Symposium on good clinical practice

Nuclear Medicine Communications

Good clinical practice: Historical background and key aspects

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Clinical research trials (both academic and industry sponsored) are increasingly playing a role in various medical disciplines, including younger fields of clinical trial interest, such as nuclear medicine research. Knowledge for and compliance with good clinical practice (GCP) is essential for anyone involved. In this review article, key aspects of GCP and the responsibilities of investigators, monitors and sponsors are described. In addition, a comprehensive overview of the historical background on the development of GCP from the US Pure Food and Drugs Act of 1906 over the Nuremberg Code, the Kefauver–Harris Amendments and the Declaration of Helsinki until now is given. Knowledge of the historical background may help understand the developments in GCP. ***Nucl Med Commun*** **26:563–574 © 2005 Lippincott Williams & Wilkins.**

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Introduction

The rapid development of instruments and techniques is propelling the relatively young discipline of nuclear medicine into a field of increasing interest for clinical trials not only at academia but also in the pharmaceutical industry [1]. Opportunities that nuclear medicine offers do not stop at the study drug efficacy and safety studies but make use of the benefits of new functional imaging techniques in the early study phases of drug development, especially for dose finding and dose regimen studies, as described, for example, by Catafau *et al.* [2]. Direct radiolabelling of new pharmaceutically active substances, allow us to show and understand how the drug works inside the body, as described by Taylor *et al.* [3]. Within the new role nuclear medicine may play in the field of clinical trials, and essentially in the context of trials sponsored by the pharmaceutical industry, compliance with good clinical practice (GCP) is essential for all investigators involved.

Rules for physicians, indeed, have a long tradition. The concept of 'good physician practice' goes back to the ancient world. Already in Hammurabi's Law (1710 BC), for example, physicians were threatened with execution upon maltreatment of patients. In Hippocrates' Oath (460 BC), good and bad practices of physicians are mentioned:

> I swear by Apollo Physician, by Aesculapius, by Health, by Panacea and by all the gods and goddesses, making them witnesses, that I will carry out, according to my ability and judgment, this oath and this indenture: To hold my teacher in this art equal to my own parents; to make him partner in my livelihood; when he is in need of money, to share mine with him; to consider his children as my own brothers, and to teach them my art, if they want to learn it, without fee or indenture; to impart precept, oral instruction, and all other instruction to my own sons, the sons of my teacher, and to indentured pupils who have taken the physician's oath, but to nobody else. I will use treatment to help the sick according to my ability and judgment, but never with a view to injury and wrong-doing. Neither will I administer a poison to anybody when asked to do so, nor will I suggest such a course. Similarly I will not give to a woman a pessary to cause abortion. But I will keep pure and holy both my life and my art. I will not use the knife, not even, verily, on sufferers from stone, but I will give place to such as are craftsmen therein. Into whatsoever houses I enter, I will enter to help the sick, and I will abstain from all intentional wrong-doing and harm, especially from abusing the bodies of man or woman, bond or free. And whatsoever I shall see or hear in the course of my profession, as well as outside my profession in my intercourse with men, if it be what should not be published abroad. I will never divulge, holding such things to be holy secrets. Now I carry out this oath, and break it not, may I gain for ever reputation among all men for my life and for my art; but if I transgress it and forswear myself, may the opposite befall me. [4,5]

Today's international standardization in clinical research resulting in the International Conference of Harmonisation (ICH) GCP Guidelines is also the effort of a long historical development. In the following, this historical

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background is given and key aspects of GCP and responsibilities of the various parties involved in the conduct of clinical trials are described.

Historical background on the development of good clinical practice

GCP developments in the United States

By the early 1900s, concern about the involvement of human subjects in medical research was part of the American political agenda. Prior to the Pure Food and Drugs Act in 1906, all drugs could be sold and bought like any other consumer good. By this, many unsafe drugs were brought to market, which often led to serious drug-related events or even deaths.

Pure Food and Drugs Act

The first landmark event in the regulation of drugs (and foods) was the Food and Drugs Act of 1906. The purpose of the Food and Drugs Act was

1. prevention of the manufacturing, sale, and transportation of adulterated, misbranded, poisonous, or spoiled drugs, foods, and liquors;
2. prevention of the shipping of aforementioned goods to or from foreign countries;
3. creation of uniform regulations and standards of purity (guidelines established by the Bureau of Chemistry);
4. ensure that companies cannot make false claims about their products and their effects;
5. provide consumers with a table of ingredients as well as the quantity of each;
6. alert consumers to potentially lethal drugs in their medicines;
7. allow purity tests on random samples of food from various parts of the nation.

Examples of lethal and habit-forming medicines available to the public at that time are given in the 1906 Congressional Record.

Lethal medicines "Grandma's Secret", "Kopp's Baby's Friend", and "Nurses' and Mothers' Treasure" contained high amounts of morphine which even in small doses were lethal to children. These medicines were sold to families by physicians and pharmacies. The ingredients and quantities were not labelled on the bottle. Parents and treating physicians were led to believe such medicines would cure their children; instead, the medicines were poisonous.

Habit-forming medicines Some medicines contained morphine and chloroform (e.g., "Dr. King's Consumption Cure", "Dr. Bull's Cough Syrup"). While some children recovered from their addictions, many suffered through life with addiction. Many adults as well became addicted to medicines, often dying because of their addiction.

Other medicines One widely used medicine at that time claimed to cure inflammation of the liver, intestine, rectum, and bladder. However, the medicine contained 75% water and 25% alcohol, and was worthless. Other popular medicines claimed to cure consumption in tuberculosis (e.g., "Dr. King's Consumption Cure"). However, these drugs actually hastened the process of the disease, as stated in *Collier's Weekly* [6]:

> The chloroform temporarily allays the cough, thereby checking nature's method of throwing off dead matter from the lungs; the opium drugs the patient into a deceived cheerfulness. The combination is admirably designed to shorten the life of any consumptive who takes it steadily. Of course, there is nothing on the label of the bottle to warn the purchaser.

In 1914, another landmark piece of anti-drug legislation was enacted: the Harrison Narcotic Act, which – originally passed as a record-keeping law – became a prohibition statute. In the course of the next 7 years, the free US market in drugs was replaced by federal drug prohibition, possessing unchallengeable authority. In 1927, an enforcement agency, first known as the Food, Drug and Insecticide Administration and then in 1930, as the Food and Drug Administration (FDA), was created. Its primary goal was to oversee compliance with the Pure Food and Drugs Act. However, neither the Pure Food and Drugs Act nor the FDA was able to prevent all unsafe drugs from appearing on the market, and many did over the course of the next 30 years.

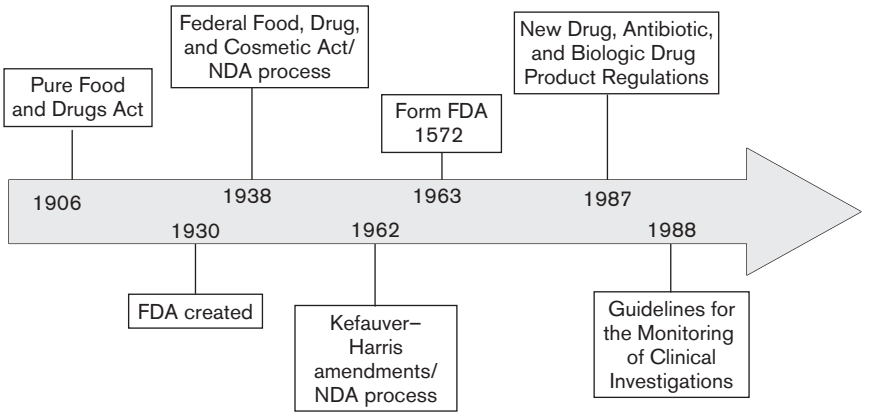
Federal Food, Drug, and Cosmetic Act

In 1938, the Federal Food, Drug, and Cosmetic Act was enacted. This specifically addressed the issue of drug safety and, for the first time, manufacturers were required to (1) test drugs for safety, and (2) present the evidence of safety testing to the FDA *prior* to marketing. This act provided the basis for a regulatory role of the United States government and marked the beginning of United States regulations such as the New Drug Application (NDA) process.

Kefauver–Harris Amendments

Although the Federal Food, Drug, and Cosmetic Act was a significant improvement over previous regulations, a need for even closer controls on marketed drugs in the United States was identified. In 1962, foetal abnormalities (severe limb deformities) linked to maternal use of thalidomide (Contergan) shook public confidence in the regulation of drug-related research. In fact, the aforementioned adverse effect of severe limb deformities was not discovered until 10,000 such infants were born in 20 countries. In response to this tragedy, the Kefauver–Harris Amendments to the Federal Food, Drug, and Cosmetic Act of 1938 were passed, requiring the FDA to

Fig. 1



Milestones in the development of good clinical practice in the United States.

evaluate new drugs for efficacy and safety [7]. In addition to protocols for all proposed clinical trials, identification and qualifications of proposed clinical investigators, preclinical (animal) data, existing human clinical data and reports by the sponsor of findings associated with the test drug, and monitoring of the progress of studies by the sponsor, the amendments also specifically required the informed consent of participants in the testing of investigational drugs.

Since 1962, these Kefauver–Harris requirements, along with a further series of regulations and acts, have come to be widely recognized as GCP guidelines within the US. These regulations and acts are as follows.

- The 1963 Regulations on the requirements of investigators to sign Form FDA 1572 for all IND studies (signatures indicate that investigators accept legal responsibility for the health and human rights of subjects).
- The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research was established through the 1974 National Research Act on the requirement of the establishment of Institutional Review Boards (IRBs) for all research funded entirely or in part by the federal government. The main reason for introducing this regulation was due to the following discovery. In the summer of 1972, the *New York Times* reported details of the so-called Tuskegee Syphilis study, sponsored by the Public Health Service. In this study, a formal study protocol did not exist. It intended to trace the natural history of syphilis in poor African-American males living in Macon County, Alabama. Study participants ($n = 399$) were not informed about the study purpose; in fact, they were misled into believing that they were being treated for syphilis. Investigators continued the study even after penicillin became widely available and prescribed for the treatment of syphilis.
- The Belmont Report was issued in April 1979 by the National Commission for Protection of Human Subjects of Biomedical and Behavioral Research. This report established boundaries between practice and research and identified three fundamental ethical principles with human participants: (1) respect for persons, (2) beneficence and (3) justice, which translated, respectively, into provisions for (1) informed consent, (2) assessment of risk and potential benefits and (3) selection of participants.
- In response to the Belmont Report, the federal regulations were modified in 1981 to require IRB approval for all drugs or products regulated by the FDA, independent of the funding source. These regulations were revised in 1991, known as the Common Rule, which expanded the scope of regulated research and provided some standardization of regulations across agencies and departments.
- New Drug Antibiotic and Biologic Drug Product Regulations, 1987.
- Guidelines for the Monitoring of Clinical Investigations, 1988.

Figure 1 summarizes GCP development milestones in the United States.

International guidelines

Early German guidelines

Guidelines for New Treatments and Scientific Studies in Man Richtlinien für neuartige Heilbehandlungen und für die Vornahme wissenschaftlicher Untersuchungen am Menschen – Reichsministerium des Inneren, from 1931, are one of the earliest international standards.

The Nuremberg Code The guidelines of the Nuremberg Code are more well-known and were created in 1947 in response to the unethical experiments and atrocities during World War II committed by Nazi investigators,

mostly physicians, who were tried before the Nuremberg Military Tribunal [8]. The amendments also specifically required the informed consent of participants in the testing of investigational drugs. The Nuremberg Code postulates the need for a scientific basis in research of human subjects, and the safety and voluntary consent of participants. Although the Nuremberg Code received little attention in the immediate aftermath of the trial, it has been internationally more and more influential in providing groundwork for standards of ethical conduct.

The Declaration of Helsinki

The Declaration of Helsinki, which is considered a key document on the ethical principles that underlie GCP, was first developed by the World Medical Association (WMA) and adopted in June 1964, at the 18th World Medical Assembly in Helsinki, Finland. The Declaration of Helsinki has been revised and updated several times since then, most recently in October 2000, at the 52nd WMA General Assembly in Edinburgh, UK. It is supported by 190 nations around the world.

The focus of the Declaration of Helsinki is on the protection of subject rights, as suggested by its introduction.

> 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.

A current copy of the Declaration of Helsinki is given in Appendix 1.

The World Health Organization and the Council for International Organizations of Medical Sciences guidelines

The World Health Organization (WHO), the United Nations specialized agency for health, was established on 7th April 1948. WHO's objective, as set out in its constitution, is the attainment by all peoples of the highest possible level of health. Health is defined in WHO's constitution as a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity.

The Council for International Organizations of Medical Sciences (CIOMS) is an international, non-governmental, non-profit organization established jointly by WHO and UNESCO in 1949. The main objectives of CIOMS are to

- facilitate and promote international activities in the field of biomedical sciences, especially when the participation of several international associations and national institutions is deemed necessary;
- maintain collaborative relations with the United Nations and its specialized agencies, in particular with WHO and UNESCO;
- serve the scientific interests of the international biomedical community in general.

In 1982 the WHO and the CIOMS issued a document entitled *Proposed International Guidelines for Biomedical Research Involving Human Subjects* to help developing countries apply the principles of the Declaration of Helsinki and the Nuremberg Code. These guidelines were amended in 1991 adding epidemiological studies. In 1992, the guidelines were again revised, resulting in the *International Guidelines for Biomedical Research Involving Human Subjects*.

As a response to the movement toward globally applicable standards for the conduct of research on human subjects, the WHO GCP guidelines were developed in 1993 and published in 1995; they apply to all research involving human subjects which is conducted in any of the WHO member states. The ethical principles included in these WHO GCP guidelines are based on the Declaration of Helsinki and the CIOMS guidelines.

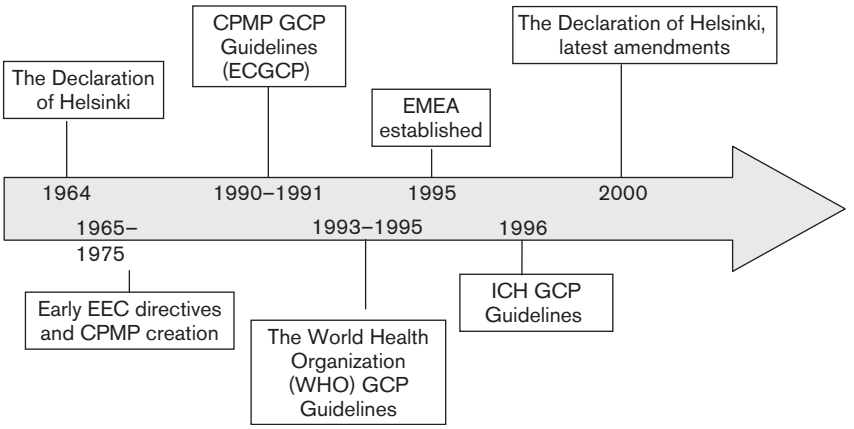
European Union directives

Over the past 50 or so years, Europe has exhibited an excellent GCP development (Fig. 2). Beginning in 1957, with the Treaty of Rome, many European countries came together to form a common market for the purpose of enhancing industrial economic development and cooperation, called the European Economic Community (EEC). In 1993, as part of this market, a single institution called the European Union (EU) was empowered by the member countries to make major policy decisions and to enhance uniformity and cooperation among member states in terms of products and services to smoothly flow across all markets within the EU.

With regard to drug development, the EU promoted the distribution of quality drugs across all EU markets, while enforcing high standards for drug quality. These standards were implemented according to the universal principles of the Declaration of Helsinki, and were further defined for the EU member states through a series of directives. Major directives to mention are

- Directive 65/65/EEC from 1965 on the harmonization of proprietary pharmaceutical medicines in Europe and the definition of medicinal products requiring product authorization;
- Directive 75/318/EEC from 1975 on protocols and analytical, pharmacological, toxicological, and clinical standards for preclinical and clinical trials;

Fig. 2



Milestones in the development of good clinical practice (GCP) internationally. CPMP, Committee for Proprietary Medicinal Products; ECGCP, a commonly used abbreviation for a document, published by the CPMP, titled *Good Clinical Practices for Trials on Medicinal Products in the European Community*; EMEA, European Medicines Evaluation Agency; EEC, European Economic Community; ICH, International Conference on Harmonisation.

- Directive 75/319/EEC from 1975 on the need for a body to regulate drug development in the EU.

In 1975, the Committee for Proprietary Medicinal Products (CPMP) was founded. Its basic goals, which are in accordance with the Declaration of Helsinki and the various directives issued by the EU were to

- coordinate and oversee the approval for the marketing of pharmaceutical products that will be marketed in more than one European country;
- oversee the monitoring of adverse effects.

In May 1990, the CPMP published a document entitled *Good Clinical Practices for Trials on Medicinal Products in the European Community* (also known as EC GCP), which became effective in July 1991.

The European Medicines Evaluation Agency

In addition to guidelines and Directive 91/507/EEC (effective date January 1992) related to GCP, the EU also published Council Regulation No. 2309/93 in July 1993, which postulated a scientific council to advise the CPMP on 'scientific and ethical issues relating to medicinal products for human and veterinary use.' This UK-based council was the European Medicines Evaluation Agency (EMEA) [9] and started its work in January 1995. Its primary goals are to coordinate, evaluate and supervise medicinal products for human and veterinary use, and to monitor member states' compliance with GCP guidelines. Since 1995, the EMEA has offered two routes for authorization of medicinal products:

- *centralized*, where applications (for products derived from biotechnology and optional for other innovative medicinal products) are made directly to the EMEA;
- *decentralized* (used by the majority of conventional medicinal products), where applications are made to the member states selected by the applicant and the procedure operates by mutual recognition of national marketing authorizations.

Development of the International Conference on Harmonisation Guidelines

In an effort to overcome international GCP inconsistencies throughout countries, the International Conference on Harmonisation (ICH) issued the *ICH Guidelines: Topic E6 Guideline for GCP* in May 1996, presenting a comprehensive, unified and global guidance to the appropriate conduct of clinical trials througout the EU, Japan and the United States. Figure 3 briefly illustrates the evolution of GCP leading to the ICH.

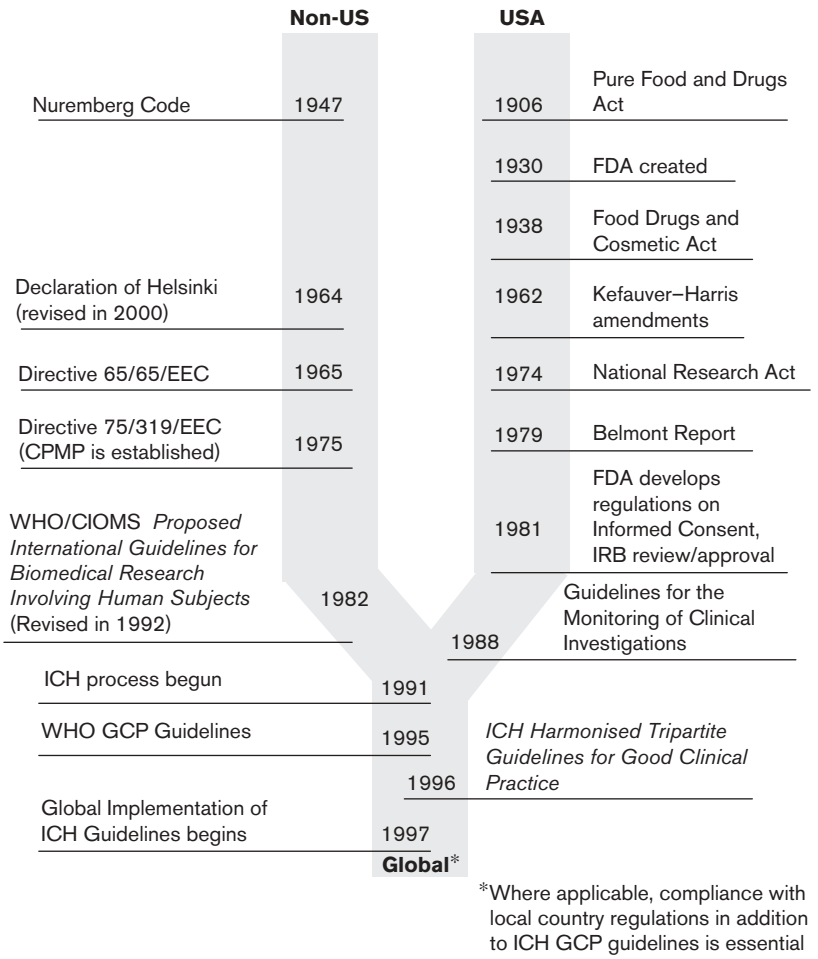
Key aspects of ICH GCP guidelines

The ICH GCP guidelines define a variety of aspects of clinical research. They are an international, ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. GCP standards in clinical research are defined to

- protect the rights, safety, and well-being of trial subjects;
- ensure the quality and integrity of data obtained from clinical testing.

Apart from GCP, the ICH also covers many other topics. For the interested reader, a listing of these can be found in Appendix 2.

Fig. 3



Evolution of good clinical practice leading to the International Conference on Harmonisation. CIOMS, Council for International Organizations of Medical Sciences. Other abbreviations as in the legend to Fig. 2.

A number of components have been incorporated into the ICH GCP guidelines to ensure the protection of trial subjects and the quality/integrity of data obtained from clinical testing. These are:

- institution review board (IRB)/independent ethics committee (IEC) review and approval of the trial protocol and other materials;
- freely obtained informed consent from each subject;
- safety monitoring requirements;
- data handling and archiving requirements;
- clinical trial responsibilities of the IRB/IEC, investigator and sponsor.

Institution review board/independent ethics committee

The IRB/IEC is an independent body, consisting of at least five members, among whom (1) at least one member's primary area of interest is in a non-scientific area; and (2) at least one member who is independent of the institution/trial site.

The IRB/IEC safeguards the rights, safety and well-being of all trial subjects. According to ICH E6 it should receive the following documents:

- trial protocol(s)/amendment(s);
- written informed consent form(s) for use in the trial;
- subject recruitment procedures (e.g., advertisements);
- written information to be provided to subjects;
- investigator brochure;
- available safety information;
- information about payments and compensation available to subjects;
- the investigator's current curriculum vitae and/or other documentation providing evidence of qualifications;
- any other documents that the IRB/IEC may need to fulfill its responsibilities.

The IRB/IEC should consider the qualifications of the investigator for the proposed trial. It should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year. The IRB/IEC may also request that more information be given to subjects when, in the judgment of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety, and/or well-being of the subjects.

The IRB/IEC should determine that the proposed protocol and/or other document(s) adequately address relevant ethical concerns and meet applicable regulatory requirements for such trials, when a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative. The IRB/IEC should determine that the proposed protocol and/or other document(s) adequately address relevant ethical concerns and meet applicable regulatory requirements for trials (i.e., in emergency situations), where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible.

Furthermore, the IRB/IEC should review both the amount and method of payment to subjects to ensure that neither presents problems of coercion or undue influence on the trial subjects. It should also ensure that information regarding payment to subjects – including the methods, amounts, and schedule of payment to trial subjects – is described in the written informed consent form and any other written information to be provided to subjects.

Informed consent

The informed consent process as defined by ICH GCP should ensure the protection of trial subjects according to the ethical principles outlined in the Declaration of Helsinki. Essentials of the informed consent process can be stratified under the following key study phases.

Pre-trial

- IRB/IEC approval of consent form;
- Consent procedures for the emergency case.

At recruitment

- No influence to enrol;
- attention to language of oral and written information:
  - language must be understandable to subject or subject's legally acceptable representative;
  - no waiver of subject's rights or sponsor's responsibility;
- full information on all aspects of trial;
- subject or subject's legally acceptable representative must agree to authorized review of confidential information;
- subject or subject's legally acceptable representative must understand they can withdraw at any time.

Prior to trial

- Consent must be documented by dated signature of
  - subject or subject's legally acceptable representative;
  - person conducting informed consent discussion;
- subject or subject's legally acceptable representative must receive copy of signed and dated consent form.

During trial in case of important new information

- Consent form must be revised and approved by IRB/IEC;
- relevant information must be provided on ongoing trial participants.

Safety monitoring

Safety monitoring comprising

- monitoring, recording, and managing of all adverse events during the course of the study;
- compliance with regulatory reporting requirements for specific types of adverse events, for example, serious adverse events and previously unknown events

is a key component of the ICH GCP guidelines.

Adverse events must be monitored carefully and recorded in detail during the course of the trial. ICH E6 Section 6 (E6 6.8.1–6.8.4) specifically recommends that, in terms of safety, the protocol should provide

- specification of safety parameters;
- procedures for eliciting reports of, and for recording and reporting, adverse events and intercurrent illnesses;
- the methods and timing for assessing, recording and analysing safety parameters;
- the type and duration of the follow-up of subjects after adverse events.

All appropriate measures should be taken to report serious adverse events to the regulatory authorities according to their requirements.

Responsibilities of the investigator

Mackintosh and Zepp, 1996, describe the life of an investigator under GCP '…demanding…, where exhaustive

regulations and the needs of sponsors bedevil you every step of the way' [10] (Fig. 4). In fact, the key responsibilities of investigators are various:

- to comply with GCP and applicable regulatory requirements;
- to ensure that he/she understands and can fulfill protocol requirements;
- to submit appropriate documentation to the IRB/IEC, sponsor and relevant authorities;
- to ensure adequate qualified staff and facilities;
- to obtain informed consent from subjects or their legally acceptable representatives;
- to provide all relevant information to study site staff and subjects;
- to receive and properly manage drug supplies;
- to oversee the rights and well-being of study subjects;
- to collect, record and report data properly and accurately;
- to ensure the confidentiality of all information as appropriate;
- to notify immediately the sponsor, IRB/IEC and regulatory authorities (as appropriate) in the case of serious adverse events;
- to make all trial-related documents available during the study;
- to confirm the integrity of the data;
- to arrange for archiving of appropriate study-related materials.

Responsibilities of the monitor

Key responsibilities of monitors as representatives of the sponsor are

- to ensure all study site staff have adequate information and facilities to conduct the trial;
- to oversee the protocol, GCP guidelines, and standard operating procedures;
- to coordinate communication between the sponsor and the investigator;
- to verify data and check that informed consent was obtained appropriately;
- to oversee proper handling of clinical supplies;
- to assist the investigator with submission of data to authorities and sponsor;
- to document site visits, phone contacts, and correspondence;
- to ensure confidentiality of subject records;
- to determine if all adverse events and serious adverse events are reported.

Responsibilities of the sponsor

Key responsibilities of the sponsor are

- to maintain written standard operating procedures;
- to agree with the investigator on the protocol and the responsibilities of the trial;
- to select the investigator and site;
- to ensure that appropriate documentation is submitted to regulatory authorities;
- to provide study personnel with all relevant information;
- to oversee proper handling of safety-related events;
- to ensure that appropriate and required reports are prepared;
- to provide compensation, insurance or indemnification (i.e., legal and financial coverage).

The '12 golden rules' of GCP

In summary, the key aspects of ICH GCP as stated in ICH E6 2.0 can be summarized – as we think – by the following '12 golden rules'.

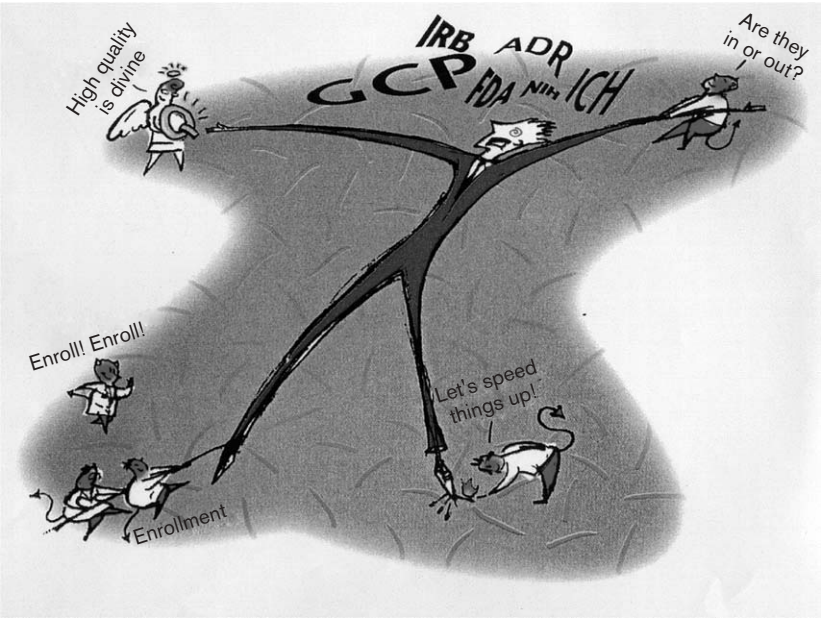
1. Know and strictly follow the study protocol.
2. Select, train and keep a log of all study team members.
3. Record data correctly.
4. Ensure adequate study equipment.
5. Obtain ethics committee approval before starting and get the written informed consent of all subjects before they take part.
6. Predict recruitment accurately and keep an up-to-date subject enrolment log.
7. Precisely document product accountability.
8. Report serious adverse events immediately to the sponsor.
9. Check laboratory sample quality and review laboratory results.
10. Maintain good trial files and archives.
11. Diligently collect and record reliable data. Keep all source documents.
12. Keep everyone fully informed.

ICH-GCP and the EU Clinical Trial Directive

Requirements for the conduct and inspection of clinical trials in Europe have been implemented in the Clinical Trial Directive (Directive 2001/20/EC) [11]. Information concerning the activities in Member States can be found via the Heads of Agencies web site [12]. Information on candidate countries for EU membership can be found at the Collaboration Agreement of Drug Regulatory authorities in European Union Associated Countries (CADREAC) web site [13].

The implementation of the new EU Clinical Trial Directive and guidance documents with its requirements often not fitting smoothly into daily practices have proven to be a real challenge. Lessons learned and areas for future clarification are to be discussed separately, as this would be beyond the scope of this article on GCP.

Fig. 4



The demanding life of an investigator. With kind permission.

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Appendix 1 World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington 2002.

A. Introduction

1. 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. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. 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 fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic principles for all medical research

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
20. The subjects must be volunteers and informed participants in the research project.
21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's

physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise be publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

Additional principles for medical research combined with medical care

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient–physician relationship.
32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix 2 International Conference on Harmonisation Topics and Guidelines

The ICH Topics are divided into four major categories:

- Quality (Q): those relating to chemical and pharmaceutical quality assurance
- Safety (S): those relating to in-vitro and in-vivo pre-clinical studies

- Efficacy (E): those relating to clinical studies in human subjects
- Multidisciplinary (M): cross-cutting topics that do not fit uniquely into just one of the above categories.

Quality (Q)

Topics	Guidelines
Q1: Stability	
Q1A(R)	Stability Testing of New Drugs and Products (Revised Guideline)
Q1B	Photostability Testing
Q1C	Stability Testing for New Dosage Forms
Q1D	Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Drug Products
Q2: Analytical Validation	
Q2A	Test Validation of Analytical Procedures
Q2B	Methodology
Q3: Impurities	
Q3A (R)	Impurities in New Drug Substances (Revised Guideline)
Q3B (R)	Impurities in New Drug Products (Revised Guideline)
Q3C	Impurities: Residual Solvents
Q4: Pharmacopeias	
Q4	Pharmacopoeial Harmonization
Q5: Biotechnological Quality	
Q5A	Viral Safety Evaluation
Q5B	Genetic Stability
Q5C	Stability of Products
Q5D	Cell Substrates
Q6: Specifications	
Q6A	Chemical Substances with Their Decision Trees
Q6B	Biotechnological Substances
Q7: GMP	
Q7A	GMP for Active Pharmaceutical Ingredients

Safety (S)

Topics	Guidelines
S1: Carcinogenicity	
S1A(R)	Need for Carcinogenicity Studies
S1B	Testing for Carcinogenicity
S1C	Dose Selection
S1C(R)	Addendum
S2: Genotoxicity	
S2A	Specific Aspects of Regulatory Tests
S2B	Standard Battery of Tests
S3: Kinetics	
S3A	Toxicokinetics
S3B	Pharmacokinetics
S4: Toxicity	
S4A	Duration of Chronic Toxicity Testing in Animals (Rodent and Non-Rodent Toxicity Testing)
S5: Reprotox	
S5A	Toxicity to Reproduction
S5B (M)	Male Fertility
S6: Biotech Safety	
S6	Safety Studies for Biotechnological Products
S7: Pharmacology	
S7	Safety Pharmacology Studies
M: Multidisciplinary	
M3	Timing of Pre-clinical Studies in Relation to Clinical Trials

Efficacy (E)

Topics	Guidelines
E1: Exposure	
E1	The Extent of Population Exposure Required to Assess Clinical Safety
E2: Clinical Safety	
E2A	Definitions and Standards for Expedited Reporting
E2B (M)	Data Elements for Transmission of ADR Reports (Maintenance) including M2
E2C	Periodic Safety Update Reports
E3: Study Reports	
E3	Structure and Content of Clinical Study Reports
E4: Dose Response	
E4	Dose–Response Information to Support Drug Registration
E5: Ethnic Factors	
E5	Ethnic Factors in the Acceptability of Foreign Clinical Data
E6: GCP	
E6	Good Clinical Practice
E7: Special Populations	
E7A	Clinical Trials in Special Populations – Geriatrics
E8, 9, 10: Clinical Trial Design	
E8	General Considerations
E9	Statistical Principles for Clinical Trials
E10	Choice of Control Group
E11: Paediatrics	
E11	Investigation of Medicinal Products in the Paediatric Population
E12: Therapeutic Categories	
E12A	Clinical Trials on Antihypertensives

Multidisciplinary (M)

Topics/Guidelines	
M1	Medical Terminology
M2	Electronic Standards for Transmission of Regulatory Information (ESTRI)
M3	Timing of Pre-clinical Studies in Relation to Clinical Trials (See Safety Topics)
M4	The Common Technical Document

For more information on the topics and guidelines, please refer to the ICH website under http://www.ich.org