HANDBOOK FOR GOOD CLINICAL RESEARCH PRACTICE (GCP)

GUIDANCE FOR IMPLEMENTATION

World Health Organization

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Contents

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 trials[1] 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 I (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), the Council for International Organizations of Medical Sciences (CIOMS), the European Agency for the Evaluation of Medicinal Products (EMEA), 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 subjects' 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 including those for:

- developing and updating the protocol, investigator's brochure, case report forms (CRFs), and other study-related documents;
- supplies procurement, 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 Practice (GMP) and by handling and storing the product according to the manufacturing specifications and the study protocol. GCP requires that sponsors control access to the inves-

tigational 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.