

CLINICAL TRIALS WITH MEDICINES IN EUROPE



REGULATORY FRAMEWORK FOR CLINICAL TRIALS WITH MEDICINES IN EUROPE

The pharmaceutical industry is the most highly regulated sector in Europe.



The Commission has tabled a proposal for a directive on Good Clinical Practice for testing medicinal products for human use. The European pharmaceutical industry- EFPIA- hopes that the text to be adopted will establish an appropriate environment for investment in clinical research in Europe and further encourage pharmaceutical innovation for the benefit of patients.

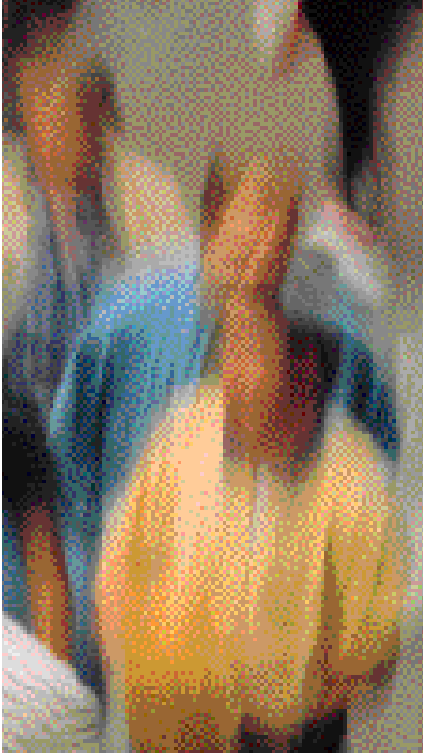
The pharmaceutical industry is the most highly regulated sector in Europe. To protect the health of patients, new drugs and treatments are legally required to undergo strict, extended and stringent tests before they are approved - at national or European level - and allowed on the market. The maximum protection for participants in these tests must be ensured.



The process of turning a new compound into a safe, efficient and marketable medicine is normally lengthy (10 to 12 years), costly (about ECU 275 million) and commercially risky (only one drug out of ten thousand will survive extensive testing in the Research & Development phase). Clinical trials, which assess the suitability of new medicines for human use, are the longest and most expensive part of developing a medicinal product.

WHAT IS A CLINICAL TRIAL ?

A clinical trial is a research study conducted in human participants to evaluate the safety and efficacy of a medicine expected to improve patient's health.



Clinical trials can only be started after a compound has survived rigorous pre-clinical development work, which involves laboratory testing (chemical/ biological/ pharmacological/ toxicological). It is only when these tests show favourable and promising results that a company can proceed to assess the medicine in humans.

WHY IS A CLINICAL TRIAL NECESSARY ?

Clinical trials are the link between the results of pre-clinical testing and actual medical practice. They allow researchers to demonstrate the efficacy and safety of a new medicine or treatment, which is a prerequisite for marketing authorisation.

Without clinical trials, therefore, a medicine could not be made available for treating patients.

It is only through clinical trials that progress will be made on new medicines and improved treatments for diseases.

WHAT ARE THE RULES GOVERNING THE CONDUCT OF CLINICAL TRIALS IN EUROPE ?



National laws govern the proper conduct of clinical trials and the protection of participants. In addition, various strict ethical and technical guidelines have been adopted at European and international levels.

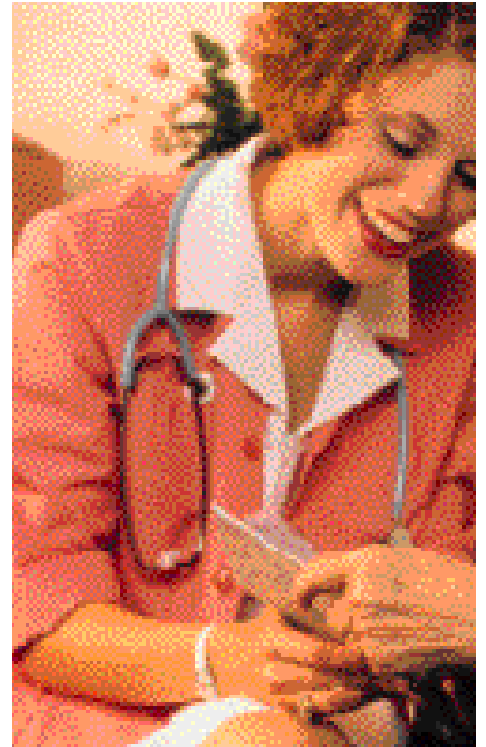
International guidelines on Good Clinical Practice - GCP- were adopted in 1997 as a result of discussions between Europe, the US and Japan within the International Conference on Harmonisation - ICH. These guidelines, which ensure that clinical trials are conducted in accordance with high standards of ethics and science, were developed from European guidelines which have been in place since 1990.

Furthermore, many specific EU guidelines are in place for clinical testing in different disease and patient categories (cancer, arthritis, heart diseases, geriatrics, pediatrics etc.).

WHAT ARE THE DIFFERENT STAGES IN A CLINICAL TRIALS PROGRAMME ?

Clinical trials are conducted progressively on an increasing number of participants as more extensive data are collected on the efficacy and safety of the tested medicine. There are usually three basic stages, called "clinical trial phases", and progress from one to the next is always dependent upon a satisfactory outcome of the previous phase.

- **PHASE I** involves the studies of effects on a few healthy human volunteers
- **PHASE II** involves clinical studies on a few hundred volunteer patients to determine the appropriate dose and learn about the activity of the product against the disease. Under certain circumstances, taking into account ethical considerations, type of disease, etc. it may involve comparison with a non-active treatment, called a placebo.
- **PHASE III** trials test the treatment on several hundred to several thousand voluntary patients, often at many different clinics or hospitals (multi-centre trials), and even in different countries (multi-state trials). These trials usually compare the new treatment with a current treatment already in use.
- **PHASE IV** takes place after marketing authorisation. It is to gather data on a product authorised for marketing and used in accordance with the approved current medical practice.



The first three phases constitute the clinical development and take from 5 to 10 years.

WHAT ABOUT THE ETHICAL DIMENSION ?

- Is the ethical dimension taken into account in clinical trials?

YES, science and ethics are inseparable in clinical trials. The primary ethical principles are codified in the Helsinki Declaration and the Council of Europe Bioethics Convention.



HOW ?

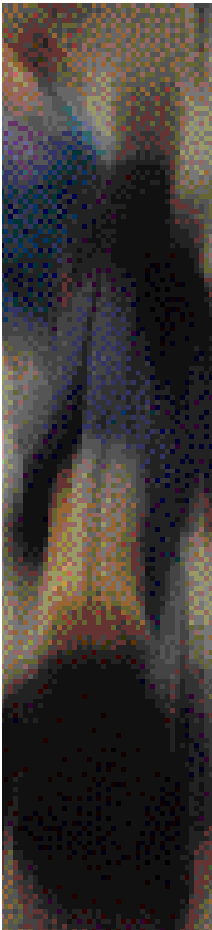
Good Clinical Practice (GCP) guidelines have their origins in the Helsinki Declaration. GCP provides for further protection of the participant in clinical research. One of the main principles of GCP states that "the rights, safety, and well-being of the trial subject are the most important considerations and should prevail over interest of science and society".

Provisions are laid down to guarantee that before any clinical trial is started the written opinion by an ethics committee ensures the protection of the rights, safety and well-being of the participant.

An ethics committee evaluates the research protocol, the suitability of the investigator, the facilities and the content of the informed consent and how this is to be obtained.

- Who sits on the ethics committee and how does it work ?

An ethics committee is an independent body (institutional, regional or national) constituted by both medical professionals and non-medical members. The rules governing its operation may differ from country to country, but must allow the committee to work independently from researchers and act in accordance with the recommendations detailed in the GCP guidelines.



WHAT ARE THE PARTICIPANTS' RIGHTS ?

HOW ARE THEY PROTECTED IN A CLINICAL TRIAL ?

● Right to detailed information

Before enrolling in a clinical trial, participants must receive clear, understandable but sufficiently detailed information on the nature of the trial and be given the opportunity to ask and receive answers to questions. The benefits and possible risks of participating in the study are also explained. A decision should not be taken immediately and individual participants are allowed time to consider their position.

● Voluntary written informed consent

Consent from the participant is required. This consent is in written form to confirm the individual subject's participation on a voluntary basis. In the case of children, handicapped and very ill patients, the written consent of their representative or legal guardian is required.

● Right to withdraw at any time

A participant can withdraw from the trial at any time without giving a reason and without any prejudice to continuing treatment.

● Patient data confidentiality

The clinical trials sponsor and the authorities must have explicit permission from the individual patient to have access to his medical files. All documents containing details of a patient's identity are filed exclusively at the investigator's site.



HOW IS A CLINICAL TRIAL CONDUCTED ?

There must be strict adherence to the research protocol that has received prior approval from the relevant independent ethics committees. Major changes are not allowed without ethics committee approval.

Monitoring by the sponsor ensures that:

- the rights and well-being of the participants are protected
- the reported trial data are accurate, complete, and verifiable from source documents
- the conduct of the trial complies with the approved research protocol, with GCP and with relevant regulatory requirements

The investigator must record, handle and store all clinical results in a way that allows their accurate reporting, interpretation and verification. The investigator must ensure the well-being of each individual subject.

Safety reporting of adverse reactions is organised according to well recognised requirements and recommendations (internationally agreed within ICH). Any serious adverse reaction must be immediately reported (within 15 calendar days) to the relevant ethics committees and health authorities.

When the trial is completed or prematurely terminated (e.g. for safety reasons) the sponsor ensures that a clinical trial report is prepared and provided to the regulatory agency(ies) as required by law. Most studies will be subject to publication in well respected clinical journals and thus available to the medical community.

IS THERE ANY INSPECTION BY THE AUTHORITIES ?

GCP guidelines require that procedures be implemented to assure the quality of every aspect of the trial. Such quality systems should be open to inspection by appropriate authorities and this is established practice with certain governments.

Clinical trials are open to inspection by authorities at any time. These authorities have the right to inspect the site and the sponsor.

WILL A DIRECTIVE IMPROVE THE CURRENT LEGAL FRAMEWORK ?

The proposed directive will help to ensure consistent and harmonised implementation of the internationally agreed ICH Good



Clinical Practice guidelines across Europe. It also covers common requirements for inspections by authorities and hence mutual recognition, by the various Member States of the findings of these inspections.

However, the proposed directive contains a number of provisions that would result in over-bureaucratic requirements causing unnecessary delays, stifling innovation with no added value to what is already in place in terms of high ethical and scientific standards.

These provisions may moreover have a damaging effect on Europe's attractiveness as location for clinical research, with inevitable consequences for Europe's scientific and economic competitiveness and hence job losses without any benefit to patients.

European **F**ederation of
Pharmaceutical **I**ndustries
and **A**ssociations



Fédération **E**uropéenne
d'**A**ssociations et d'**I**ndustries
Pharmaceutiques

EFPIA has been representing the interests of Europe's research-driven pharmaceutical industry since 1978. Its membership encompasses both national pharmaceutical associations and companies.

EFPIA is the Industry's spokesman at European supranational bodies such as the European Union institutions.

The mission of EFPIA is, with its constituent members, to foster a policy climate that enables the European pharmaceutical industry to meet the healthcare expectations of Europe's present and future generations.

Further details about the federation and its activities can be obtained from :

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