

## Good Clinical Practice (GCP): A review

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### ABSTRACT

Good Clinical Practice (GCP) is an international ethical and scientific quality standard designed to conduct, performance, monitor, audit, record, analyse and report clinical trials. It protects the rights, integrity and confidentiality of trial subjects. Clinical research trails are increasingly playing a role in various medical disciplines. GCP guidelines are used in clinical trials through out the globe with the main aim of protecting and preserving human rights. In this review article the historical background and the events that led up to the formation of these guidelines, key trial activities and principles of GCP are discussed.

**Keywords:** GCP, Clinical Trials, Managing trial data, CROs

### INTRODUCTION<sup>[1]</sup>

Good Clinical Research Practice (GCP) is a process that incorporates established ethical and specific 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 skill fully 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. "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

**How to cite this article:** B Shamim; Good Clinical Practice (GCP): A review; PharmaTutor; 2014; 2(9); 20-29

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 Specific Group on Principles for Clinical Evaluation of Drugs. The Specific 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 specific 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 wellbeing of subjects and ensures that investigations are scientifically sound and advance public health goals. The objectives of this are 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.

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 (EMEA), and the United States Food and Drug Administration (FDA).

### SCOPE<sup>[1]</sup>

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.

### HISTORICAL BACKGROUND:<sup>[2]</sup>

In 1938, the Federal Food, Drug and Cosmetic Act was enacted by the Food and Drug Administration (FDA) and for the first time, manufacturers were required to test drugs for safety and present the evidence of safety testing to the FDA prior to marketing<sup>[3]</sup>. In 1947, the Nuremberg Code was created as a result of the unethical and horrific experiments carried out during World War II at Nazi war camps by German physicians, who were subsequently tried and charged at the Nuremberg Military Tribunal. This code states the need for a scientific basis in research on human subjects and voluntary consent and protection of participants<sup>[4, 5]</sup>. The Universal Declaration of Human Rights (December 10th 1948) was also adopted and proclaimed by the United Nations after the atrocities of World War II and it further reiterated the human factor involved in medical experiments. In 1964, the Declaration of Helsinki was developed by the World Medical Association, forming the basis for the ethical principles that underlie the ICH-GCP guidelines we have today. The focus of this declaration is the protection of the rights of human subjects and this is clear in its introduction<sup>[6]</sup>: “The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. It is the duty of the physician to promote and

safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty" In 1962 the world was once again shocked by the severe foetal limb deformities linked to the use of maternal thalidomide. In fact this drug reaction was only discovered after 10,000 infants were born in over 20 countries worldwide. In response to this, the Kefauver- Harris Amendments were passed which required the FDA to evaluate all new drugs for safety and efficacy <sup>[3]</sup>. Another important milestone in the formation of the ICH-GCP guidelines was The Belmont Report which was issued in April 1979 by the National Commission for Protection of Human Subjects of Biomedical and Behavioural Research <sup>[7]</sup>. The principles of this report are as follows:

1. **Respect for Persons:** This principle acknowledges the dignity and freedom of every person. It requires obtaining informed consent from research subjects (or their legally authorised representatives)
2. **Beneficence:** This principle requires that researchers maximise benefits and minimise harms associated with research. Research related risks must be reasonable in light of the expected benefits.
3. **Justice:** This principle requires equitable selection and recruitment and fair treatment of research subjects.

In 1982, the World Health Organization (WHO) and the Council for International Organizations of Medical Sciences (CIOMS) issued a document entitled 'International Guidelines for Biomedical Research Involving Human Subjects'. This document was released to help developing countries apply the principles of the Declaration of Helsinki and the Nuremberg Code <sup>[3]</sup>. Worldwide, many organisations and committees issued various documents and guidelines on the same issue, and a decision was taken to consolidate all these guidelines into one universal guideline to be used globally.

In an effort to overcome international GCP inconsistencies throughout the countries, the International Conference for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) issued the ICH Guidelines: Topic E6 Guideline for GCP. This guideline was approved on 17 July 1996 and implemented for clinical trials from 17 January 1997. The participants of these guidelines were representatives of authorities and pharmaceutical companies from the EU, Japan and the United States as well as those of Australia, Canada, the Nordic countries and WHO <sup>[8]</sup>.

#### KEY TRIAL ACTIVITIES INCLUDE: <sup>[1]</sup>

##### **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.

##### **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. 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.

#### **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; computer hardware and software, electronic patient diaries, and other specialized equipment. 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.

#### **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.

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.

#### **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.

#### **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.

#### **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).

#### **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 enrolment in the study or performing any specific study procedures.

**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 investigational 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.

**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.

**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.

**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.

**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. 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.

#### **Quality assurance of the trial performance and data**

Quality assurance (QA) verifies through systematic, independent audits that existing quality control systems 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.

#### **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 enrolment;

- 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.

#### **PRINCIPLES OF GCP:<sup>[1]</sup>**

**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 (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.

These principles are self-explanatory and, when summarised, simply mean: All clinical trials should be conducted in accordance with ethical principles, sound scientific evidence and clear detailed protocols. The benefits of conducting trials should outweigh the risks. The rights, safety and wellbeing of trial participants are of paramount importance and these should be preserved by obtaining informed consent and maintaining confidentiality. The care must be given by appropriately qualified personnel with adequate experience. Records should be easily accessible and retrievable for accurate reporting, verification and interpretation. Investigational products should be manufactured according to Good Manufacturing Practice <sup>[8]</sup>. It is also important to

mention the participants of GCP in clinical trials and their respective responsibilities.

### CONCLUSION

The events that led up to the culmination of the GCP guidelines brought forth public awareness that there was a need to control and regulate clinical trials dealing with drugs and human subjects lies in historical background that led to

the formulation of GCP guidelines in the United States and Europe and also to the formation of the ICH. The violation of human rights played a large role and that is why the Declaration of Helsinki and The Nuremberg Code remain as the framework of the present guidelines. Today the GCP guidelines are become a global law which safeguards humanity.

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