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REGIONAL OFFICE FOR EUROPE

EUR/ICP/DRVE 94 01/MT 01
ORIGINAL: ENGLISH

CLINICAL PHARMACOLOGICAL EVALUATION IN DRUG CONTROL: ENSURING QUALITY OF CLINICAL TRIALS

Report from the 19th European Symposium

Bad Neuenahr, Germany
12–13 December 1995

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1996 EUR/HFA target 31

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QUALITY OF CARE AND APPROPRIATE TECHNOLOGY

By the year 2000, there should be structures and processes in all Member States to ensure continuous improvement in the quality of health care and appropriate development and use of health technologies.

ABSTRACT

Clinical trials are an essential step in the development of safe and efficacious new drugs. Registration of new drugs in future could depend on mutual recognition of such trials. They must therefore be of high quality and adhere to high ethical standards. This can be assured through the application of good clinical practice procedures incorporating strict requirements for ethical conduct, quality assessment and high scientific standards. The personal rights of volunteers and patients in clinical trials must be protected. Countries with no experience of good clinical practice need to establish regulatory, biomedical and ethical standards as the basis for the necessary legislation.

Keywords

PHARMACOLOGY, CLINICAL
DRUG AND NARCOTIC CONTROL
QUALITY CONTROL
CLINICAL TRIALS
EUROPE

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INTRODUCTION

The 19th European Symposium on Clinical Pharmacological Evaluation in Drug Control was held in Bad Neuenahr, Germany, on 12–13 December 1995. The purpose of the Symposium was to explain to representatives of countries of central and eastern Europe (CCEE) and the newly independent states (NIS) the concept of good clinical practice (GCP) in ensuring the quality of clinical trials of drugs and medicinal products.

The Symposium was attended by 38 participants. The Chairperson was Professor Eigill F. Hvidberg and Mr Einar Magnusson was Rapporteur. Annex 2 contains a list of background documentation, Annex 3 the programme and Annex 4 the list of participants.

Mr Fonnesbæk Rasmussen (Acting Regional Adviser of the Pharmaceuticals Programme at the WHO Regional Office for Europe) welcomed the participants on behalf of Dr J.E. Asvall, World Health Organization (WHO) Regional Director for Europe, and thanked the Government of the Federal Republic of Germany and the United Kingdom Know-How Fund for their generous support.

In his welcome to the participants, Dr Hermann Josef Pabel (Deputy Minister of Health of the Federal Republic of Germany) stressed the complexity of clinical trials and the difficulty of controlling them. Approval of clinical trials could be no better than the trials themselves. Procedural and ethical standards such as those laid down by WHO, European Union (EU) and International Conference on Harmonization (ICH) were thus essential tools in ensuring that trials adhered to the highest possible standards.

Dr Idänpään-Heikkila (Director, Division of Drug Management and Policies at WHO headquarters) greeted the participants on behalf of the WHO Director-General, Dr Hiroshi Nakajima. He drew attention to WHO's constitution, which requires the Organization to develop, establish and promote international standards with respect to food and biological, pharmaceutical and similar products. WHO thus had the explicit and constitutional responsibility to promote initiatives directed towards the international harmonization of technical standards, wherever and whenever appropriate in the health sector.

GOOD CLINICAL PRACTICE

Professor Eigill F. Hvidberg (National Board of Health, Denmark) described GCP as a set of standards and principles by which clinical drug studies provide documentation on the clinical qualities of a medicinal product. The principal objective of the clinical development of drugs is to produce efficient, safe, dependable, relevant and affordable medicinal products of the highest pharmaceutical quality for patients now and in the future. Although GCP is expensive for all parties in the short term, it saves money in the long term.

The term good clinical practice has come into use to describe the strict ethical, quality assessment and scientific requirements necessary in order to develop safe and efficacious new drugs and perform clinical trials of high quality and ethical standards. The concept has spread rapidly, and registration of new drugs may in the future depend on mutual recognition of clinical trials. Countries that have not yet introduced GCP therefore urgently need to establish regulatory, biomedical and ethical standards and to plan for their introduction.

The first guidelines to good clinical practice were introduced by the Federal Drug Administration in the USA. Many other countries have subsequently introduced their own guidelines. The third International Conference on Harmonization, which had just taken place in Yokohama, has attempted to harmonize them in the interests of public health worldwide and of the international trade in pharmaceutical products.

The ICH has defined a clinical trial as "Any systematic description of a study of any therapeutic, prophylactic or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations and analysis are fully integrated into a single report". Such trials should be based on the following principles.

1. Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki[1] and that are consistent with GCP and the applicable regulation(s).

2. Before a trial is initiated, the foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society as a whole. A trial should only be initiated and continued if the anticipated benefits justify the risks.

3. The rights, safety and wellbeing of the trial subjects are the most important considerations and should prevail over the interests of science and society.

4. The available clinical and nonclinical information on a product being investigated should be adequate to support the proposed clinical trial.

5. Clinical trials should be scientifically sound and described in a clear and detailed protocol.

6. A trial should be conducted in compliance with the protocol and amendment(s) that have received prior approval (or a favourable opinion) from the institutional review board or independent ethics committee.

7. The medical care given to and medical decisions made for subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

8. Each individual involved in conducting a trial should be qualified by education, training and experience to perform his or her respective task(s).

9. Freely given informed consent should be obtained from every subject prior to his or her participation in a clinical trial.

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

11. Records that could identify subjects should be protected according to the privacy and confidentiality rules of the appropriate regulation(s).

[1] See Annex 1.

12. Products under investigation should be manufactured, handled and stored in accordance with applicable good manufacturing practice. They should be used in accordance with the approved protocol and amendment(s).

13. Procedures assuring the quality of every aspect of the trial should be implemented.

WHO's guidelines for good clinical practice

WHO recognizes the need to assure the scientific integrity of clinical data used to determine the safety, efficacy and quality of every medicinal product. Innovative products, wherever they have been developed, must be assessed on the basis of adequate pharmaceutical and biological data generated in accordance with common standards of good clinical practice.

WHO's guidelines for good clinical practice[2] for trials on pharmaceutical products aim to set globally applicable standards for biomedical research on human subjects. They were drawn up in 1991–1993 in consultation with representatives of drug regulatory agencies, academia and the pharmaceutical industry in Member States. They are based on the Declaration of Helsinki and the *International ethical guidelines for biomedical research involving human subjects*[3] and accord with provisions already promulgated in Australia, Canada, Japan, European Union (EU) and Nordic countries and the United States.

The guidelines are addressed to investigators, ethics review committees, pharmaceutical manufacturers and other sponsors of research, monitors, statisticians and drug regulatory authorities. They provide guidance on provisions and prerequisites for clinical trials, protection of trial subjects, safety monitoring, record keeping and data management, and the handling of and accountability for the pharmaceutical products being investigated. They also discuss special features and requirements for multicentre trials.

Although the guidelines apply specifically to studies undertaken during the commercial development of drugs before and after they are registered, many of the elements are of wider relevance to biomedical research. They can also help editors to decide whether to publish specific reports on research, particularly where a study could influence the use or terms of the marketing authorization for a pharmaceutical product.

WHO Programme for Pharmaceuticals in CCEE/NIS

Dr Natela Menabde (WHO Regional Office for Europe) introduced the Regional Office's Programme for Pharmaceuticals in CCEE/NIS. WHO's assistance to official drug regulatory agencies in these countries is mainly concerned with policy and management, supply and logistics, quality assurance and rational use of drugs.

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[2] WHO Technical Report Series, No. 850, 1995 (*The use of essential drugs. Annex 3: Guidelines for good clinical practice (GCP) for trials on pharmaceutical products:* Sixth report of the WHO Expert Committee).

[3] *International ethical guidelines for biomedical research involving human subjects.* Geneva, Council for International Organizations of Medical Sciences (CIOMS), 1993.

The key problems in CCEE/NIS are:

- the availability and affordability of essential drugs;
- pharmaceutical reforms being undertaken without any clearly defined drug policy, legislative framework or (in some countries) appropriate regulations;
- lack of information about new drugs, leading to inappropriate prescription and use of drugs.

CCEE/NIS urgently need to develop national drug policies (NDP) listing priorities and indicating ways of achieving them. An NDP should aim to ensure the provision of drugs that are relevant to the health care needs of the population. Aspects to be considered in the development of an NDP include the government's role in supplying drugs, the distribution of responsibilities between the public and private sectors, control measures, and the choice, quality, availability, affordability and rational use of drugs.

The main steps in formulating an NDP are:

- proper organization of the policy-making process
- identification of problems
- analysis of existing problems
- formal endorsement of the policy
- launch of the policy.

The Pharmaceuticals Programme can help by:

- sending a fact-finding mission
- analysing information
- developing recommendations
- discussing recommendations at national level
- writing a detailed report and plan of action
- organizing study tours of key officials to a country with a developed pharmaceutical sector
- organizing a meeting to discuss an NDP
- developing an NDP document
- developing a detailed plan for implementing an NDP
- coordinating international assistance.

OVERVIEW OF GOOD CLINICAL PRACTICE IN EUROPE

The first national documents referring to the proper conduct of clinical studies in Europe were produced in France in 1986. Guidelines and regulations in this field have rapidly become international and increasingly stringent. They now include ethics and quality assurance, and the connection between GCP and marketing authorizations has become more visible.

The EU promulgated a Note for Guidance in 1991. Although this is not officially binding on EU Member States, most of the text has been incorporated in a Directive and GCP standards are now required for documentation submitted with new drug applications. About 10 Member States have included the Note in their own drug laws and regulations, while GCP requirements in the few European nations outside the EU are very similar.

The practical implementation of GCP may be the most critical step. The positive cooperation of all concerned – industry, investigators, local drug authorities, ethics committees – is needed. Although the development of GCP has possibly been slower than expected in some places and is initially rather expensive, GCP is now considered the standard for clinical trials in most of western Europe.

Country presentations

Albania

Dr Gezim Bocari (Chairman, Albanian Pharmacological Committee) said that clinical trials in Albania are not meeting GCP requirements. WHO has helped the Albanian Government to draw up a modern and sophisticated drug law and an essential drug list with 200 drugs, and an ethics committee would be established soon. However, the law is not being followed because the regulatory authority is weak and Albanian professionals lack experience. He asked for help from WHO and participants from other countries in drawing up the relevant requirements and implementing them in his country.

Armenia

Dr Samvel Azatyan (Director of Department of Drug Safety and Rational Use, Yerevan) described how clinical trials were organized under the Soviet system. Clinical trials were performed on limited groups of patients in central clinics (e.g. All-Union Centre of Surgery, Scientific Centre of Oncology and the Scientific Centre of Cardiology). These clinical trials were sometimes carried out without the informed consent of the patient, the receipt of the Ethics Committee's opinion or according to standard operating procedures. The technology of the trials was not always adequate.

The difficult economic situation is creating further problems for clinical trials of new drugs, such as a lack of financing, of modern methods of investigations in hospitals and of special reagents. The small size of the population is a further obstacle.

Article 10 of Armenia's drug law covers clinical trials of new drugs in accordance with international GCP requirements, including the protection of trial subjects, the creation of an independent ethics committee, informed consent and standard operating procedures.

Hungary

Mr Kálmán Várady (National Institute of Pharmacy, Budapest) reported that clinical trials in Hungary have been regulated since 1987. In 1994 the main concepts of GCP were progressively introduced as legal requirements and have now been incorporated into the new Medicines Act. The EU GCP guidelines were translated into Hungarian and issued by the National Institute of Pharmacy as an official document in 1992. Working under the supervision but independently of the Ministry of Welfare, the Institute is responsible for authorizing clinical research matters, clinical trials, drug registration, good clinical, laboratory and medical practice, pharmacy inspections and post-marketing surveillance.

Before starting the first clinical trials with a new chemical or biological entity, the sponsor (a pharmaceutical company) or an investigator applies for authorization from the National Institute of Pharmacy by sending the following documents to the Central Scientific Ethical Committee:

- a summary application form
- a summary of product characteristics
- brief expert reports on chemical, pharmaceutical, biological and clinical issues
- chemical, pharmaceutical, biological, toxicological and pharmacological documentation
- the clinical development plan
- the protocol and care report form
- a description of the information given to the patient and his or her informed consent.

Approval currently takes four to six months. The ethics committees are playing a crucial role in the current fluid political/ethical situation. It is illegal to perform a clinical trial without approval from the authorities. Parallel submissions to the regional or local ethics committees do not save time because their members base their decisions on those of the Central Ethics Committee.

The National Institute of Pharmacy charges for GCP inspections. These are usually carried out by two experts, often a pharmacist and a medical expert, who write a report. The applicant receives a brief summary of their observations.

In 1995, 36 clinical trials were carried out, of which 32 complied with GCP.

Kyrgyzstan

Professor Dogdurbek Adambekov (Pharmacological Committee of the Ministry of Health, Bishkek) said that a Pharmaceutical Department (Standardization and Control of Drugs) had been established in the Ministry of Health in 1992. Clinical trials are under the supervision of the Pharmacopoeia Committee, which refers to the Pharmaceutical Department.

The former Soviet regulations are still in force. No comprehensive drug legislation exists as yet, but a drug act has been drafted with the assistance of WHO. Article 13 of this draft law includes requirements for clinical trials, and Article 14 includes provisions for the rights of the patients. This law will probably be passed by Parliament in the near future.

Slovakia

Mr Pavol Gibala (State Institute for the Control of Drugs, Bratislava) described the laws and regulations in force in Slovakia. Clinical trials are inspected and are supposed to be carried out according to GCP. Detailed regulations concerning clinical trials and GCP are being drawn up to clarify the responsibilities of sponsors and investigators. Management of the clinical trials will be extremely important, and investigators will have to be properly qualified. Certificated post-education in this field is very much needed.

REGULATORY PREREQUISITES FOR IMPLEMENTING GCP

Dr Ursula Gundert-Remy (Department of Clinical Pharmacology, University of Göttingen, Germany) said that the acceptance by EU member states of the GCP guidelines meant that western European countries should now introduce GCP and ensure that all the parties involved in the clinical trial system accepted the concept and regulations. The first step is to establish a regulatory framework defining the procedures and incorporating them in legislation. Inevitably there would be problems, and countries were already finding different solutions that respected their national traditions and existing national structures. Certain points could be helpful to countries considering the introduction of GCP.

Regulatory framework

Legislation

The requirement to perform clinical trials according to GCP means that several of the constituents of GCP must be incorporated in legislation. Where no law exists, one should be drawn up covering regulations for the performance of clinical trials. The following points should be included:

- notification and approval of the trials, including the prerequisites and conditions (preclinical data, trial protocols, etc.);
- monitoring of procedures, audits and inspections respecting protection of personal data;
- reporting of adverse effects;
- ethics committees and their obligations;
- insurance.

Ethics committees

One of the aims of GCP is to reassure the public that clinical trials are performed in line with the ethical principles laid down in international guidelines such as the Declaration of Helsinki and the *European guidelines on good clinical practice*.[4] This reassurance is given by the review of trial protocols by an independent ethics committee before the trial starts. Ethics committees may be centralized or decentralized. Members may be elected or nominated by public institutions. Where there is more than one ethics committee, communication between them should be organized to guarantee a common standard.

GCP inspectorates

Inspectorates staffed by appropriately trained personnel must be established to carry out governmental audits (inspections).

Administrative procedures

The appropriate administrative procedures must be put in place. These may vary from country to country.

Linkage to the drug approval system

Approval of drugs is based on clinical trial reports as well as documentation of quality and preclinical safety. As clinical trials have to be performed in accordance with GCP rules, clinical trial reports must be linked to the control of their conduct. A central register of trials should be established in conjunction with the notification system so that officials responsible for assessing requests for approval can check the trial reports.

Dr Stanislav Primozic (Faculty of Pharmacy, Ljubljana) illustrated the different ways in which drug regulatory authorities evaluate new chemical entities and generics (Fig. 1).

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[4] *European guidelines on good clinical practice.* 1st ed. Surrey, Brookwood Medical Publications, 1993 (NLN 35GCP).

Fig. 1. Standards and criteria for evaluation of new drugs

NEW MOLECULAR ENTITIES (Single producer, under patent)	**STANDARDS/CRITERIA**	**GENERICS** (Multisource, post-patent)
Drug registration dossier		
Pharmaceutical/chemical tests	Good manufacturing practice Good clinical practice	Pharmaceutical/chemical tests
	European Pharmacopeia United States Pharmacopeia Japanese Pharmacopeia, etc.	
Pharmacological/toxicological tests	Good laboratory practice	
Clinical trials I, II, III, IV and pharmacokinetic tests	Good clinical practice (Good laboratory practice)	Bioequivalence tests
Other criteria		
	Affordability	
	Therapeutic equivalence	
	Therapeutic substitution	

Development plan

The development plan should include the preclinical and clinical phases, biomedical requirements for the safe and adequate conduct of clinical trials, and post-marketing studies (phase IV). Phase IV trials should be justified and controlled according to GCP to stop them being carried out with the sole aim of promoting or selling a drug. Article 1.1 of the WHO guidelines for GCP states: "It is important for anyone preparing a trial of a medicinal product in humans that the specific aims, problems and risks or benefits of a particular clinical trial be thoroughly considered and that the chosen options be scientifically sound and ethically justified."

GCP inspections

Dr Michael Schmidt (Ministry of Labour, Health and Social Affairs, Baden-Württemberg, Germany) described the organization of the GCP inspectorate in Germany and gave an overview of some practical aspects of the inspection of clinical trials.

The German Drug Law of 1976 stipulates that inspections of clinical investigations by the competent health authorities must focus on the protection of the human subjects of trials. The inspectorate is therefore responsible for protecting participants in clinical trials, educating physicians and discovering deviations.

Standards for the planning, methodology, conduct, reporting and documentation of clinical trials are laid down in a guideline to national GCP standards for inspection and registration which must be respected by sponsors, physicians and authorities.

Inspections consist in collecting and scrutinizing data concerning clinical trials. This is particularly necessary for data which could be criticized, for instance as regards which doctors or patients take part. The reasons for an inspection can include:

- to make a routine check
- the physician is making a large number of trials
- special subjects are taking part in the trial (e.g. elderly people, children)
- poor notification
- complaints by participants.

On-site inspections can cover:

- how physicians are chosen and by whom (is there a "black list" of physicians?)
- information given to patients and physicians
- insurance
- toxicological results
- quality assurance system
- data handling
- documentation
- good medical practices in relation to test substances.

BIOMEDICAL PREREQUISITES FOR COMPLIANCE WITH GCP

Professor Andrzej Czarnecki (Drug Institute, Central Register of Clinical Trials and Pharmacoepidemiology Centre, Warsaw) described the long and costly process from the development of a new drug to its post-marketing surveillance, and the efficacy and safety studies which are the main purpose of clinical trials.

It takes about ten years and five stages to develop a drug from the moment a compound is synthesized. First the pharmacology is tested and checked. Then various toxicological tests are carried out including tests for oncogenicity and reproductive and genetic toxicity. Once the basic information is gathered the new chemical entity may enter four phases of clinical trials. These are the stages to which GCP requirements apply.

Preclinical safety evaluation

Professor G. Kreutz (Federal Institute of Drugs and Medical Devices, Germany) explained the interface between toxicology and pharmacology in clinical trials, and described studies performed *in vitro* and in animals before drugs are tried on humans. Preclinical safety evaluation is a dynamic process under which toxicological safety is evaluated relative to clinical experience at each stage. The primary goals of preclinical safety evaluation are:

- the identification of a safe dose to initiate clinical trials in humans;
- the identification of potential target organs of toxicity and investigations of possible outcomes;
- the identification of parameters which it is important to monitor during clinical safety testing.

Division of responsibilities

It is important that all parties concerned in clinical trials are aware of their responsibilities.

- Sponsors are responsible for giving all relevant information regarding a drug, with updates, to the drug regulatory authority. This includes chemical (choice of investigators), pharmaceutical (choice of sites), toxicological (insurance), pharmacological (monitoring/auditing) and clinical (adverse events analysis) information. The sponsor must also have an independent quality control programme and audit the trial.
- The investigator must record all data precisely on a case report form, check it carefully and report all adverse events.
- The monitor must check the investigator's reports.
- Finally, the relevant authorities must exercise control and inspection, and everyone involved should ensure that all documentation is complete and accurate.

ETHICS

Dr Gaut Gadeholt (Norwegian Medical Control Authority, Oslo) introduced the session by going through the Declaration of Helsinki.

Most of the articles in the Declaration of Helsinki are self-evident. Others highlight the differences and potential conflicts between good science (producing reliable results at the lowest possible cost) and ethics. Ethical considerations are heavily influenced by safety considerations. Good ethical decisions can hardly be taken without a thorough analysis of the risks involved. For this reason members of a review board should have a broad knowledge of medicine and access to relevant clinical and toxicological information about the drugs involved.

The idea of ethical review is the authority to say NO, but there are different ways to do this. For example, ethics committees often say that it is not recommended that a trial should be carried out.

The basic principles to be looked for in a trial are that:

- it is scientifically sound
- there is a protocol, including a statement on ethics, and outside reviews
- the personnel are qualified
- it is important enough to justify the risks involved
- the risks have been assessed
- the privacy and integrity of the patient are assured
- it will be terminated if the risks are higher than expected
- the results are published accurately
- patients have been given all the appropriate information and have given their informed consent
- no pressure has been put on patients to give their consent
- any guardians have given their consent.

High risks may be ethically acceptable if the potential benefit is high. In such cases participants must be thoroughly and honestly informed.

The use of placebo controls is scientifically the best way to identify a therapeutic effect. Ethically this may be problematic because the control patients will not be treated. The risks of not treating a disease must be assessed as part of the ethical analysis. Article 5 of the Declaration of Helsinki lays down that "Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society".

A study designed to document a therapeutic effect as equally good as an established treatment may need a higher number of patients than a placebo-controlled study. The ethics of exposing a higher number of patients to an experimental form of treatment whose risks are poorly known should also be discussed. Control questions could include: is the placebo (in)active? What are the characteristics of the relevant comparator drug? What is the relevant dose?

Bias should be avoided.

Some special problem areas include:

- investigations of drugs in patients with medical conditions that are considered contraindications to the treatment (this is an important point in establishing precautions that may permit treatment in the future);
- investigations in people who cannot understand the risk;
- investigations of new chemical entities where analyses of medical and preclinical data may be required to show that the study is unethical in human subjects;
- investigations of new chemical entities which have shown no evidence of being safer or more efficacious than established therapies.

PRACTICAL IMPLEMENTATION OF GCP

Professor Hvidberg explained that there were several grounds – scientific, ethical, economic, educational – for implementing GCP. Implementation cannot happen, however, until the necessary legislation and the entire infrastructure for conducting high quality clinical trials are in place, including clinical expertise, medical facilities, a regulatory administrative apparatus and an ethics reviewing system. Just as important, sponsors and investigators must be aware of their responsibilities and committed to the concept of GCP. Finally, adequate resources must be allocated to all those involved.

There was no one system for implementing GCP. Countries had different legal systems, administrative traditions and attitudes towards drug treatment and a varying willingness to allocate resources. Even in the most developed countries it has taken years to establish GCP standards and to implement them. Small steps compatible with a country's medical and regulatory status and traditions will eventually push in the right direction. There is usually a long educational period preceding any action to improve the science of clinical trials. Cultural differences are also significant.

Any country contemplating introducing GCP should establish a small committee to go seriously through the points raised at this Symposium to judge whether national conditions could accommodate GCP requirements. The next stage is to draw up a plan.

As to whether GCP would improve drug therapy, Professor Hvidberg considered that GCP would:

- protect trial subjects undergoing experimental therapeutic treatments;
- ensure the generation and reporting of dependable data for the benefit of future patients;
- encourage better and more effective use of resources;
- generate standards which would eventually affect drug therapy in general; and
- alert clinicians to the need for objective and scientifically based results as the necessary basis of drug therapy.

CONCLUSIONS AND RECOMMENDATIONS

1. The difficult economic situation and lack of financial independence for professionals in many CCEE/NIS means that countries are at different stages in introducing clinical trials and GCP. Some countries would need time to reach general European standards. WHO could help by supporting twinning projects between countries that are more and less developed in this regard.

2. Inspection is a check on a trial, not an evaluation or police control of it. Inspectors should have full access to all documentation concerning a trial and the legal right to stop it. It is also very important that they inspect the written consents of the patients and the dates on which these were given.

3. Ethical matters are difficult. It is important to find the balance between the protection of trial subjects, benefit for the patient, the advantage to society, scientific progress and freedom of research.

4. The independence of ethics committees is an important and sensitive matter. There should be more than one ethics committee in each country.

5. Experience has shown that clinical trials sponsored by pharmaceutical companies are usually better than those not sponsored by the pharmaceutical industry.

6. Some countries have enacted legislation regarding the right of the public to have access to information. This could create problems with the confidentiality of data. Confidentiality must be kept within the law. The ethical attitude of the investigator is very important in this connection. The subject must be made aware of and consent to the fact that personal information about him or her may be scrutinized during the monitoring, auditing or inspection of the trial by authorized persons (the sponsor or relevant authorities), and that such information relating to his or her participation in the trial will be treated as confidential and will not be made publicly available. (This principle may need to be modified in the light of national laws and regulations.)

7. Applicants should have very good reasons for conducting clinical trials with children, and such trials should be subject to strict controls.

8. The Regional Office should:

   - be prepared to comment on drug laws;
   - include GCP in the Programme for Pharmaceuticals and its projects;
   - distribute a questionnaire to the participants and collect documents and information about GCP with the aim of analysing and comparing the situation between the countries;
   - draw up a simple guide for implementing GCP; and
   - be prepared to organize another symposium after two years if funds are available.

9. Participants should establish working groups to develop GCP in their countries.

Annex 1

DECLARATION OF HELSINKI

RECOMMENDATIONS GUIDING PHYSICIANS IN BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS[5]

INTRODUCTION

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission.

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".

The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the aetiology and pathogenesis of disease.

In current medical practice most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

In the field of biomedical research a fundamental distinction must be recognized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research, the essential object of which is purely scientific and without implying direct diagnostic or therapeutic value to the person subjected to the research.

Special 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.

Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, the World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

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[5] Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th World Medical Assembly, Venice, Italy, October 1983; and the 41st World Medical Assembly, Hong Kong, September 1989.

BASIC PRINCIPLES

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and on a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor, provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical 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 his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participation at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her or may consent under duress. In that case the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incapacity makes it impossible to obtain informed consent, or when the subject is a minor, permission from the responsible relative replaces that of the subject in accordance with national legislation.

    Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

MEDICAL RESEARCH COMBINED WITH PROFESSIONAL CARE (CLINICAL RESEARCH)

1. In the treatment of the sick person, the physician must be free to use a new diagnostic and therapeutic measure, if in his or her judgement it offers hope of saving life, re-establishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient – including those of a control group, if any – should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician–patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent Committee (I,2).

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

NON-THERAPEUTIC BIOMEDICAL RESEARCH INVOLVING HUMAN SUBJECTS (NON-CLINICAL BIOMEDICAL RESEARCH)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the physician to remain the protector of the life and health of that person on whom biomedical research is being carried out.

2. The subjects should be volunteers – either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgement it may, if continued, be harmful to the individual.

4. In research on man, the interest of science and society should never take precedence over considerations related to the wellbeing of the subject.

Annex 2

BACKGROUND DOCUMENTATION

Declaration of Helsinki. Recommendations guiding physicians in biomedical research involving human subjects. Adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964. Amended by the 29th World Medical Assembly, Tokyo, Japan, October 1975; the 35th World Medical Assembly, Venice, Italy, October 1983; and the 41st World Medical Assembly, Hong Kong, September 1989.

WHO Technical Report Series, No. 850, 1995 (*The use of essential drugs. Annex 3: Guidelines for good clinical practice (GCP) for trials on pharmaceutical products:* Sixth report of the WHO Expert Committee).

International ethical guidelines for biomedical research involving human subjects. Geneva, Council for International Organizations of Medical Sciences (CIOMS), 1993.

Good clinical practice for trials on medicinal products in the European Community. EEC Note for Guidance. *Pharmacology and toxicology,* **67**: 361–372 (1990).

European GCP guidelines. 1st ed. Surrey, Brookwood Medical Publications, 1993 (NLN 35GCP).

Inspection: requirements, strategies and consequences: report on a Nordic Workshop, Stockholm, 19–20 September 1994. Uppsala, Nordic Council on Medicines, 1994.

Guidelines and recommendations for European ethics committees. Brussels, European Forum for Good Clinical Practice, 1995.

Clinical trials of medicinal products. Danish guideline on notification according to the Medicines Act. Denmark, The National Board of Health, 1993.

Annex 3

PROGRAMME

Monday, 11 December

18.00 – 19.00	Registration
19.30	Welcome dinner-buffet hosted by the Federal Ministry of Health, Bonn

Tuesday, 12 December

08.00	Registration
09.00	**Opening session: Setting the scene**
	Welcome addresses Mr Kurt Fonnesbæk Rasmussen, Acting Regional Adviser for Pharmaceuticals, WHO Regional Office for Europe Dr Hermann Josef Pabel, Ministry of Health, Bonn
	Opening remarks Dr J. Idänpään-Heikkila, Director, Division of Drug Management and Policies, WHO headquarters
	Introduction Professor Eigill F. Hvidberg *(Chairperson)*, National Board of Health, Denmark
	Overview of WHO's assistance to official drug regulatory agencies in CCEE/NIS Dr Natela Menabde, WHO/EURO Programme for Pharmaceuticals in CCEE/NIS
10.30	*Coffee break*
11.00	**Session 1: Overview of the GCP situation in Europe**
	Introduction by Professor Eigill F. Hvidberg
	Mr Kálmán Várady, Hungary Dr Samvel Azatyan, Armenia Professor Dogdurbek Adambekov, Kyrgyzstan Open discussion
13.00	*Lunch*
14.00	**Session 2: Regulatory prerequisites for implementing GCP**
	Introduction by Professor Ursula Gundert-Remy, Department of Clinical Pharmacology, University of Göttingen, and Dr Michael Schmidt, Ministry of Labour, Health and Social Affairs, Baden Württemberg
	Legislation Ethics committee system GCP inspectorates Administrative procedures Linkage to the drug approval system Open discussion
15.30	*Coffee break*
16.00 – 17.30	Session 2 (continued)
19.00	*Dinner*

Wednesday, 13 December

09.00	**Session 3: Biomedical prerequisites for GCP compliance**
	Introduction by Professor Andrzej Czarnecki, Drug Institute, Warsaw
	Nonclinical requirements Clinical requirements Biostatistics The phases of clinical drug development Investigators' and sponsors' responsibilities Open discussion
10.30	*Coffee break*
11.00	Session 3 (continued)
12.30	*Lunch*
13.30	**Session 4: Ethics**
	Introduction by Dr Gaut Gadeholt, Norwegian Medicines Control Authority, Oslo
	Criteria for ethics requirements National/regional examples Open discussion
15.00	*Coffee break*
15.30	**Session 5: Practical implementation of GCP**
	Introduction by Professor Eigill F. Hvidberg
	How and when would you implement GCP in your own country? Open discussion
17.00	Closure of the Symposium
19.00	*Farewell dinner*

Annex 4

PARTICIPANTS

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