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Quality Control and Quality Assurance in Human Experimentation

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1. Introduction

During the 20th, century the awareness of the need for the ethical treatment of human subjects participating in experimentation has evolved. Various incidents over the years have sparked the creation of government entities dedicated to the regulation of human experimentation. This has brought about the creation of regulations whose objective is the protection human subjects throughout the experimentation process. These regulations call for many checks and balances with the objective of protecting the individual under experimentation through quality control procedures in the monitoring process of the experiment. The quality is assured through auditing the process by independent professionals. This chapter will describe the history of the development of Good Clinical Practices (GCP) and an analysis of some applicable documents and practices developed by the Food and Drug Administration of the USA, and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). FDA (USA), EMA (EU) and Pharmaceuticals and Medicines Safety Bureau (Japan) as well as pharmaceutical industry representatives of the USA, EU and Japan form the ICH. ICH guidelines provide a unified standard for designing, conducting, recording and reporting clinical trials involving the participation of human subjects and other necessary activities related to human experimentation. ICH is especially concerned with harmonizing the regulatory requirements of its sponsor countries; USA, EU and Japan. It describes the necessary activities and documentation that would allow the evaluation of the ethical conduct of a clinical trial and assure the quality of the information derived from such a study. Many countries all over the world are now including these guidelines in their regulations and are effectively adhering to them.

A significant part of human experimentation is conducted in the development of new drugs for the treatment of human disease as well as devices and instruments used in medical practice. This chapter will also describe the development process, the logic behind it, the non-clinical testing that is necessary for the drug/device development process, the clinical phases of drug development, the role of the ethics committees and Institutional Review Boards in the approval process to conduct human experimentation as well as the role of the government agencies which regulate human experimentation.

2. Evolution of ethical conduct in human experimentation

Since the 5th century B.C. the most prevalent code of ethical conduct for the medical profession has been and still is the "Hippocratic Oath"¹. It is widely believed to have been written by Hippocrates, often regarded as the father of western medicine. The original text of the Hippocratic Oath is usually interpreted as one of the first statements of a moral of conduct to be used by physicians, assuming the respect for all human life. It has been modified over time in many occasions but the spirit of the concept has been preserved.

It was not until after the end of World War II that the United States authorities conducted in their occupied zone several trials for war crimes committed by the Nazis in Nuremberg². The trials were formally named the "Trials of War Criminals before the Nuremberg Military Tribunals". They were held before US military courts, not before the International Military Tribunal. The defendants were accused of unethical human experimentation and other atrocities. On August 19th, 1947 the tribunal delivered its verdict including their opinion on human experimentation. The Nuremberg Code that emerged from these trials consists of 10 points that represent a set of ethical research principles for human experimentation. The Nuremberg Code includes concepts like: voluntary consent of the research subject; experimentation with clear fruitful objectives; experimentation in humans should be preceded by animal experimentation; the conduct of research in humans should not produce physical or mental injury nor results in death of the study subjects; the experimentation should be conducted with a view of introducing the minimal possible risk to the individual during the experimentation and conducted by a qualified person. It also includes the concept that the subject should be at liberty to stop the experiment at any time for any reason. Likewise, the experimenter should be prepared to terminate the experiment if in their judgment there is any reasonable chance that it may harm the research subject. Subsequently in 1948 the World Medical Association introduced the Declaration of Geneva³ as a modernization of the Hippocratic Oath. It was designed as a formulation of that oath's moral truths that could be comprehended and acknowledged modernly. The Declaration of Geneva has been amended in 1968, 1984, 1994, 2005 and 2006.

Another important historical document addressing human experimentation is the Declaration of Helsinki⁴ adopted in 1964 by the World Medical Association in Helsinki, Finland. It is a set of ethical principles for the medical community specifically related to human experimentation and is widely regarded as a cornerstone document for human research. It has been revised six times since its adoption, the last revision being in 2008. The Declaration of Helsinki adopted the ten principles first stated in the Nuremberg Code and tied them to the Declaration of Geneva. It addresses clinical research reflecting the changes in medical practice. Its various revisions introduced the concept of independent review committees, now known as Institutional Review Board or Independent Ethics Committees; the management of the inclusion of minors in clinical research and the recognition of vulnerable groups; addressed the use of placebos; and the inclusion of human volunteers in clinical trials. This document was not meant to be legally binding but has influenced national and regional regulation and legislation around the world. It introduced the concept that ethical considerations must take precedence over laws and regulations.

In the USA, the Belmont Report⁵ was created by the now named Department of Health and Human Services with the title "Ethical Principles and Guidelines for the Protection of Human Subjects of Research". The report was issued in April 1979 prompted in part by problems arising from the Tuskegee Syphilis Study (1932-1972). The Tuskegee Syphilis Study was designed to observe the clinical evolution of syphilis. The patients, 399

impoverished Black individuals from Macon county, Alabama, who thought they were receiving free health care from the government were never told they had syphilis nor were they treated for it. The Belmont Report incorporates the principles of the Nuremberg Code, the Declaration of Geneva and the Declaration of Helsinki. These documents influenced significantly the legislation and creation of regulations for the ethical conduct of human experimentation in the USA. Sections 45 (government sponsored studies, 45 CFR) and 21 (private and industry sponsored studies, 21 CFR) of the Code of Federal Regulations (CFR) base many of their regulations on these important ethical documents and have influenced in many important ways human experimentation in the US and around the world.

3. Regulatory environment

The U.S. Food and Drug Administration (FDA) ⁶ was created in 1906 by the Federal Food, Drug, and Cosmetic Act, the Wiley Act. The purpose was to prevent the manufacturing, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs, medicines, and liquors. The FDA evolved over the years to require manufacturers to submit a New Drug Application (NDA) for each newly introduced drug and provide data that demonstrates the safety of the product (1938), and later (1962) to establish efficacy, in order to show that the products were effective for their claimed indication. Several amendments to the law have followed to reflect the evolution and emerging issues in the drug development and approval process, which remain today in the crossroads where science, medicine, politics and business intersect. Because a new drug approval is based largely on clinical data obtained by experiments in humans, the FDA has vested significant effort in ensuring the quality of the clinical data and the conditions under which they are obtained. The set of regulations and guidelines the FDA publishes constitute what is collectively known as good clinical practices or GCP. Through these FDA sets the minimum standards for the conduct of clinical trials, the collection of data and data management and reporting of clinical studies.

The European Medicine Agency, EMA⁷ (formerly known as EMEA, European Agency for the Evaluation of Medicinal Products), was founded in 1995 and is a decentralized agency of the European Union responsible for the scientific evaluation of medicines developed by pharmaceutical companies for use in the European Union. Its main function is the promotion and protection of public human and animal health, through the evaluation and supervision of medicines for human and animal use. They are responsible for the evaluation of European Marketing Authorizations for human and veterinary use medicines. The agency monitors the safety of marketed products and provides scientific advice to companies on the development of new medicines. The agency constantly works to forge close ties with partner organizations around the world, including the World Health Organization, the FDA and the other regulatory authorities.

In Japan the Pharmaceuticals and Medical Devices Agency (PMDA) ⁸ working with the Ministry of Health implements measures for securing the efficacy and safety of drugs, cosmetics and medical devices. The PMDA also has forged close ties with other regulatory agencies, namely the EMA and FDA as partners in the formation of the International Conference on Harmonization (ICH).

The International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) ⁹ was created in 1990. This organization brings together the regulatory authorities and pharmaceutical industry of Europe, Japan and the

US. The purpose is to discuss scientific and technical aspects of drug registration with the goal of harmonizing drug development and registration across the world. The Global Cooperation Group of this organization has been working to harmonize the increasingly global approach to drug development, so that the benefits of international harmonization for better global health can be realized worldwide. ICH's mission is to achieve greater harmonization to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner. ICH has developed a series of guidelines to help regulate the clinical drug development process. The instruments developed include a standardized medical terminology system (MedDRA) to use in the capturing, registering, documenting and reporting adverse events during human experimentation. ICH maintains, develops and distributes MedDRA. ICH also developed a standardized package for the submission of new drug applications, the Common Technical Document (CTD) which has been adopted around the world as the gold standard for new medical products submissions. The CTD assembles all the quality, safety and efficacy information required for regulatory submissions in a common format to facilitate the regulatory review process. The CTD has simplified the assembly of the regulatory packages since reformatting for submissions to different regulatory agencies is not necessary anymore. Another area where ICH has worked to improve is international electronic communication by evaluating and recommending Electronic Standards for the Transfer of Regulatory Information (ESTRI). ESTRI has developed recommendations for electronic individual case safety reports and electronic CTDs. Furthermore, ICH has developed guidelines to standardize and harmonize the areas involved in the drug development process. These include guidelines on quality of the product being developed; on safety focusing on nonclinical studies to uncover potential risks for humans; on efficacy, which is concerned with the design, conduct and safety clinical trials; and other guideless like the ones developed by ESTRI. The clinical guidelines include clinical safety (E1-2), clinical study reports (E3), dose response studies (E4), ethnic factors (E5), Good Clinical Practice (E6), clinical trials (E7-11), clinical evaluation by therapeutic category (12), clinical evaluation (E14), and pharmacogenomics (E15-16). The GCP (E6) document describes the responsibilities and expectations of all participants in the conduct of clinical trials, including investigators, monitors, sponsors and IRBs. It is one of several GCP guidelines published by various organizations, like the World Health Organization (WHO), Pan American Health Organization (PAHO), FDA and EMA. ICH's E6 is the GCP guideline most commonly accepted worldwide. It has been adopted by many countries in their regulations and accepted as the gold standard of GCP for clinical drug development. We will discuss E6 in more detail.

4. Nonclinical drug testing

Animal testing is an imperfect predictor of drug activity in humans. It constitutes the best practical experimental models for identifying and measuring the pharmacologic activity of the drug and predicting its effects in humans. *In vivo* and *in vitro* animal testing is the first major activity in the drug development process. The purpose is to characterize the toxicology, pharmacokinetic activity, and pharmacological activity of the candidate compounds prior to administration to human beings. FDA (21CFR58) as well as ICH (S guidelines) have developed standards for such testing. Initially, short-term effects are evaluated to decide if the drug is sufficiently safe for administration to humans and at what dose should the human testing start. As the drug development in human beings

progresses, additional animal studies are conducted. These animal studies include long-term drug administration, and specialized animal tests are conducted to support longer administration in humans. These experiments allow the observation of drug effects that would be impractical or unethical to study in humans. Researchers can observe the effects of the compound over the lifespan of an animal, test dose responses and maximum doses; assess the effects on reproduction, pregnancy and the embryos; effects on genes; assess potential for carcinogenicity; evaluate mechanisms of action of the drug; and characterize the site, degree and duration of action of the compound. Regulatory agencies are involved in determining the amount and type of animal testing required to initiate drug development in humans as well as the requirements to support the whole clinical development program.

The regulatory agencies, specifically FDA, set the minimum standards for laboratories conducting these nonclinical tests through the publication and enforcement of Good Laboratory Practice (GLP)¹⁰. To ensure the quality and integrity of the data derived, nonclinical laboratories are required to implement quality systems to conduct their experiments and to abide by the animal welfare laws of the country. GLPs establish basic standards for the conduct and reporting of non clinical safety testing, including the organization of the laboratory, personnel qualifications, physical structure of the facility, equipment, maintenance procedures, and operating procedures. It requires the use of a written protocol and its structure, including its purpose, who is sponsoring the study, procedure for identification and evaluation of the test animals or test system. GLP details how to report nonclinical studies, the storage and retrieval of records and data, and the retention of records. FDA conducts inspections to monitor compliance with GLP requirements. Nonclinical laboratories may be disqualified if the laboratory facility fails to comply with the regulations, and the noncompliance affects adversely the results of the study.

In addition, FDA may provide advice to sponsors on the adequacy of the nonclinical testing plans before animal testing has begun, and evaluate independently the results and conclusions of the nonclinical testing. FDA has developed guidances for nonclinical testing also. Other regulatory authorities, namely European Community and Japan, have also developed their testing standards. ICH has stepped in in an effort to harmonize these standards with the Safety guidelines (S).

The basic toxicology studies undertaken to identify and measure a drug's adverse effects in the short- and long-term may include any or all of the studies shown in table 1 depending on the drug, intended use and duration of exposure in clinical trials (Table 1).

The responsibility of the conduction of these animal experiments falls on the sponsor, the animal laboratory and the regulatory authorities. Quality systems are required to guarantee the quality of the data generated. The Sponsor monitors the study and conducts audits, the laboratory needs to have proper standard operating procedures and guidelines in accordance with the regulations and prevailing laws as well as a quality group to ensure compliance with said regulations and laws, and the regulatory authorities perform inspections to make sure the regulations and laws are being complied with.

5. The clinical phases of drug development

In the FDA regulations and regulations by health authorities around the world accept 3 phases of drug development¹¹. A fourth phase is frequently included during the post

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| Acute toxicity studies | Measure the short-term adverse effects of one of more doses administered over no more than 24 hours. Provide information on appropriate dosage for multiple dose studies, potential target organs, timeline of drug induced effects, species specific toxicity, potential acute toxicity in humans and estimate the safe acute dose for humans. |
| Subacute or subchronic toxicity studies | Evaluate toxic potential over 14 to 90 days depending on the proposed clinical indication and duration of exposure. They are designed to assess the progression and regression of drug induced lesions. |
| Chronic toxicity studies | Determine the risk in relation to the anticipated dose and duration of treatment, potential target organs, reversibility of observed toxicity and the no observed effect level. These studies last 180 days to 1 year of exposure. |
| Carcinogenicity studies | To observe the generation of malignant tumors in animals. Generally they are required for drugs which are intended to be used for chronic conditions for 6 months or more, or to be intermittently used over the years for chronic or intermittent conditions. These studies are usually in rodents and last for 2 years. |
| Special toxicity studies | These are studies appropriate for specific formulations, route of administration, or conducted in particular animal models relevant to a human condition, disease or age. They include immunotoxicity studies. |
| Reproductive toxicity studies | For drugs to be used in women of childbearing potential. They include fertility and general reproductive performance, teratology and perinatal/postnatal development. |
| Genotoxicity studies | Mutagenicity studies. Are used to assess the likelihood of the drug causing genomic damage that could induce cancer development. |
| Toxicokinetic studies | Used to describe the systemic exposure achieved in animals and its relationship to the drug concentration, dose and time course of the toxic effect. The purpose is to contribute in the assessment of the relevance of these findings to clinical safety, and support the choice of species and dose regimen in other nonclinical studies as well as the design of subsequent nonclinical studies. |

Table 1. Basic Nonclinical Toxicology Studies.

approval period. These are not mandates that determine the specific structure or design of clinical trials. Although these phases are in general to be conducted sequentially, frequently they overlap. Clinical development programs commonly proceed in the following stages:

5.1 Phase I

This is the phase where initial introduction of an investigational product to humans. The drug is administered cautiously to a few patients or normal human volunteers (usually less than 80), to gain an understanding of the pharmacology, and basic safety of the drug, including tolerability, activity, pharmacodynamics, pharmacokinetics, mechanism of action in humans and optimal route of administration. Drug metabolism, structure-activity relationships and studies in which investigational drugs are used as research tools to explore biological phenomena or disease processes are also included in this phase. The first evidence of the drug efficacy in humans may also be observed in these phase. Subjects are monitored very closely. The studies in Phase II are designed based on the results obtained during this phase.

5.2 Phase II

In this phase a small group of patients are tested, usually 100 to 200, who suffer from the condition the drug is intended to treat or diagnose. The studies include well controlled, closely monitored trials. The investigational product is administered with the objective of increasing the understanding of the safety profile and the initial observations on the efficacy of the drug in the proposed disease. In this phase the aim is to establish a foundation for the phase III trials. The information gathered includes dose, dose regimen and fine tuning of the target population.

5.3 Phase III

The drug in this phase is used in much larger groups of patients, several hundred or thousands, who suffer from the condition that the compound is supposed to treat. This phase includes controlled and uncontrolled studies. The idea is to gather additional safety and efficacy information to determine the benefit-risk ratio of the drug. In this phase the trials follow more rigorous standards since they will serve as the primary basis for the approval of the drug to be marketed.

5.4 Phase IV

In addition to these 3 phases, regulatory authorities may require additional studies after approval to clarify some finding observed during the development program or to produce additional safety data, or treat special populations (e.g. the elderly, patients with renal function impairment, children, etc.). In a general sense the clinical development process continues long after the drug has been approved for marketing. Collection and evaluation of adverse experiences and other information collected while the drug is in the market provides the sponsor and regulatory authorities of a continuous flow of data that allows ongoing review and reassessment of safety and efficacy of the drug. The concept of risk minimization action plans have been introduced recently. Risk minimization action plans are strategic plans to minimize a drug's known risks and for the regulatory agency to monitor the sponsor's implementation of the plan. These postmarketing commitments range from comprehensive literature reviews to large controlled trials. These post marketing

studies are usually called post approval trials or phase IV trials. Phase IV trials can be undertaken at the request of the regulatory agency as part of a postapproval commitment, as a specific regulatory agency requirement, or at a company's own decision to learn more about their product.

6. Quality systems in clinical research¹²

Many aspects of Good Manufacturing Practice (GMP) apply to the drug development process. Quality is a measure of the ability of a product, process, or service to satisfy stated or implied needs. A high quality product is one that meets these needs. For human experimentation, quality may apply to data generation and management, or, the processes involved in the implementation of the trials. Quality systems for human experimentation are the formalized practices, e.g. monitoring programs, auditing programs, complaint handling systems, etc., for periodically reviewing the adequacy of the activities and practices during human experimentation, and for revising such activities and practices so that data and process quality are maintained. For human experimentation GCPs are the basis for implementation of quality systems through quality management. This is done through the coordination of activities by the sponsors of the experiments, the clinical investigators and their staff, the institutional review boards and independent ethics committees, and by regulators to direct and control the operations with respect to quality. Quality management consists of three components: quality control, quality assurance, and quality improvement.

In the case of human experimentation, **Quality Control** is the steps taken during the implementation of the clinical trial to ensure the quality of the data generated and the processes involved. These include investigator supervision, sponsor monitoring, and any review by the regulatory authorities, to ensure that the trial meets the protocol and procedural requirements and is reproducible. **Quality Assurance** is the systematic process to determine whether the quality control system is working and effective. In clinical trials this is usually done by the sponsor through independent auditing of quality control activities, and also by the regulatory authorities through inspection of the quality systems and activities.

With the knowledge obtained from the quality assurance, audits and activities changes are made to the systems and activities with the purpose of increasing the ability to fulfill the quality requirements for the moment and in the future. This process can be called **Quality Improvement**.

Another activity central to maintaining and improving quality in clinical trial is the process of monitoring. Monitoring is a quality control activity conducted by the sponsor or a representative of the sponsor. The purpose is to ensure that the research data are accurate, complete, and verifiable from source documents. GCP guidelines (ICH E6)⁹ defines monitoring as "the 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, good clinical practices, and the applicable regulatory requirements." Monitors usually compare the data in the case report forms designed for the study and the source documents, i.e., with the medical chart of the patient, physician notes, laboratory results, etc. Monitors also make sure that the activities related to protecting the rights and welfare of the study subjects were carried out appropriately. On the other hand, auditing is an independent quality assurance activity used by the sponsor to evaluate the effectiveness of the monitoring program. Auditing procedures are similar to the monitoring activities. The

difference is that monitoring occurs only during the execution of the clinical study, auditing occurs at any time during or after the clinical study is completed. In addition to quality audits there are inspections conducted by the regulatory authority(ies). An inspection is the act of conducting an official review of documents, facilities, records, and any other resources the authorities deem related to the clinical study. The inspection may be at the clinical trial site, at the sponsor’s facilities, and/or at the Contract Research Organization (CRO) facilities, or at any other establishment the authorities deem appropriate. CROs are organizations which are normally contracted by sponsors to monitor their clinical studies. CROs may also conduct a complete development program for a sponsor on occasions, or deliver part of the activities related to the development of the investigational product. The purpose of monitoring is to determine if the research was conducted in compliance with national and local laws and regulations for the conduct of research and the protection of human subjects.

All parties involved in human experimentation (sponsors, clinical investigators, Institutional Review Boards/Independent Ethics Committees, and regulatory authorities) need to adopt and implement quality systems for the processes and activities they are responsible for. This includes clinical research facilities. Clinical research should include **Quality Systems** to measure the quality of clinical research through the use of standard operating procedures (SOPs), study protocol compliance, internal monitoring and the sponsor’s monitoring activities. This is accomplished through training of the personnel involved in clinical trial activities, internal and external audits, and accountability of the personnel.

A Typical quality system would include production and process control, equipment and facilities control; records, documents and change controls; material controls, design controls and corrective and preventive action. (Figure 1). This system can easily be adapted for the development of medical devices.

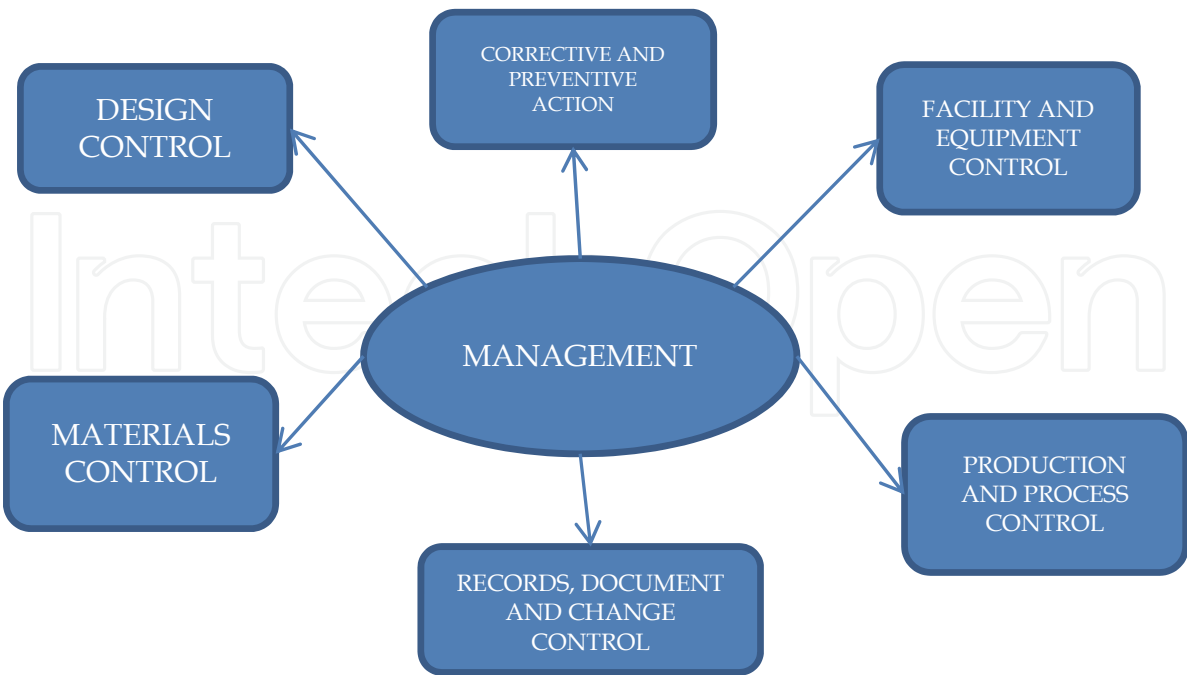


Fig. 1. Typical quality system. This system can easily be adapted to a medical device development facility.

A **Quality System** for an investigational clinical center may be also adapted from this diagram to include the following areas under the control of the clinical investigator (Figure 2):

- Facility and Equipment Evaluation and Documentation
- Source Documentation Generation, Integrity and Retention
- Consent Process and Documentation
- Safety Management and Reporting Processes and Documentation
- Investigational Product Accountability and Integrity and Documentation
- Site Staff Qualifications, Training, and Documentation
- Corrective and Preventive Action Development and Implementation Facility

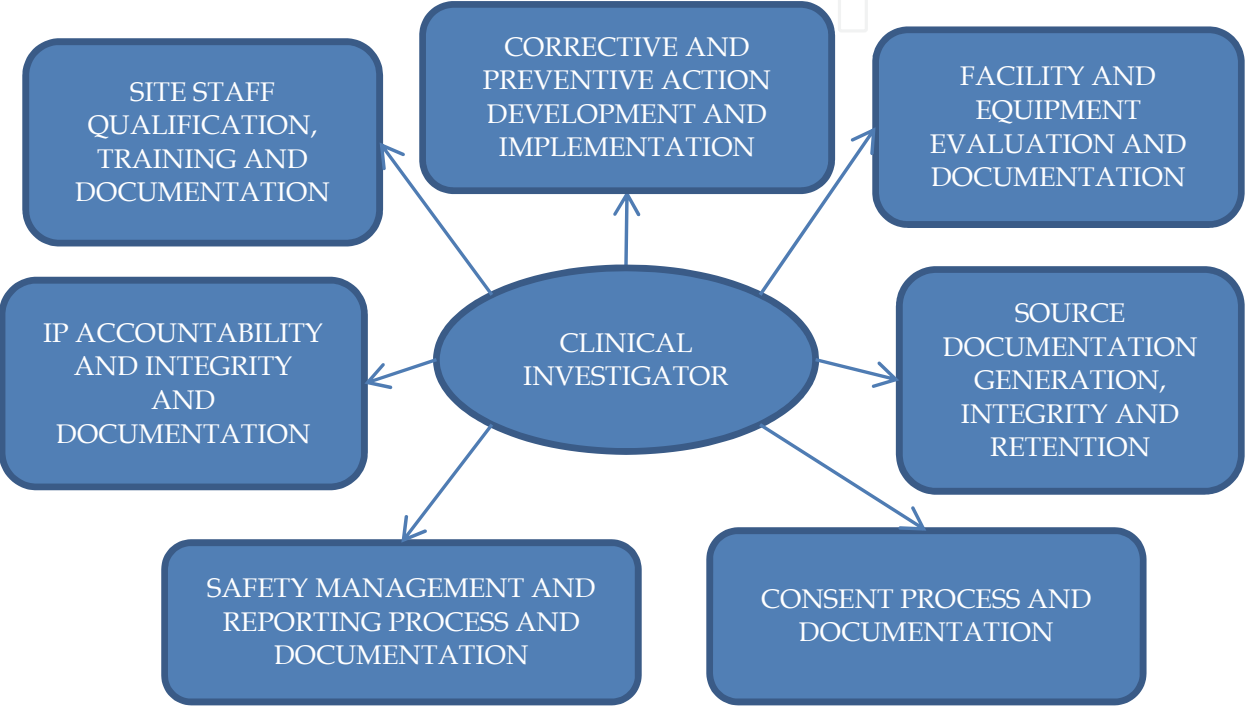


Fig. 2. The organization of a clinical investigational site.

These represent the activities required in a well run clinical investigational site. The investigator is responsible for all activities. The site should have guidelines and/or standard operating procedures for each these areas and activities. In addition, the investigator should have sufficient personnel who are properly trained and qualified to conduct these activities. It is also important that the facility are appropriate in size and configuration to accommodate all these areas.

7. FDA Bioresearch monitoring ¹²

The Food and Drug Administration's (FDA) bioresearch monitoring program (BIMO) was established in 1977 with input from the drug, biologics, medical device, veterinary medicine, and food areas. Chapter 48 of the FDA’s Compliance Program Guidance Manual is dedicated to Bioresearch Monitoring and delineates the inspection and reporting procedures for studies under FDA jurisdiction. The stated objectives of the bioresearch monitoring program are: to protect the rights, safety, and welfare of subjects involved in FDA-regulated

clinical trials; verify the accuracy and reliability of clinical trial data submitted to FDA in support of research or marketing applications; and assess compliance with FDA's regulations governing the conduct of clinical trials. The purpose of the program is to provide instructions for FDA's field personnel for conducting such inspections.

BIMO developed compliance programs to provide uniform guidance and specific instructions for inspections of clinical investigators, sponsors and monitors, in-vivo bioequivalence facilities, Institutional Review Boards, and nonclinical laboratories involved in the testing of investigational products. The purpose of these programs is to adapt a Quality System framework for the oversight and management of clinical studies.

The most useful elements of a quality system that applies to clinical studies are: corrective and preventive action (CAPA) and management controls. CAPA procedures can be adapted to ensure effective and efficient clinical study management.

The application of CAPA to clinical research activities involve:

- Identification of non-conformances, e.g. protocol deviations, errors of omission or transcription.
- Investigation of the cause of the problem identified
- Identification of the actions needed to correct and prevent recurrence of the problem
- Verification that the corrective action is effective
- Making sure that the information is appropriately disseminated
- Submission of the information for management review on problems identified and actions taken
- Documentation of the process

Management controls involve the appointment of a management representative responsible for the research, in this case the investigator or sub Investigator, and to conduct management reviews.

Figure 3 shows the relationship between CAPA, management reviews and audits, external (sponsor monitoring, third party or FDA) and internal through monitoring internal activities.

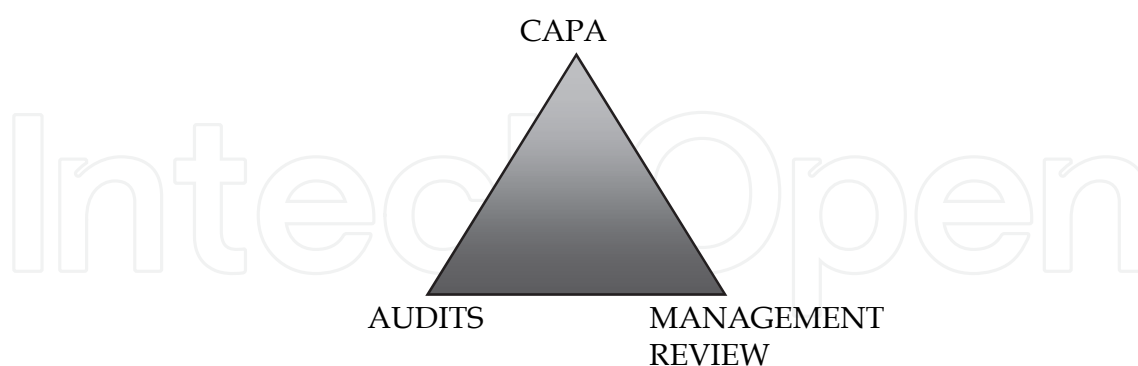


Fig. 3 Relationship between CAPA, Management Reviews and Audits.

Although FDA inspections are focused on clinical investigators, they are of great importance to sponsors. The inspections are designed to determine how well sponsors performed their responsibilities for the conduct of the study; should the inspections uncover serious problems it may result in rejection of the data essential for drug approval. As a result the sponsor may face inspections and compliance actions if it is found to have worked with noncompliant investigators and did not take corrective action.

8. Good clinical practice (E6)⁹

Good Clinical Practices (GCP) is not a set of instructions on how to develop a product or how to design human experiments. GCP is a series of general principles that must be observed during the conduct of human experimentation. This GCP guideline provides a unified standard for designing, conducting, recording, and reporting clinical trials that involve human subjects. Compliance with this guideline provides public assurance that the rights, well-being, and confidentiality of the trial subjects are protected and that the results of the study are credible. GCP are part of the quality systems to cover testing of medicinal products and devices, and conducting clinical studies in human beings. Their objective is to provide a unified standard for the European Union, Japan, and the United States, with consideration to existing GCPs of Australia, Canada, the Nordic countries as well as the World Health Organization, and to facilitate the mutual acceptance of clinical data by the regulatory authorities. It includes also the minimum information that should be included in the information to the investigator, which are the documents considered essential, their purpose, and how to file them. Many countries around the world have adopted these guidelines as their own. The ICH guideline on GCP (E6) outlines the 13 principles of good clinical practices. These principles are in line with the Nuremberg Code, the Declaration of Helsinki and the Belmont Report. These guidelines should be adopted by IRBs/IECs, sponsors, and clinical investigators as well as regulatory authorities who oversee or conduct clinical trials.

8.1 Principles of GCP

1. Clinical studies should be conducted according to ethical principles
2. Foreseeable risks and inconveniences should be weighed against anticipated benefit to the subjects
3. The rights, safety and well-being of the trial subjects should be the most important consideration and prevail over scientific or societal interests.
4. Available preclinical and clinical information on a product should be adequate to support the proposed trial
5. A clinical trial should be scientifically sound and described in a clear detailed protocol.
6. A clinical trial should be conducted in compliance with a protocol previously approved by an IRB/IEC.
7. Medical care given to, and decisions made on behalf of, trial subjects should be always the responsibility of a qualified physician or qualified dentist.
8. Each individual involved in conducting the trial should be qualified by education, training, and experience to perform his/her respective tasks.
9. Freely given informed consent should be obtained from every study subject prior to clinical trial participation.
10. All clinical trial information should be recorded, handled, and stored in a way that allows accurate reporting, interpretation, and verification.
11. The confidentiality of the records should be protected
12. The investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practices (GMP), and used in accordance with the approved protocol.
13. Systems with procedures that assure the quality of every aspect of the trial should be implemented.

The GCP outline the duties of the IRBs/IECs, sponsors, and the clinical investigators.

8.2 Independent Ethics Committees (IECs) and Institutional Review Boards (IRBs)

Their main responsibility is to safeguard the rights, safety, and wellbeing of all trial subjects, with special attention to the inclusion of vulnerable subjects to the trial. The IRB/IEC is required to have standard operating procedures and maintain written records of their meeting and decisions. The composition and authority under which the IRB was established should be documented in writing. All meetings, notification to members, and schedules should be disseminated in writing. In summary all information and documentation of activities should be documented and transparent.

The IRB/IEC should consider the qualifications of the investigator, ensure that all subjects have freely provided their informed consent to be included in the study, ensure that payments to the subject for participation in the trial are not coercive or exercise undue influence, and continuously review the progress of the experimentation at intervals appropriate to the degree of risk to human subjects, but at least once per year. The IRB can request additional information if in the judgment of the IRB members the additional information would add meaningfully to the protection of rights, safety and/or well-being of the trial subjects. The IRB should always determine that a protocol or the information provided adequately addresses relevant ethical concerns and meets applicable regulatory requirements.

The IRB is usually composed of at least 5 members, at least one member whose primary area of interest is nonscientific, and at least one member who is independent of the trial site. The investigator may provide information on any aspect of the trial but should not participate in deliberations or in the vote, or opinion of the IRB.

8.3 The informed consent process

For the implementation of the informed consent the investigator should comply with all regulatory requirements and adhere to GCP and the ethical principles originating in the Declaration of Helsinki. The subject should be thoroughly informed of the experiment to be conducted, the risks and the potential benefits. Ample time should be given to the subject to make his/her decision to participate in the study. It should be very clear what the experimentation is all about. No coercion should be applied on the potential study subject.

The informed consent document should include explanations of the following:

- The trial involves research, and some parts of it are experimental.
- The purpose of the trial and the voluntary nature of the subject's participation.
- The treatment and probability for random assignment to treatment. That is in a double blinded study neither the patient nor the investigator may know which treatment is being administered.
- The trial procedures. Including potential for risky procedures and their potential consequences.
- The subject's responsibility to follow the indications from the investigator.
- Reasonable foreseeable risks or inconveniences to the subject, and embryo, fetus or nursing infant, if applicable.
- Reasonable expected benefits.
- Alternative forms of treatment for the condition under investigation and their potential risks and benefits.
- Compensation for trial related injury.
- Payment to the subject, if any.

- Expenses for the subject, if any.
- That the subject's original medical records may be accessed by regulatory authorities, IRB/IEC, the monitor and auditors for verification of the information.
- That confidentiality will be maintained and not be made public.
- All new information related to the trial that becomes available that may be relevant to the subject's willingness to continue to participate in the trial will be forwarded to the subject.
- Who to contact with questions or in the event of a trial related injury
- Foreseeable circumstances or reasons under which the subject's participation in the trial may be terminated.
- The duration of the trial and approximate number of subjects involved.

8.4 The investigator

The investigators supervise the study staff to ensure they follow established procedures for the conduct of the study. They should be qualified by training, education and experience to conduct clinical trials. The investigators should be thoroughly familiar with GCP, the product under investigation and the study protocol. Investigators are responsible for all medical decisions. In their role they obtain approval to conduct the study from the IRB/IEC; ensure that informed consent is obtained freely and without coercion before the study starts; establish and maintain the subjects' case histories; transcribe the subjects' medical data from the medical files to a case report form for the sponsor; ensure the accuracy, completeness, legibility, and timeliness of the data reported; promptly report all adverse events and other problems; document and explain any deviations from the study protocol; be responsible for the accountability and proper storage as well as the use according to the protocol of the investigational product; and provide all required reports at the end of the study to the sponsor.

Investigators should be in contact with the IRB/IEC and the sponsor frequently. Communications involve,

- Before initiating the trial, obtain a written and dated approval/favorable opinion from the IRB/IEC to start the study
- Provide the IRB/IEC with a copy of the information on the product under investigation (the Investigator's Brochure, IB) and any amendments to the IB during the study.
- Report promptly any serious adverse event or laboratory abnormality immediately to the sponsor, the regulatory authorities and the IRB/IEC, and follow up with a detailed written report with any additional information requested.
- For patients who die during the study the investigator should supply the sponsors, regulatory authorities and the IRB/IEC with all pertinent information on the event.

Upon completion of the trial the investigator should inform the sponsor, the IRB/IEC and the regulatory authorities with a summary of the trial outcome, and any other report required by applicable regulation.

8.5 The sponsor

Sponsors are responsible implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that the trials are conducted, and data are generated, documented and reported in compliance with the protocol, GCP, and applicable regulatory requirements. Sponsors are also responsible for securing agreement from all

involved parties to ensure direct access to clinical trial related sites, source documents, and reports for the purpose of monitoring and auditing by the sponsor, CRO and regulatory authorities. Agreement with the investigators or any other party involved in the study should be in writing.

Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been properly processed, for securing the services of monitors to ensure compliance of clinical investigators and verify that the study is carried out according to the approved study protocol. Sponsors also audit the monitor's performance, other quality control activities and systems to ensure performance. The monitors hired by the sponsor to review the records at the clinical centers, and report their finding to the sponsor in written reports of all visits and trial related communications.

Sponsors may transfer in writing any or all their obligations to a contract research organization (CRO), but the ultimate responsibility for the quality and integrity of the data always resides with the sponsor. CROs have the same obligations as the sponsor.

The sponsor is responsible for the medical expertise. Qualified medical personnel should be readily available to advise on trial related matters. An external consultant may be appointed for this function.

Sponsors are responsible for the trial design, trial management, trial data handling, and retention of documents for the specified period required by law and regulations. They are also responsible for the selection of qualified investigators and to apply with the regulatory authorities to conduct the trial.

Finally, the sponsor is responsible to provide insurance or indemnification to the investigator against claims arising from the trials, except for claims arising from malpractice and/or negligence.

8.6 Regulators

The regulators may inspect all parties who conduct or oversee clinical research and verify the information submitted to the regulatory authorities. Regulatory agencies inspect specifically clinical investigators, pharmaceutical companies, device companies, CROs, IRBs/IECs, as well as nonclinical laboratories, to ensure the accuracy and validity of the data generated, and to ensure that the rights and welfare of the research subjects are protected. The regulatory inspectors evaluate how well sponsors, monitors, clinical and non clinical investigators, CROs, and IRBs/IECs comply with the regulations. They may require certain conditions for a study to proceed. They develop policies and procedures for reviewing product applications and for the conduct of GCP inspections as exemplified by the FDA's BIMO compliance programs.

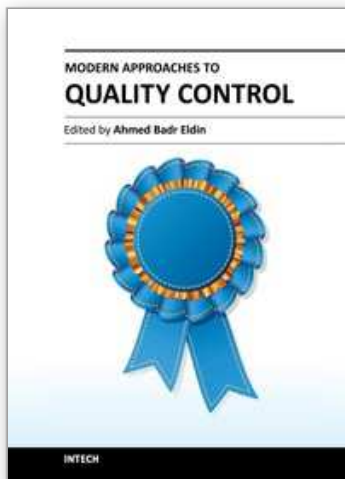
9. Conclusion

Over the last century the scientific community has developed a better understanding of how to protect and respect the rights, safety and wellbeing of research subjects. For centuries the Hippocratic Oath was the only ethical guidance for physicians and scientists on how to treat subjects, and specifically research subjects. The development of Good Clinical Practice was the result of various incidents that resulted in the Nuremberg Code, the Declaration of Geneva, the Declaration of Helsinki and the Belmont Report. ICH is an attempt to harmonize GCP in the most advanced democracies. Today, many regulatory agencies around the globe use these principles to regulate human experimentation in their countries.

The responsibility of GCP is shared by all parties involved in human experimentation, investigators, sponsors, ethics committees, regulatory authorities, and research subjects. To guarantee the quality and accuracy of the data generated during human experimentation Quality Systems have been developed and are applied around the world.

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