or warrants immediate update of informed consent." (Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI., *Regulatory Reporting and other Communication of Safety Information from Clinical Trials*)

What happens if the IEC/IRB determines that it must withdraw its approval/favourable opinion of the trial?

The IEC/IRB should notify the clinical investigator and study sponsor of all decisions (favourable or unfavourable) in writing. Because a study may not proceed without approval/favourable opinion of an IEC/IRB, in some cases, it may be necessary to prematurely terminate or suspend the study (See ICH E6, Section 4.12). Should a study

be prematurely terminated, any subjects currently participating should be notified and procedures for withdrawal of enrolled subjects should consider the rights and welfare of the subjects.

In other cases, the unanticipated risk(s) might be appropriately managed through a protocol change (e.g. eliminating a study arm, introducing additional safety monitoring or testing, etc.) Note, however, that except where necessary to eliminate an immediate hazard(s) to trial subjects, the investigator should not implement any deviation from, or changes of, the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IEC/IRB of a protocol amendment (see ICH E6, Section 4.5).

“Ethical review committees generally have no authority to impose sanctions on researchers who violate ethical standards in the conduct of research involving humans. They may, however, withdraw ethical approval of a research project if judged necessary.” (CIOMS, International Ethical Guidelines, Commentary to Guideline 2)

If the benefit-risk profile of the study changes and/or substantive protocol modifications are made, how should the information be communicated to study subjects?

How is this documented?

“Sponsors and investigators have a duty to... renew the informed consent of each subject if there are significant changes in the conditions or procedures of the research or if new information becomes available that could affect the willingness of subjects to continue to participate... ” (CIOMS, International Ethical Guidelines, Guideline 6)

Periodically in long-term studies, the investigator should also consider renewing consent (e.g. in long-term studies involving elderly subjects).

Communicating the new information to study subjects should follow customary procedures for obtaining and documenting informed consent.

What is an Independent Data and Safety Monitoring Board (DSMB, also known as an independent Data Monitoring Committee [DMC])?

An independent data and safety monitoring board (DSMB) is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from one or more ongoing clinical trials. The DSMB advises the sponsor regarding the continuing safety of current trial participants and those yet to be recruited to the trial, as well as the continuing validity and scientific merit of the trial.

“At intervals defined by the protocol, the DSMB reviews and evaluates the data on clinical efficacy and safety collected during the study, and assesses reports on cumulated serious adverse events (SAEs). The DSMB may also be requested by the sponsor to conduct emergency reviews of data to assess safety-related issues.” “At the conclusion of the review, the DSMB provides a written recommendation to the sponsor regarding whether a protocol should be amended and/or a study should proceed based on its review of the data and the progress report submitted by the sponsor.” (Operational Guidelines for the Establishment and Functioning of Data and Safety Monitoring Boards, WHO TDR).

An important function of a DSMB “... is to protect the research subjects from previously unknown adverse reactions; another is to avoid unnecessarily prolonged exposure to an inferior therapy.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 11)

Should DSMBs [DMCs] be established for every study?

All clinical trials require safety monitoring but not all trials require monitoring by a formal committee that may be external to the trial organizers, sponsors and investigators. DSMBs have generally been established for large, randomized multi-site studies that evaluate treatments intended to prolong life or reduce risk of a major adverse health outcome such as a cardiovascular event or recurrence of cancer. DSMBs are generally recommended for any controlled trial of any size that will compare rates of mortality or major morbidity, but a DSMB is not required or recommended for most clinical stud-

ies. DSMBs are generally not needed, for example, for trials at early stages of product development. They are also generally not needed for trials addressing lesser outcomes, such as relief of symptoms, unless the trial population is at elevated risk of more severe outcomes.

“In most cases of research involving human subjects, it is unnecessary to appoint a DSMB. To ensure that research is carefully monitored for the early detection of adverse events, the sponsor or the principal investigator appoints an individual to be responsible for advising on the need to consider changing the system of monitoring for adverse events or the process of informed consent, or even to consider terminating the study.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 11)

“... DSMBs are of value in the following situations:

- large randomized, multi-center high morbidity/mortality trials;
- studies where data could justify early study termination or where the design or executed data accrual is complex;
- early studies of a high-risk intervention;
- studies carried out in emergency situations in which informed consent is waived;
- studies involving vulnerable populations; or,
- studies in the early phases of a novel intervention with very limited information on clinical safety or where prior information may have raised safety concerns.”

(Management of Safety Information from Clinical Trials, Report of CIOMS Working Group VI. Appendix 5, *Data and Safety Monitoring Boards*)

Implementation

Sponsors, IECs/IRBs, DSMBs (if applicable), and regulators share responsibility for ongoing safety evaluations of the investigational product(s).

The **investigator** reports unanticipated problems involving risks to subjects and provides periodic progress reports at intervals ap-

appropriate to the degree of risk to sponsors and IECs/IRBs in accordance with the national/local laws and regulations. The investigator provides adequate, accurate, and objective information on risks and benefits during informed consent of study subjects, and renews the consent of the subject to continue in the study, as appropriate.

The **sponsor** monitors the study and performs safety evaluations of the investigational product(s) by analysing data received from the investigator(s) and the DSMB (if one has been appointed). The sponsor also assures reporting (including expedited reporting to investigator(s), IEC(s)/IRB(s), and the regulatory authority(ies) of adverse reactions that are both serious and unexpected.

As the study progresses, the **IEC(s)/IRB(s)** conducts follow-up reviews appropriate to the degree of risk, but generally at least once per year, including review of the investigator's progress reports to determine if the benefits still outweigh the risks.

The **regulatory authority** reviews data submitted in research or marketing permits and may require modification to a protocol as a condition to its proceeding and/or may suspend or terminate a protocol based on an unacceptable benefit-risk profile in accordance with applicable laws and regulations.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Responsibilities (ICH E6, Section 3.1)

- Procedures (ICH E6, Section 3.3)

- Communicating a Decision (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 8)

- Follow-up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 9)

For **clinical investigators**, refer to:

- Progress Reports (ICH E6, Section 4.10)

- Safety Reporting (ICH E6, Section 4.11)

- Premature Termination or Suspension of a Trial (ICH E6, Section 4.12)

- Clinical Trial Protocol and Protocol Amendment(s), General Information (ICH E6, Section 6)

Investigator's Brochure (ICH E6, Section 7)

For **sponsors**, refer to:

Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee (ICH E6, Section 5.5)

Notification/Submission to Regulatory Authorities (ICH E6, Section 5.10)

Adverse Drug Reaction Reporting (ICH E6, Section 5.17)

Monitoring (ICH E6, Section 5.18)

Premature Termination or Suspension of a Trial (ICH E6, Section 5.21)

Clinical Trial Protocol, General Information (ICH E6, Section 6)

Investigator's Brochure (ICH E6, Section 7)

For **regulators**, refer to:

Surveying and Evaluating Ethical Review Practices, a complementary guideline to the Operational Guidelines for Ethics Committees that Review Biomedical Research, WHO, 2002

See also:

The Council for International Organizations of Medical Sciences (CIOMS) Management of Safety Information from Clinical Trials: Report of CIOMS Working Group VI, Geneva, 2005.

Discussion of the WHO Principles of GCP

GCP Principle 4: Benefit-Risk Assessment

GCP Principle 5: Review by IEC/IRB

Definitions for:

Adverse Drug Reaction (ADR) (ICH E6, 1.1)

Adverse Event (AE) (ICH E6, 1.2)

Approval (in relation to Institutional Review Boards) (ICH E6, 1.5)

Independent Data Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee) (ICH E6, 1.25)

Independent Ethics Committee (IEC) (ICH E6, 1.27)

Informed Consent (ICH E6, 1.28)

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR) (ICH E6, 1.50)

Unexpected Adverse Drug Reaction (ICH E6, 1.60)

PRINCIPLE 9: INVESTIGATOR QUALIFICATIONS

Qualified and duly licensed medical personnel (i.e., physician or, when appropriate, dentist) should be responsible for the medical care of trial subjects, and for any medical decision(s) made on their behalf.

“The experiment should be conducted only by scientifically qualified persons. The highest degree of skill and care should be required through all stages of the experiment of those who conduct or engage in the experiment.” (The Nuremberg Code)

“Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person...” (Declaration of Helsinki)

Application

Principle 9 is applied through the responsibilities of the clinical investigator to the study subject and through the sponsor’s selection of qualified investigator(s). (See also GCP Principle 10, *Staff Qualifications*)

Questions and Answers

Where may information about a clinical investigator’s qualifications be obtained?

The investigator’s curriculum vitae or other statement of education, training and experience may provide initial information about the investigator’s qualifications to provide medical care and to conduct clinical research. Other sources of information about an investigator’s qualifications may include medical licensing boards, malpractice registries, and/or disciplinary bodies that may have information about the investigator’s history of medical practice. References from those familiar with the investigator’s clinical and/or research practice may provide useful adjunctive information.

May a non-medical person serve as a principal investigator?

“Investigator” is defined as the “person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator.” (ICH E6, Section 1.34)

In most clinical research, the investigator will be a physician, dentist, or (in accordance with national/local laws, regulations, and licensure provisions) equivalent medical professional.

Where permitted under national/local laws and regulations, a non-physician may serve as a principal investigator. However, implicit in this designation are: 1) that the non-physician be qualified to personally conduct or supervise the investigation; and 2) the non-physician would need to secure the services of a physician as a subinvestigator to perform those study functions requiring medical expertise. (For example, a Ph.D. pharmacologist may be listed as a principal investigator on a pharmacokinetic study with a physician subinvestigator. Another example might be a clinical psychologist principal investigator with a physician subinvestigator.)

Within GCP, what is the investigator’s responsibility for the medical care of trial subjects?

The investigator is responsible for protecting the rights, safety, and welfare of subjects under his/her care during a clinical trial. This implies that (1) the investigator is able to ensure access to a reasonable standard of medical care for study subjects for medical problems arising during participation in the trial that are, or could be related, to the study intervention, and (2) the investigator or other medically qualified individuals are readily available to provide such care during the study.

“Although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so. Such services typically include treatment for diseases contracted in the course of the study.

It might, for example, be agreed to treat cases of an infectious disease contracted during a trial of a vaccine designed to provide immunity to that disease, or to provide treatment of incidental conditions unrelated to the study. ... When prospective or actual subjects are found to have diseases unrelated to the research or cannot be enrolled in a study because they do not meet the health criteria, investigators should, as appropriate, advise them to obtain, or refer them for, medical care.” (CIOMS, International Ethical Guidelines, Commentary on Guideline 21)

Implementation

The **investigator** is responsible for providing, or ensuring that subjects have access to, medical care for medical problems arising during their participation in the trial that are, or could be related to the study intervention, and for following the subjects’ status until the problem is resolved.

“It is recommended that the investigator inform the subject’s primary physician about the subject’s participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.” (ICH E6, Section 4.3)

Primary responsibility for selecting qualified clinical investigators to conduct a study resides with the **sponsor**.

The **IEC(s)/IRB(s)** is responsible for ensuring that the rights and welfare of study subjects are protected. Consideration of investigator qualifications and experience and the adequacy of the site (including the supporting staff, available facilities, and emergency procedures) by the IEC/IRB will ensure that subjects have access to appropriate care for medical problems arising during participation in the trial.

National and/or local **regulatory authorities** have indirect responsibility related to clinical investigator qualifications. Regulators (1) establish licensing and practice standards for physicians and other medical personnel, (2) enforce compliance with such standards, and (3) impose disciplinary actions, as appropriate, on physicians and

other medical personnel who fail to meet such standards. Different regulatory agencies and authorities may be responsible for the oversight of clinical research vs. the licensure and oversight of medical professionals; exchange of information among regulatory agencies is encouraged in such circumstances.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

Responsibilities (ICH E6, Section 3.1)

Documentation (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 5.3)

Elements of the Review (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2)

For **clinical investigators**, refer to:

Investigator's Qualifications and Agreements (ICH E6, Section 4.1)

Medical Care of Trial Subjects (ICH E6, Section 4.3)

Safety Reporting (ICH E6, Section 4.11)

For **sponsors**, refer to:

Medical Expertise (ICH E6, Section 5.3)

Investigator Selection (ICH E6, Section 5.6)

Allocation of Duties and Functions (ICH E6, Section 5.7)

Ethical Obligations of External Sponsors to Provide Health-Care Services (CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects, Guideline 21)

For **regulatory authorities**, refer to:

WHO Guidelines for good clinical practice (GCP) for trials on pharmaceutical products, 1995

GCP Compliance Monitoring Programs by Regulatory Authorities (Good Clinical Practice: Document of the Americas, PAHO, Chapter 7)

Ethical Obligations of External Sponsors to Provide Health-Care Services (CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects, Guideline 21)

See also:

Discussion of the WHO Principles of GCP
GCP Principle 10: Staff Qualifications

Definitions for:

Investigator (ICH E6, 1.34)

Subinvestigator (ICH E6, 1.56)

Well-being (of the trial subjects) (ICH E6, 1.62)

PRINCIPLE 10: STAFF QUALIFICATIONS

Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s) and currently licensed to do so, where required.

GCP requires that the clinical investigator is appropriately qualified by education, training, and experience to conduct the clinical trial. GCP also requires that each clinical investigator will have adequate resources available, including sufficient staff, who are also appropriately qualified by education, training, and experience, to assist him/her with the trial and ensure the safety of study subjects.

Application

Principle 10 is chiefly applied through the clinical investigator's selection of appropriate staff to assist with the conduct of the study.

Questions and Answers

What does it mean to be "qualified" to conduct clinical research and how is this implemented within GCP?

GCP requires generally that individuals who conduct research have appropriate education, training, and experience to assume responsibility for the conduct of the trial. The investigator should have knowledge of applicable laws and regulations and broad knowledge of internationally accepted principles and practices for the conduct of clinical research within GCP, including ethical requirements for the protection of human subjects involved in the research. The investigator should also have training or expertise appropriate to carry out the requirements of the specific study protocol.

The investigator should understand and be qualified to execute the responsibility to personally supervise any individual to whom a study task is delegated. The investigator should further ensure that any individual to whom a study task is delegated is qualified by education, training, and experience to perform the delegated task, for example

that the assigned task falls within the scope of the individual's professional license(s). When delegating tasks, the investigator should consider, among other things, whether the tasks require formal medical training and whether national or local licensing requirements apply to such duties. (Duties that warrant such consideration, include, but are not necessarily limited to, the following: screening evaluations, including medical histories and assessment of inclusion/exclusion criteria; physical examinations; assessment of adverse events; assessments of primary study endpoints (e.g., tumor response, global assessment scales); control of investigational products.)

The investigator should ensure that staff are (1) familiar with the study protocol and investigational product; (2) appropriately trained to carry out trial-related duties; (3) informed/aware of their obligations to protect the rights, safety and welfare of the study subjects; and (4) informed of any requirements imposed by the national regulatory authority for GCP and the conduct of clinical studies.

What does it mean to be qualified by “education, training, and experience”; that is, what does each of these terms embrace?

Education refers to degrees, certification, and/or licensing earned as a result of formal schooling or courses of study at an institution of higher learning (e.g., M.D., Ph.D., R.N., board certification in a specified field, medical licenses). Training generally refers to short, focused programs on specific topics (e.g., a two-week training program in research ethics, an online course on GCP, “investigator training” provided by the study sponsor related to a specific protocol) and/or mentoring by an appropriately educated, trained, and experienced professional. Experience includes direct participation in activities that provide additional expertise in a specific area (e.g., various positions a physician has held during his/her practice of medicine, previous work assisting another investigator in conducting clinical research, experience as an investigator in a previous study).

Where may information about the qualifications of an investigator or the investigator's staff be obtained?

A curriculum vitae or other statement of education, training, and experience for each staff member may provide initial information about the staff member's qualifications. Other sources of information may include medical licensing boards, malpractice registries, and/or disciplinary bodies. References from those familiar with the individual's past clinical and/or research experience may provide useful adjunctive information.

How should an investigator inform a sponsor about the individuals to whom duties have been delegated?

Maintaining a list of individuals to whom the investigator has assigned each trial-related duty may assist the sponsor and regulators alike in determining which staff members were authorized to carry out specific duties during the course of the trial.

Implementation

The **investigator** bears primary responsibility for (1) selecting qualified staff to assist in the conduct of the investigation; (2) ensuring that study staff receive appropriate training, related to ethics and consent procedures as well as requirements of the specific protocol; (3) establishing clear procedures for activities related to the conduct of the study; (4) assigning tasks to staff, based on their qualifications, experience, and professional licenses; and (5) personally supervising staff to ensure that they satisfactorily fulfill their study-related duties. Although the investigator may delegate tasks to members of his/her staff, nevertheless, the investigator retains overall responsibility for the study and ensuring that his/her staff complies with applicable laws and regulations for human subject protection and the conduct of clinical research.

The **IEC/IRB** is responsible for ensuring that the rights and welfare of study subjects are protected. Consideration of the site's characteristics (e.g., number and qualifications of supporting staff, available

facilities and equipment, and emergency procedures) will allow the IEC/IRB to evaluate the adequacy of the site, and ensure that subjects' welfare is not compromised during the trial.

Sponsors have the responsibility for selecting appropriately qualified investigators to conduct the study; part of that consideration is ensuring that investigators have sufficient staff (also with appropriate qualifications) available, who are appropriately trained to conduct all study-related activities, and who understand how to capture and document required observations and data.

In accordance with national and/or local laws and regulations, **regulatory authorities** may inspect study sites to determine if the conduct of the study is in compliance with local laws/regulations. Such inspections would include finding out who was assigned responsibility for conducting various study-related activities (e.g., screening subjects to determine if they meet inclusion/exclusion criteria; obtaining informed consent; conducting physical examinations; collecting and analysing study data; recording, transcribing, or reporting data to the sponsor; administering the investigational product to subjects), and determining whether these activities were appropriately assigned and within the scope of the staff member's professional license(s).

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Elements of the Review (WHO Operational Guidelines for Ethics-Committees that Review Biomedical Research, Section 6.2)

For **clinical investigators**, refer to:

- Investigator's Qualifications and Agreements (ICH E6, Section 4.1)
- Adequate Resources (ICH E6, Section 4.2)
- Investigational Product(s) (ICH E6, Section 4.6)

For **sponsors**, refer to:

- Medical Expertise (ICH E6, Section 5.3)
- Trial Design (ICH E6, Section 5.4)
- Trial Management, Data Handling, Recordkeeping, and Independent Monitoring Committee (ICH E6, Section 5.5)

Investigator Selection (ICH E6, Section 5.6)

Allocation of Duties and Functions (ICH E6, Section 5.7)

For **regulatory authorities**, refer to

Conducting the Inspection (A Guide to Clinical Investigator Inspections, PAHO, Annex 4, Section 2)

See also:

Discussion of the WHO Principles of GCP

GCP Principle 9: Investigator Qualifications

Definitions for:

Investigator (ICH E6, 1.34)

Subinvestigator (ICH E6, 1.56)

Well-being (of the trial subjects) (ICH E6, 1.62)

PRINCIPLE 11: RECORDS

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Principle 11 embraces the concepts of data quality and data integrity as well as appropriate procedures for data handling and record-keeping. Also implicit in this principle is the preparation and maintenance of essential documents: i.e., documents (including source documents) that individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced.

Application

Principle 11 is applied through: 1) the understanding and application of basic elements of data quality and integrity; 2) adherence to the study protocol as well as applicable written procedures for collecting, recording, reporting, maintaining and analysing clinical trial information; and 3) the preparation of essential documents (including source documents), at all stages throughout the conduct of the clinical trial.

Questions and Answers

What is “clinical trial information”? What is meant by “essential documents”?

The term, “clinical trial information,” encompasses all study related data, materials, and documents. The term includes “[a]ll records, in any form (including, but not limited to, written, electronic, magnetic, and optical records; and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.” (ICH E6, 1.22)

Essential documents are “... those documents that individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor, and monitor with the standards of GCP and with all applicable regulatory requirements.” Essen-

tial documents are "... usually audited by the sponsor's independent audit function and inspected by the regulatory authority(ies) as part of the process to confirm the validity of the trial conduct and the integrity of the data collected." (ICH E6, Section 8)

Examples include:

- Source data: "All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies)." (ICH E6, 1.51)
- Source documents: "Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial)." (ICH E6, 1.52)
- Case report forms: "... [P]rinted, optical, or electronic document[s] designed to record all of the protocol-required information to be reported to the sponsor on each trial subject." (ICH E6, 1.11)
- Correspondence between any of the parties who conduct or oversee the research (e.g. approval/favourable decision by the IEC/IRB; reports of adverse events submitted to the sponsors, IECs/IRBs, and regulators; monitor's reports to the sponsor)
- Other study related documents and materials (e.g. study protocol, protocol amendments, investigator's brochure, clinical investigator's curriculum vitae, approved consent form, subjects' signed consent forms, subject screening logs, documentation of investigational product destruction, advertisements used to recruit subjects, reports by independent data monitoring committees)

What is meant by “recording”?

“Recording” is the act of writing down or otherwise committing to durable medium (e.g., paper, electronic medium, etc.) information or data to provide evidence of what has occurred or has been observed. All of the parties who conduct or oversee clinical trials are responsible for preparing records (i.e. “essential documents”) that document their activities and data or observations related to the trial.

What is meant by “data quality”? What is meant by “data integrity”? How are the terms related, and how are data quality and integrity achieved within GCP?

“Data quality” refers to the essential characteristics of each piece of data; in particular, quality data should be:

- accurate
- legible
- complete and contemporaneous (recorded at the time the activity occurs)
- original
- attributable to the person who generated the data.

“Data integrity” refers to the soundness of the body of data as a whole. In particular, the body of data should be credible, internally consistent, and verifiable.

Quality and integrity are both essential for data to be relied upon for regulatory decision-making. Data quality and integrity are achieved when each piece of data is collected in accordance with the study protocol and procedures, giving attention to each of the quality characteristics above, and subsequently handled (e.g. transcribed, analysed, interpreted, reported) so that the quality characteristics of the original data (i.e. accuracy, legibility, completeness, etc.) are preserved.

What is meant by “handling”? How are “quality and integrity” preserved as data and documents are “handled”?

Handling refers to how data are maintained, analysed, interpreted, and shared, transmitted, or reported to others. For example, source data are often transcribed by the investigator into a case report form (CRF), which in turn is submitted to the sponsor for further handling.

Establishing SOPs to identify the various steps in data handling (at both investigator and sponsor sites) and to articulate the associated roles and responsibilities of investigator and sponsor staff may help preserve quality and integrity as data is handled.

Study monitoring also helps to ensure that data quality and integrity are preserved throughout the study by, for example, verifying that data transmitted to the sponsor in the CRF accurately reflect information about the study subject that was recorded in the medical records or case histories.

“Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes and corrections. ... Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor’s designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.” (ICH E6, Section 4.9)

Who must keep clinical trial information and for how long?

What is meant by the term “storage”?

All of the parties who conduct or oversee research involving human subjects are expected to keep records and materials related to their specific trial responsibilities and activities for the period of time required by national/local laws and regulations, or if such laws do not exist, in accordance with GCP standards.

Within GCP, generally, “[e]ssential documents should be retained until at least 2 years after the last approval of a marketing applica-

tion... and until there are no pending or contemplated marketing applications... or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the sponsor.” (ICH E6, Section 4.9)

“Storage” (or “archiving”) implies that records are appropriately stored for future use, for example, to ensure their preservation and to enable direct access to the records when required by the sponsor, IEC/IRB, monitor or regulatory authorities. “The investigator/institution should take measures to prevent accidental or premature destruction of these records.” (ICH E6, Section 4.9)

Why is it necessary for IECs/IRBs, investigators, sponsors, and monitors to maintain clinical trial information?

Clinical trial information should be maintained to allow accurate reconstruction and evaluation of the trial’s conduct and verification of the trial’s results.

How do investigators know which records should be maintained and the methods for maintaining them?

The study protocol generally specifies the information to be captured and the methods to be used (e.g., by providing “[s]amples of the standardized case-report forms to be used...,” describing “... the methods of recording therapeutic response (description and evaluation of methods and frequency of measurement), the follow-up procedures, and, if applicable, the measures proposed to determine the extent of compliance of subjects with the treatment...,” “[m]ethods of recording and reporting adverse events or reactions...” (CIOMS, International Ethical Guidelines, Appendix 1).

Record-keeping and retention requirements may also be specified by national or local law and regulations.

What is meant by “reporting”? How are essential documents and data combined to report the outcome of the trial?

Reporting is the act of providing information or data to another party. National laws and regulations may require certain information to be reported within specific time frames, for example, reports of serious unanticipated adverse events.

Responsibility for reporting clinical trial information and results is shared by:

- the study sponsor, who reports adverse events to regulators, and prepares summary reports about clinical studies for inclusion in applications to obtain research permits or to market an investigational product;
- the monitor, who prepares and submits written reports of monitoring visits and trial-related communications to the sponsor;
- the clinical investigator who submits, for example, case report forms (CRFs) to the sponsor; progress reports or written summaries of the trial’s status to the institution, the IEC/IRB, and the sponsor; safety reports (e.g., adverse event reports, laboratory anomalies) to the sponsor and IEC/IRB; final reports upon completion of the trial to the sponsor, IEC/IRB, and regulatory authorities;
- the IEC/IRB, which notifies the investigator and institution, and sometimes the regulatory authority(ies) about trial-related decisions and opinions (e.g., decisions to suspend or terminate a study), the reasons for such decisions/opinions, and procedures for appealing them.

“The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports. Data reported on the CRF, which are derived from source documents should be consistent with the source documents or the discrepancies should be explained.” (ICH E6, Section 4.9; see also, ICH E6, Section 4.10: Progress Reports; ICH E6, Section 4.11: Safety Reporting, and ICH E6, Section 4.13: Final Report(s) by Investigator/Institution.)

What is meant by “interpretation” of clinical trial information and how is this achieved within GCP?

“Interpreting” clinical trial information refers to analysing the meaning and significance of data and other observations and information collected during the clinical trial. The study protocol generally describes the overall plan for interpreting clinical trial data. Sponsors, in close collaboration with the investigator(s), generally analyse and interpret clinical trial data and prepare summaries as part of an application for approval to market an investigational product. Such summaries and analyses enable regulators to make a determination about the safety and/or effectiveness of a product that is the subject of a research permit or marketing application.

The sponsor

- “... should utilize appropriately qualified individuals” [e.g., biostatisticians, clinical pharmacologists and physicians, as appropriate] “to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.” (ICH E6, Section 5.5)
- should include in the study protocol a “... description of the statistical methods to be employed, including timing of any planned interim analysis(es), ... the level of significance to be used, ... procedure for accounting for missing, unused, and spurious data, procedures for reporting any deviations from the original statistical plan... selection of subjects to be included in the analyses...” (ICH E6, Section 6.9)

How should clinical trial results be publicly reported?

“Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. ... Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.” (Declaration of Helsinki)

The study protocol may include:

- “[i]n the case of a negative outcome, an assurance that the results will be made available, as appropriate, through publication or by reporting to the drug registration authority.” (CIOMS International Ethical Guidelines, Appendix 1)
- “[c]ircumstances in which it might be considered inappropriate to publish findings, such as when the findings of an epidemiological, sociological or genetics study may present risks to the interests of a community or population or of a racially or ethnically defined group of people.” (CIOMS International Ethical Guidelines, Appendix 1)

Who should have access to clinical trial records?

Sponsors, monitors, IECs/IRBs, and regulators generally require direct access to all information pertaining to the conduct and oversight of the clinical trial. Direct access means that these parties have “[p]ermission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial.” (ICH E6, 1.21)

“Any or all of the documents addressed in this guidance may be subject to, and should be available for, audit by the sponsor’s auditor and inspection by the regulatory authority(ies).” (ICH E6, Section 8)

Note that consent forms should inform study subjects “[t]hat the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject’s original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations, and that by signing a written informed consent form, the subject or the subject’s legally acceptable representative is authorizing such access.” (ICH E6, 4.8) (See also GCP Principle 7: *Informed Consent*)

In addition, sponsors, monitors, investigators and regulators should be aware of the need to handle clinical trial information in a manner

that protects the privacy and confidentiality of trial subjects. These parties should also be fully informed about national/local laws/regulations related to privacy and confidentiality. (See also GCP Principle 12: *Confidentiality/Privacy*)

Implementation

IECs/IRBs, investigators, sponsors, and regulators all bear responsibility for documenting their activities within GCP, and maintaining records pertaining to duties related to the conduct or oversight of the clinical trial for the time required under national or local law and regulations. All parties are responsible for ensuring the accuracy, completeness, legibility and availability (as necessary) of such documents.

IECs/IRBs document their reviews of study protocols and informed consent/recruitment/ advertising materials through minutes that capture the IECs'/IRBs' deliberations and through copies of correspondence with the clinical investigator.

Investigators prepare and maintain case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation.

Sponsors ensure that study protocols address appropriate data handling and record-keeping requirements and design CRFs appropriately to facilitate the capture of all significant trial-related data and observations. Sponsors also secure the services of monitors to ensure compliance of the clinical investigators, and verify that the study was carried out according to the approved study protocol.

Regulators rely on clinical trial information to support regulatory decision-making and may inspect all of the parties involved in conducting or overseeing research. Critical to regulatory inspection is direct access to and review of existing clinical trial records. As part of an inspection, regulators compare records at the clinical investigator site and sponsor site with data and reports submitted to the regulatory authority to verify the information submitted. Regulators also prepare and maintain records of their inspections and findings.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

- Responsibilities (ICH E6, Section 3.1)
- Procedures (ICH E6, Section 3.3)
- Records (ICH E6, Section 3.4)
- Communicating a Decision (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 8)
- Follow-up (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 9)
- Documentation and Archiving (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 10)

For **clinical investigators**, refer to:

- Communication with IRB/IEC (ICH E6, Section 4.4)
- Compliance with Protocol (ICH E6, Section 4.5)
- Records and Reports (ICH E6, Section 4.9)
- Progress Reports (ICH E6, Section 4.10)
- Safety Reporting (ICH E6, Section 4.11)
- Final Report(s) by Investigator/Institution (ICH E6, Section 4.13)
- Clinical Trial Protocol and Protocol, General Information (ICH E6, Section 6)
- Essential Documents for the Conduct of a Clinical Trial (ICH E6, Section 8)

For **sponsors**, refer to:

- Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee (ICH E6, Section 5.5)
- Record Access (ICH E6, Section 5.15)
- Adverse Drug Reaction Reporting (ICH E6, Section 5.17)
- Monitoring (ICH E6, Section 5.18)
- Audit (ICH E6, Section 5.19)
- Clinical Trial/Study Reports (ICH E6, Section 5.22)
- Clinical Trial Protocol and Protocol (ICH E6, Section 6)
- Essential Documents for the Conduct of a Clinical Trial (ICH E6, Section 8)
- Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (ICH E2A)

Guidance on Data Elements for Transmission of Individual Case Safety Reports (ICH E2B)

Statistical Principles for Clinical Trials (ICH E9)

For **regulatory authorities**, refer to:

A Guide to Clinical Investigator Inspections (Good Clinical Practices: Document of the Americas, PAHO, Annex 4)

GCP Compliance Monitoring Programs by Regulatory Authorities (Chapter 7, Good Clinical Practices: Document of the Americas, PAHO)

Surveying and Evaluating Ethical Review Practices (WHO Operational Guidelines,)

Statistical Principles for Clinical Trials (ICH E9)

See also:

Discussion of the WHO Principles of GCP

GCP Principle 2: Protocol

GCP Principle 6: Protocol Compliance

GCP Principle 7: Informed Consent

GCP Principle 12: Confidentiality/Privacy

GCP Principle 14: Quality Systems

Definitions for:

Case Report Form (ICH E6, 1.11)

Clinical Trial/Study Report (ICH E6, 1.13)

Compliance (in relation to trials) (ICH E6, 1.15)

Direct Access (ICH E6, 1.21)

Documentation (ICH E6, 1.22)

Essential Documents (ICH E6, 1.23)

Interim Clinical Trial/Study Report (ICH E6, 1.32)

Monitoring (ICH E6, 1.38)

Monitoring Report (ICH E6, 1.39)

Original Medical Record (ICH E6, 1.43)

Protocol (ICH E6, 1.44)

Source Data (ICH E6, 1.51)

Source Documents (ICH E6, 1.52)

Standard Operating Procedures (SOPs) (ICH E6, 1.55)

PRINCIPLE 12: CONFIDENTIALITY/PRIVACY

The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

“The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient’s information and to minimize the impact of the study on the subject’s physical and mental integrity and on the personality of the subject.” (Declaration of Helsinki)

“The investigator must establish secure safeguards of the confidentiality of subjects’ research data. Subjects should be told the limits, legal or other, to the investigators’ ability to safeguard confidentiality and the possible consequences of breaches of confidentiality.” (CIOMS, International Ethical Guidelines, Guideline 18)

Application

Principle 12 is applied (1) through appropriate procedures to protect the privacy of the subject, and (2) by document and data control to protect the confidentiality of the subject’s information.

Principle 12 is also applied through the informed consent process which requires as an essential element that certain explanations be provided to the subject about the confidentiality of the subject’s records and about access to those records by monitor(s), auditor(s), the IEC/IRB, and the regulatory authority(-ies).

Questions and Answers

What is meant by “privacy”? What is meant by “confidentiality”?

Privacy embraces the concept that each individual should have the right to control personal and sensitive information about him/her. Privacy implies that such information, which may be contained in medi-

cal records, personal diaries, or elsewhere, will be protected and not disclosed without the knowledge/permission of the individual to whom it pertains.

Privacy may not be absolute, however. For example, some information, such as exposure to a communicable disease, may be subject to limited disclosure under public health laws; access to information contained in clinical study records may be required by regulators to verify data submitted in a marketing application. Thus, individuals who participate in clinical trials should be told the extent to which their information will be protected and the circumstances under which the information will be disclosed, to whom, and the purpose(s) for doing so.

Confidentiality embraces the concept that parties who obtain private information from patients and subjects will (1) protect the information itself and any records that contain such information from deliberate or accidental disclosure; (2) develop and follow procedures for release of the information only to authorized parties who have a legitimate need for it, including notification of the patient/subject prior to any disclosure.

Who is responsible for protecting the confidentiality of the subjects' private information?

At all times throughout the investigation, all parties (sponsor, monitor, IEC/IRB, investigator, investigator's staff, and regulators) should protect subjects' private information and ensure that all data are secured against unauthorized access. This applies but is not limited to subjects' case report forms (CRFs), source data, source documents, and safety reports.

"It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject." (Declaration of Helsinki)

How is confidentiality implemented within GCP?

“... Investigators should arrange to protect the confidentiality of such information by, for example, omitting information that might lead to the identification of individual subjects, limiting access to the information, anonymizing data, or other means.” (CIOMS, International Ethical Guidelines, Commentary to Guideline 18)

Other mechanisms to protect information include, but are not limited to:

- coding or encryption of data;
- restricting access to study records and subjects’ medical files (e.g., passwords on electronic files, files secured in locked cabinets or secured storage areas);
- maintaining subjects’ names and identifying information separately from case report forms;
- establishing and following procedures to ensure subjects’ private information and trial data are protected.

Why should potential risks related to release of private information be disclosed to study subjects?

Each subject needs to consider whether risks related to release of private information are sufficiently controlled, such that he/she is still willing to participate in the investigation.

“Research relating to individuals and groups may involve the collection and storage of information that, if disclosed to third parties, could cause harm or distress.” (CIOMS, International Ethical Guidelines, Commentary to Guideline 18)

“Prospective subjects should be informed of limits to the ability of investigators to ensure strict confidentiality and of the foreseeable adverse social consequences of breaches of confidentiality. Some jurisdictions require the reporting to appropriate agencies of, for instance, certain communicable diseases or evidence of child abuse or neglect. Drug regulatory authorities have the right to inspect clini-

cal-trial records, and a sponsor's clinical-compliance audit staff may require and obtain access to confidential data. These and similar limits to the ability to maintain confidentiality should be anticipated and disclosed to prospective subjects." (CIOMS, International Ethical Guidelines, Commentary to Guideline 18)

How should subjects be informed of the measures that will be used to protect their private information? How should potential risks related to release of private information be disclosed to study subjects?

The informed consent document should describe (1) who will have access to personal data of the research participants, including medical records and biological samples; (2) the measures taken to ensure the confidentiality and security of research participants' personal information; and (3) the potential risks to subjects if such measures are breached (e.g., stigma, loss of reputation, potential loss of insurability, etc.).

"... During the process of obtaining informed consent the investigator should inform the prospective subjects about the precautions that will be taken to protect confidentiality." (CIOMS, International Ethical Guidelines, Commentary to Guideline 18)

"Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:...

"(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access."

"(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regula-

tions, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential." (ICH E6, Section 4.8)

"The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection." (ICH E6, Section 5.15)

Implementation

IECs/IRBs review/approve the informed consent procedures and document to ensure, among other things, that there is adequate explanation regarding (1) the risks related to release of the subject's private information, (2) how the confidentiality of the subject's records will be maintained, and (3) persons who may have access to the subject's records (e.g., monitor(s), auditor(s), the IEC/IRB, and the regulatory authority(-ies)).

Investigators should (1) implement procedures to protect and restrict access to study records and private information (e.g., password protection for files, keeping study records in secured areas), (2) follow national/local laws and regulations relating to privacy and confidentiality, (3) ensure that study staff are aware of and receive appropriate training related to their responsibility and procedures to be used for protecting subjects' private information and records, (4) ensure that study staff follow the procedures established for this purpose, and (5) ensure that the consent form and process inform study subjects about the procedures to be used to protect their private information and the circumstances under which their medical and study records may be viewed by regulators, sponsors, monitors, and/or the IEC/IRB.

Sponsors ensure that sites (1) allow regulators, IECs/IRBs, and monitors direct access to records necessary to verify compliance with national/local laws and regulations pertaining to the conduct of clinical trials, and (2) inform subjects about, and obtain their consent for, such access.

Regulatory authorities need to (1) be alert to issues of subject confidentiality, and (2) review sponsors', clinical investigators', and IECs'/IRBs' compliance with applicable national/local laws and regulations for handling private information and informing subjects about these issues.

For more information (including Roles and Responsibilities)

For **IECs/IRBs**, refer to:

Responsibilities (ICH E6, Section 3.1)

Elements of the Review, Protection of Research Participant Confidentiality (WHO Operational Guidelines for Ethics Committees that Review Biomedical Research, Section 6.2.4)

For **clinical investigators**, refer to:

Informed Consent of Trial Subjects (ICH E6, Section 4.8)

Safety Reporting (ICH E6, Section 4.11)

For **sponsors**, refer to:

Trial Management, Data Handling, Recordkeeping, and Independent Monitoring Committee (ICH E6, Section 5.5)

Record Access (ICH E6, Section 5.15)

Monitoring (ICH E6, Section 5.18)

Clinical Trial Protocol and Protocol Amendments, Direct Access to Source Data/Documents (ICH E6, Section 6.10)

For **regulatory authorities**, refer to:

Confidentiality in the Survey and Evaluation Processes (Surveying and Evaluating Ethical Review Practices, a complementary guideline to the Operational Guidelines for Ethics Committees the Review Biomedical Research, WHO, 2002), Section 8

Safeguarding Confidentiality (Guideline 18, CIOMS International Ethical Guidelines for Biomedical Research Involving Human Subjects, Geneva 2002)

See also:

Discussion of WHO GCP Principles

GCP Principle 2: Protocol

GCP Principle 3: Risk Identification

GCP Principle 4: Benefit-Risk Assessment

GCP Principle 7: Informed Consent

GCP Principle 11: Records

Definitions for:

Audit (ICH E6, 1.6)

Confidentiality (ICH E6, 1.16)

Direct Access (ICH E6, 1.21)

Inspection (ICH E6, 1.29)

Original Medical Record (ICH E6, 1.43)

Subject Identification Code (ICH E6, 1.58)

Well-being (of the trial subjects) (ICH E6, 1.62)

PRINCIPLE 13: GOOD MANUFACTURING PRACTICE

Investigational products should be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice (GMP) and should be used in accordance with the approved protocol.

“The sponsor should ensure that the investigational product(s) ... is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labeled in a manner that protects the blinding, if applicable... ” (ICH E6, Section 5.13)

Application

Principle 13 is applied through 1) appropriately characterizing the investigational product (including any active comparator(s) and placebo, if applicable), 2) adhering to applicable Good Manufacturing Practice (GMP) standards in the manufacturing, handling and storage of the investigational product, and 3) using the product according to the approved study protocol.

Questions and Answers

What is meant by “applicable” Good Manufacturing Practice” (GMP)?

“Good Manufacturing Practice (GMP) is a system for ensuring that products are consistently produced and controlled according to quality standards.” “...GMP covers all aspects of production, from the starting materials, premises and equipment to the training and personal hygiene of staff. Detailed, written procedures are essential for each process that could affect the quality of the finished product. There must be systems to provide documented proof that correct procedures are consistently followed at each step in the manufacturing process – every time the product is made.” “...WHO has established detailed guidelines for good manufacturing practice. Many countries have formulated their own requirements for GMP based on

WHO GMP.” (WHO, *Good Manufacturing Practice in Pharmaceutical Production*)

Compliance with GMP standards is intended to:

- assure consistency between and within batches of the investigational product and thus assure the reliability of clinical trials;
- assure consistency between the investigational product and the future commercial product and therefore the relevance of the clinical trial to the efficacy and safety of the marketed product;
- protect subjects of clinical trials from poor-quality products resulting from manufacturing errors (omission of critical steps such as sterilization, contamination and cross-contamination, mix-ups, incorrect labeling, etc.), or from starting materials and components of inadequate quality; and
- document all changes in the manufacturing process.

“...[T]he principles of GMP should be applied, as appropriate, to the preparation of [investigational] products.” (WHO, *Good Manufacturing Practice in Pharmaceutical Production*)

In accordance with national/local laws and regulations, GMP compliance may be a requirement. Where not required by national/local laws and regulations, GMP standards provide important guidance to the manufacture of quality investigational products.

What constitutes handling and storage of the investigational product(s)?

In addition to packaging, labeling, quarantine and release associated with the manufacturing process at the production site, handling of the product by the sponsor also includes shipping, return, and final disposition of the investigational products.

“Investigational products should be shipped in accordance with the orders given by the sponsor. A shipment is sent to an investigator only after the following two-step release procedure: (i) the release of the product after quality control (“technical green light”); and (ii) the

authorization to use the product, given by the sponsor (“regulatory green light”). Both releases should be recorded. The sponsor should ensure that the shipment will be received and acknowledged by the correct addressee as stated in the protocol. A detailed inventory of the shipments made by the manufacturer should be maintained, and should make particular mention of the addressee’s identification. Returned investigational products should be clearly identified and stored in a dedicated area. Inventory records of returned medicinal products should be kept.”(WHO, *Good Manufacturing Practice in Pharmaceutical Production*)

With respect to storage, “[t]he sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.” (ICH E6, Section 5.13)

“The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof...” (ICH E6, Section 5.14)

At the site, the investigator is responsible for ensuring that the investigational product(s) are “... stored as specified by the sponsor ... and in accordance with applicable regulatory requirements” ... [and] “are used only in accordance with the approved protocol.” (ICH E6, Section 4.6)

Implementation

Responsibility for implementing this principle is shared by sponsors (or contract manufacturers/ contract research organizations), investigators, and regulators.

Sponsors implement this principle directly or indirectly through contract, by developing and characterizing the investigational product.

They make the necessary notifications/submissions to the applicable regulatory authority(ies), identify GMP requirements, if any, that may apply to the manufacturing, handling and storage of the investigational product, and ensure compliance with those requirements. Sponsors manufacture the investigational product directly or have it manufactured under contract at a manufacturing site in accordance with applicable GMP. They are responsible within GCP for the handling, storage, distribution and final disposition of the investigational product(s).

The sponsor also develops the study protocol and investigator's brochure, monitors protocol compliance, and ensures that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational products for the trial and documentation thereof.

Investigators are responsible for familiarity with the investigator's brochure and for conducting the research in compliance with the protocol, including any instructions for storing and handling investigational products. Investigators are responsible for explaining correct use (including handling and storage) of the investigational product to the study subjects. Investigators also ensure that any unused investigational products are returned to the sponsor after the trial is completed.

In accordance with national/local laws and regulations, **regulators** may establish GMP requirements for investigational products, review manufacturing data submitted in support of research permits or marketing applications, and/or inspect manufacturing facilities. Because investigational products may be imported, regulators should be familiar with the manufacturing requirements in the country of origin and their conformance with international GMP standards.

Regulators may also inspect investigators for compliance with the study protocol, including instructions for storing and handling investigational products.

For more information (including Roles and Responsibilities)

For guidelines on Good Manufacturing Practices and Inspection, refer to:

WHO, *A Compendium of Guidelines and Related Materials, Volume 2: Good Manufacturing Practices and Inspections*

(http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpthree_inves.html)

Active Pharmaceutical Ingredients for Use in Clinical Trials (GMP for Active Pharmaceutical Ingredients, ICH Q7A, Section XIX)

For **clinical investigators**, refer to:

Compliance with Protocol (ICH E6, Section 4.5)

Investigational Product(s) (ICH E6, Section 4.6)

For **sponsors**, refer to:

Manufacturing, Packaging, Labeling, and Coding Investigational Products (ICH E6, Section 5.13)

Supplying and Handling Investigational Product(s) (ICH E6, Section 5.14)

Monitoring (ICH E6, Section 5.18)

Noncompliance (ICH E6, Section 5.20)

For **regulatory authorities**, refer to:

WHO, *A Compendium of Guidelines and Related Materials, Volume 2: Good Manufacturing Practices and Inspections*

(http://www.who.int/medicines/organization/qsm/activities/qualityassurance/gmp/gmpthree_inves.html)

Active Pharmaceutical Ingredients for Use in Clinical Trials (GMP for Active Pharmaceutical Ingredients, ICH Q7A, Section XIX)

See also:

Discussion of the WHO Principles of GCP:

GCP Principle 6: Protocol Compliance

Definitions for:

Comparator (Product) (ICH E6, 1.14)

Compliance (in relation to trials) (ICH E6, 1.15)

Contract Research Organization (CRO) (ICH E6, 1.20)

Investigational Product (ICH E6, 1.33)

Monitoring (ICH E6, 1.38)

PRINCIPLE 14: QUALITY SYSTEMS

Systems with procedures that assure the quality of every aspect of the trial should be implemented.

Application

Principle 14 is applied through development of procedures to control, assure, and improve the quality of data and records and the quality and effectiveness of processes and activities related to the conduct and oversight of clinical research.

Questions and Answers

What is meant by “quality” in the context of a clinical trial?

“Quality” is a measure of the ability of a product, process, or service to satisfy stated or implied needs. A high quality product readily meets those needs.

In the context of a clinical trial, quality may apply to data (e.g., data are accurate and reliable) or processes (e.g., compliance with the study protocol and GCP; ensuring informed consent; adequate data handling and record-keeping, etc.). (See WHO GCP Principles 6: *Protocol Compliance*; 7: *Informed Consent*; 11: *Records*)

A common way to assure data and process quality is through the development and application of standard operating procedures (SOPs) that define responsibilities, specify records to be established and maintained, and specify methods and procedures to be used in carrying out study-related activities. SOPs coupled with close personal supervision of the trial’s conduct by the clinical investigator and careful monitoring by the sponsor help to ensure that processes are consistently followed and activities are consistently documented. As a result, data collected using such procedures and under such supervision should ordinarily be reliable enough for regulatory decision-making.

What are “quality systems” with respect to clinical trials?

“Quality systems” for clinical trials are formalized practices (e.g., monitoring programs, auditing programs, complaint handling systems) for periodically reviewing the adequacy of clinical trial activities and practices, and for revising such practices as needed so that data and process quality are maintained.

How are quality systems implemented within GCP?

Within GCP, quality systems are implemented through quality management: that is, through coordination of activities by the sponsor, by the investigator(s) and site staff, by the IEC(s)/IRB(s) and by regulators to direct and control their operations with respect to quality. Quality management embraces three major components: quality control; quality assurance; and quality improvement.

What is the distinction between “quality control”, “quality assurance”, and “quality improvement”?

“Quality control” means the steps taken during the generation of a product or service to ensure product/service quality. For a clinical trial, “quality control” encompasses steps taken during the clinical trial (e.g., investigator supervision, sponsor monitoring, and any on-going review by regulatory authorities) to ensure that the trial meets protocol and procedural requirements and is reproducible.

“Quality assurance” refers to a systematic process to determine whether the quality control system is working and effective. Most often, quality assurance in clinical trials is implemented by the sponsor through independent auditing of quality control activities and, where applicable, by regulatory authorities through inspection of quality control systems and activities. Quality assurance audits may be performed during the course of the clinical trial and/or upon trial completion.

“The purpose of a sponsor’s audit, which is independent of and separate from routine monitoring or quality control functions, should be to

evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.” (ICH E6, Section 5.19)

“Quality improvement” refers to a systematic process for taking the knowledge gained through quality assurance audits and activities and using this knowledge to make changes in systems and activities in order to increase the ability to fulfill quality requirements then and for the future.

What is study monitoring?

Monitoring is “[t]he act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).” (ICH E6, 1.38; see also ICH E6 Section 5.18, generally, for detailed guidance on study monitoring.)

What is the difference between monitoring, auditing, and inspecting?

Monitoring is a quality control activity conducted by the sponsor or a representative of the sponsor to ensure that the research is conducted in accordance with the study protocol, GCP, and applicable regulatory requirements and that research data are accurate, complete, and verifiable from source documents. Monitors generally compare source documents with case report forms and seek to resolve any discrepancies. Monitors also try to verify that activities related to protecting the rights and welfare of study subjects (e.g., prior approval of the IEC/IRB, obtaining legally effective informed consent from all study subjects) were appropriately carried out.

Auditing is an independent quality assurance activity used by the sponsor to evaluate the effectiveness of a monitoring program and/or specific monitoring activities. Auditing is distinguished from monitoring by the fact that monitoring is carried out while the study is in progress (see discussion of “Quality control” above) whereas auditing can occur anytime during or after the study.

An inspection is “[t]he act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor’s and/or contract research organization’s (CROs) facilities or at other establishments deemed appropriate by the regulatory authority(ies).” (ICH E6, 1.29) The purpose of such inspection is to determine whether research was conducted in compliance with national/local laws and regulations for the conduct of research and the protection of human subjects.

Implementation

All of the parties who conduct and oversee clinical trials (sponsors, clinical investigators, IECs/IRBs, and regulatory authorities) should adopt and implement quality systems for the processes and activities for which they are responsible.

Sponsors secure the services of monitors to ensure compliance of the clinical investigators and verify that the study was carried out according to the approved study protocol. Sponsors also audit the monitors’ performance and other quality control activities and systems to ensure each system’s performance.

Monitors review study records at the sites, report their findings to the sponsor, and prepare written reports that document each site visit or trial-related communication.

Investigators supervise to ensure that study staff follow established procedures for the conduct of the study, e.g. obtaining IEC/IRB approval of the study, obtaining informed consent from subjects, establishing and maintaining subjects’ case histories, transcribing data from subjects’ medical files to the CRFs, reporting adverse events and other unanticipated problems, etc.

IECs/IRBs develop and adopt SOPs for reviewing studies and informing the clinical investigator of any required modifications to the study protocol, and for assuring that such modifications are in place before

the study proceeds. In accordance with national/local laws and regulations, IECs/IRBs may develop SOPs to allow IEC/IRB members or a third party to observe the consent process to verify that subjects are being provided the opportunity to ask questions about the study and that subjects receive a copy of the informed consent document. IECs/IRBs implement systems to assure that continuing review of the study takes place at intervals appropriate to the degree of risk, and that investigators are notified so that they may provide the necessary documentation to the IEC/IRB in advance of the deadline.

In accordance with applicable laws/regulations, **regulators** may inspect all parties that conduct or oversee research and verify the information submitted to the regulatory authority. Regulators may ask for sponsors' monitoring plans as a condition of allowing a study to proceed. Regulatory authorities also optimally develop SOPs and quality systems for internal regulatory activities, including policies and procedures for reviewing product applications and for the conduct of GCP inspections.

For more information (including Roles and Responsibilities)

For **sponsors**, refer to:

- Quality Assurance and Quality Control (ICH E6, Section 5.1)
- Trial Management, Data Handling, Recordkeeping, and Independent Data Monitoring Committee (ICH E6, Section 5.5)
- Monitoring (ICH E6, Section 5.18)
- Audit (ICH E6, Section 5.19)
- Noncompliance (ICH E6, Section 5.20)
- Monitoring Arrangements (Clinical investigation of medical devices for human subjects, Part 2: Clinical investigation plans, International Standards Organization (ISO), 14155-2, 4.34)

For **monitors**, refer to:

- Monitoring (ICH E6, Section 5.18)

For **clinical investigators**, refer to:

- Investigator's Qualifications and Agreements (ICH E6, Section 4.1)

For **IECs/IRBs**, refer to:

Composition, Functions, and Operations (ICH E6, Section 3.2)

Procedures (ICH E6, Section 3.3)

WHO Surveying and Evaluating Ethical Review Practices: A complementary guideline to the Operational Guidelines for Ethics Committees that Review Biomedical Research.

For **regulatory authorities**, refer to:

Noncompliance (ICH E6, Section 5.20)

GCP Compliance Monitoring Programs by Regulatory Authorities (Chapter 7, Good Clinical Practices: Document of the Americas, PAHO)

A Guide to Clinical Investigator Inspections (Annex 4, Good Clinical Practices: Document of the Americas, PAHO)

Optional Guideline for Good Clinical Practice Compliance and Quality Systems Auditing (European Network of GCP Auditors and other GCP Experts [ENGAGE], European Forum for Good Clinical Practice, August 1997)

See also:

Discussion of the WHO Principles of GCP

GCP Principle 2: Protocol

GCP Principle 6: Protocol Compliance

GCP Principle 11: Records

Definitions for:

Audit (ICH E6, 1.6)

Audit certificate (ICH E6, 1.7)

Audit report (ICH E6, 1.8)

Audit trail (ICH E6, 1.9)

Compliance (in relation to trials) (ICH E6, 1.15)

Direct Access (ICH E6, 1.21)

Monitoring (ICH E6, 1.38)

Monitoring Report (ICH E6, 1.39)

Quality Assurance (QA) (ICH E6, 1.46)

Quality Control (QC) (ICH E6, 1.47)

Standard Operating Procedures (SOPs) (ICH E6, 1.55)

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National good clinical practice and other guidelines

Australia

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India

Ethical guidelines for biomedical research on human subjects.

<http://icmr.nic.in/ethical.pdf>

Japan

Ministry of Health, Labour and Welfare. "Standards on the Implementation of Clinical Trials on Drugs (New GCO)"

South Africa

Guidelines for good practice in the conduct of clinical trials in human participants in South Africa.

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United States of America

Good clinical practice in FDA regulated clinical trials.

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