

Essential Good Clinical Practice



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Chapter 1: Introduction to good clinical practice

Factors affecting clinical trials

Everyone involved in clinical trials in humans has a responsibility to ensure that the trials are conducted to the highest possible standards.

Around 25 years ago there were few rules and regulations affecting clinical trial conduct. Most sponsors and investigators were free to design and undertake trials as they wished. A few voluntary codes existed.

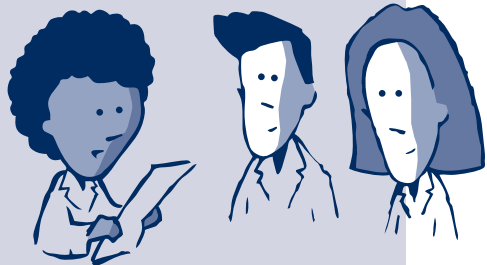
Today, human clinical research is heavily regulated. A quality standard called good clinical practice (GCP) should be followed in all trials, wherever they are conducted.

Declaration of Helsinki

The most notable code of practice that underpins medical research in humans is the Declaration of Helsinki. It is a set of ethical principles established by the World Medical Association (WMA). It has been modified on many occasions since it was first published in 1964, following a General Assembly of the WMA in Helsinki (hence its name).

The Declaration of Helsinki provides protection for subjects who take part in trials. It ensures that subjects are provided with information on the risks and benefits of participation; requires informed consent to be obtained; prohibits coercion by investigators; and allows subjects to withdraw from the trial at any time without detriment to their future care.

There have been many controversial aspects to the Declaration of Helsinki, in particular the use of placebo (inactive substance) in trials and the requirement to provide the best proven treatment at the end of a trial. The latest version of the Declaration of Helsinki (Seoul, 2008) can be obtained from the WMA website at <www.wma.net>.



Other regulations and guidelines

A process called ICH (International Conference on Harmonisation) has generated guidance documents for virtually every stage of drug development, from non-clinical to human studies.

Within the European Union (EU) framework – expanded to the European Economic Area (EEA), with the agreed involvement of Norway, Iceland and Liechtenstein – directives and regulations have been developed to try to harmonise procedures throughout Europe. These have been incorporated into the national laws of EEA Member States. Whilst there has not been complete harmonisation between European countries, there are many similar procedures, making pan-European trials easier to perform.

In Europe, directives must be passed into Member States' laws within a specified time, but may be 'gold plated' to add additional requirements within that country. Regulations are binding for all EU Member States.



The regulations in the USA – published in the *Federal Register* and referred to as the Code of Federal Regulations (CFR) – affect most commercial research because, more often than not, trials performed globally will be used to support marketing applications in the USA.

There are also strict data protection laws (affecting the transfer and processing of trial subjects' data).

Inspectors from the regulatory authorities visit sponsors and investigators to check that the laws and regulations are being followed.

Europe accounts for about one-third of patients recruited into clinical trials submitted as part of marketing authorisations. Another third of the data are generated in the USA, leaving a large proportion generated outside Europe and North America. For maximum credibility, these trials should be performed in accordance with internationally recognised GCP.

Chapter 2: General GCP responsibilities and subject protection

The investigator and study site

The success of any clinical trial is down to the selection of a suitable investigator and study site personnel. They must be appropriately qualified, trained and have the experience and expertise to undertake the trial. The sponsor must carefully consider the personal and professional qualities of the investigator. GCP requires the sponsor to undertake a thorough site assessment to ensure that both the investigator and the proposed trial site are suitable.



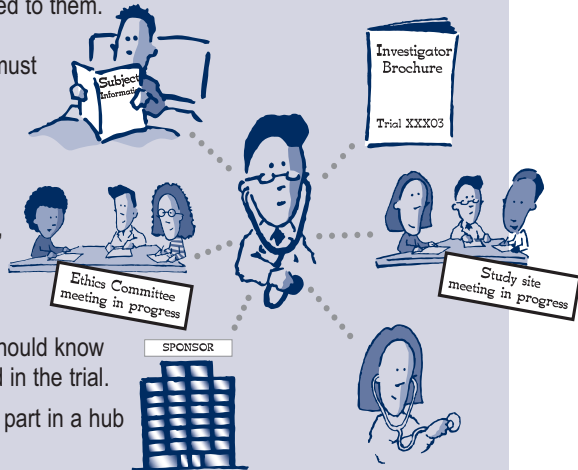
The investigator must have time to undertake the study, sufficient potential trial subjects, and suitable facilities and supporting staff.

It is usual for the principal investigator – ie. the person who is responsible for the overall conduct of the trial – to delegate duties to other members of the study team. However, it is important that members of the study team only perform the duties delegated to them.

They must be legally allowed to undertake those duties, which must be within their experience and capabilities. The sponsor must check compliance with this requirement.

Before they take part in a study, all staff should be properly trained and briefed. They should be aware of and should follow the study protocol, and should know about the medicines being used in the trial.

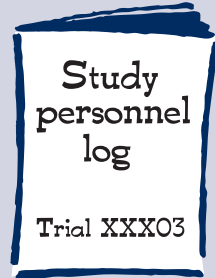
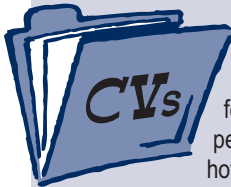
The investigator plays a central part in a hub of trial activities and processes.



Log of study personnel

It is important for investigators to keep a log of the site personnel involved in the study. This log should document who was involved, their qualifications, when they were involved (start and end dates/times, depending on the nature of the study) and what their trial-related duties were.

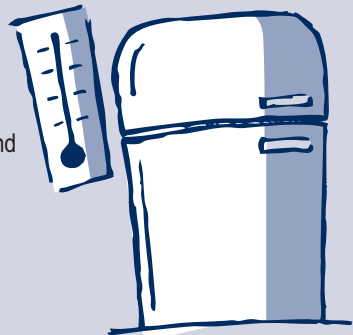
In order to demonstrate that a person involved in a trial is suitably experienced and has the qualifications required, an up-to-date signed and dated curriculum vitae (CV) should be provided by that person. This should be kept on file and updated when appropriate. CVs are particularly important for team members who have significant trial-related duties, such as obtaining the consent of subjects, undertaking assessments and completing record forms. CVs might not be required for personnel with minor, supervised roles; however, if in doubt a CV should be kept on file.



Equipment requirements

The study site must have the relevant equipment and facilities in order to perform the trial. Equipment used in a trial must be suitable, properly maintained and calibrated; records should be available to confirm this. For example, a refrigerator used to store trial samples should have a temperature alarm in case of failure; its temperature and condition should be regularly checked by

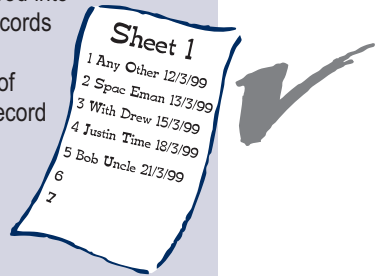
study staff (signing a log of activity); and the refrigerator should ideally be dedicated to the trial to avoid cross-contamination. The equipment and facilities must be available to the trial when required.



Subject enrolment log

Information about subjects who have been screened and entered into the trial should be recorded in a subject enrolment log. This records subjects' names and their unique study numbers. It may also include their dates of birth, health service numbers and dates of participation in the trial. Only the investigational site keeps a record of the subjects' identities.

The subject enrolment log is an important document, as it is unique to the study site and is the main way in which a subject can be identified later.



Subject protection

Ethics committee opinion

The favourable opinion ('approval') of an independent ethics committee (IEC) (or institutional review board (IRB) as they are called in some countries) is required before the trial can begin. IECs/IRBs are made up of medical and non-medical members. It is their job to ensure that the rights, safety and well-being of the trial subjects are protected.

To obtain an opinion, a comprehensive package of documents and information has to be submitted to the IEC/IRB. In Europe, a standard application form is used. The IEC/IRB will then review the application and provide its opinion. In Europe, this opinion is to be given within 60 days, unless the product is a biological or gene/cell therapy, when longer review periods are permitted (90 days). In other regions there may be no timeline established and obtaining an ethics committee opinion may be a significant rate-limiting step.

Some of the submitted documents need to be approved by the IEC/IRB, whilst others are submitted to help the IEC/IRB make its decision. The documents needing specific approval are

- the final version of the study protocol and any subsequent amendments
- the documentation used to provide information to and obtain the consent of the subject (and any updates), eg. subject information sheets and consent forms
- the materials used to recruit study subjects, such as advertisements and posters.

The IEC/IRB should review its opinion/approval annually. Sponsors and investigators should ensure that this occurs.



Consent procedures

Freely given written informed consent is required before any subject enters the trial and any trial-related assessments are undertaken (including those that would usually be conducted as part of normal clinical practice: if the data are recorded for the trial, they are considered trial-related!)

Each prospective subject must be provided with information verbally and in writing using an approved subject information sheet. In some countries (eg. the USA), the document may need to bear the stamp of the approving ethics committee.

ICH GCP Section 4.8.10 requires the information sheet to contain 20 items of information. The subject information sheet tends to be quite a long document, but should be presented in a simple, plain-language format.

Subjects should be given ample time to decide about the trial. They must not be coerced into participation. They are always free to withdraw from the study at any time, even though they initially gave consent to participate. It is good practice to check that the subject understands the information before he/she signs the consent form.

When subjects cannot consent for themselves (eg. children), are unable to read or write, or are mentally impaired, special consent procedures exist. These are laid down in national law. In these cases a witness or a legal representative may be required.



Updates to consent forms

If information becomes available during the course of a clinical trial that might affect the subject's willingness to participate – for example if a large number of serious adverse reactions become evident – the consent form should be updated and the subject informed of the new information. It might be necessary in these cases to suspend subject recruitment until the ethics committee has reviewed and approved the use of the updated information sheet and consent form. The sponsor should advise the investigator on how best to proceed in these circumstances.



Test your knowledge

- 1. According to GCP, how should the investigator show that he/she has the appropriate qualifications and experience to do the study?**
 - A) Providing an up-to-date, signed and dated CV
 - B) Providing a copy of the certificate of medical registration
 - C) Providing the CV used to obtain the current position
- 2. True or false? Trial sponsors are required to have insurance to cover the compensation of trial subjects in the event of product-related damage and also to indemnify investigators.**
- 3. How should a researcher become familiar with the investigational product to be used in a clinical trial?**
 - A) Undertaking a self-designed pilot study in a few patients prior to the study
 - B) Obtaining and reading the up-to-date Investigator's Brochure from the sponsor of the trial
 - C) Reading literature relevant to that therapeutic area
- 4. How does GCP require the informed consent of a trial subject to be obtained?**
 - A) Obtain written informed consent from each subject before they undertake any study-related procedures
 - B) Obtain verbal consent as long as this is undertaken before the study starts
 - C) Obtain consent once it has been determined that the subject is suitable for the study after undertaking baseline assessments