

THE CONCEPT AND IMPLEMENTATION OF GOOD CLINICAL PRACTICE IN TRIALS

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All clinical studies in humans have to be undertaken to a minimum standard, defined as good clinical practice.

This article explains the concept and how it is implemented in the drug development process

Scientific assessment and achievement of quality, safety and efficacy form the three main criteria that any company wishing to place a medicinal product on the market must satisfy. In the determination of the efficacy of a new compound, a series of clinical trials are carried out, whose purpose is to assess the risk:benefit ratio, at the later stages of development, against either a placebo or a well-established medicinal product.

Phase I clinical studies are carried out in 50 to 100 healthy volunteers who do not have the condition under investigation or any other illness. Initial doses will be as low as possible that will produce an expected effect. Only if there is no discernible effect will the dose be increased gradually.

Phase II studies represent the first occasion that the investigational product is given to patients with the actual condition that the product is intended to treat. In order to ascertain the correct dosage levels for therapeutic effects and unwanted side effects, the drug is given to different groups of patients

at different dosages. The number of patients treated in such trials is still relatively small, numbering between 200 and 400.

The major and most expensive stage of the clinical development programme is the Phase III study. To enable a valid statistical interpretation of the results, the trial may involve more than 3,000 patients, often in many different locations and even in different countries. Some patients are given the investigational drug; others, a placebo product or a known market leader. The trial is usually conducted "double-blind", which means that prescribers do not know which patients are being given the test product and which the placebo or market leader, and each group is switched during the trial. This ensures objective and statistical assessment of the treatment under investigation.

WHAT IS GOOD CLINICAL PRACTICE?

A minimum standard has been set for the performance of clinical trials that involve human subjects. Good clinical practice (GCP) ensures the validity of clinical trial data and covers the design, conduct, recording and reporting of clinical trials. It also ensures that the rights, welfare, and safety of subjects involved in trials are maintained and are consistent with the principles stated in

the World Medical Association Declaration of Helsinki, entitled "Ethical principles for medical research involving human subjects".

Guideline CPMP/ICH/135/95, entitled "Good clinical practice", was developed under the auspices of the International Conference on the Harmonisation of the Technical Requirements for the Registration of Human Pharmaceuticals (ICH process) and is applicable in the European Union, the United States and Japan. Clinical trial data that have been developed according to this guideline should therefore be acceptable by regulatory authorities in each of the three regions, together with Australia, Canada, the Nordic countries and the World Health Organization, which was also involved in its development.

The definition of GCP given in the guideline is: "A standard for the design, conduct, performance monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected."

Glossary A comprehensive glossary of terms used in the conduct of clinical trials is given in the guideline. It can be found at www.emea.eu.int/pdfs/human/ich/013595en.pdf

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THE PRINCIPLES OF ICH GCP

The basis for conducting a clinical trial is that there must be some likely benefit from doing so and that any potential risks associated with the trial are outweighed by the potential benefits. The trial is not conducted to advance science; the rights, well-being, and safety of trial subjects are the paramount considerations.

Preclinical studies Sufficient preclinical studies should have been carried out, covering both clinical and non-clinical aspects of the medicinal product under investigation, to understand what the expected effects of the product will be. The most important document for a clinical trial is the protocol: this must have been approved by the institutional review board (IRB) or independent ethics committee (IEC). (For convenience, the term IEC will be used in this article.)

Medical care Participants in the trial must be under the medical care of a qualified physician (or, where appropriate, a qualified dentist) whose training, education and experience must be adequate for the task assigned. Each subject must have indicated that they have freely given informed consent to participate in the trial.

Records Accurate recording, analysis and auditing of all clinical trial information is vital. Records that might identify subjects must be handled to maintain full confidentiality and in accordance with all current regulatory requirements. Equally importantly, the investigational products must be manufactured, handled, and stored in accordance with current good manufacturing practice (GMP), and in accordance with the written protocol.

INDEPENDENT ETHICS COMMITTEES

Independent ethics committees (IECs) exist to protect the well-being of subjects recruited into clinical trials and to ensure that the protocol is adequate and professional. To assess this, the IEC expects to be able to study the following documents:

- Trial protocol (and any amendments)
- Written informed consent forms
- Subject recruitment procedures
- Written information provided to potential subjects
- The investigator's brochure
- Available safety information
- Information about payments and compensation available to participants
- The investigator's curriculum vitae and proof of qualifications

Ongoing trials are reviewed by the IEC at intervals dependent upon the risk to subjects in the trial, but at least once a year.

The IEC has to determine whether the protocol for a trial with a non-therapeutic agent carried out with the consent of the subject's legally acceptable representative satisfies ethical concerns and relevant regulatory requirements. The IEC also has to

safeguard the well-being of a trial subject when prior consent to participate in the trial cannot be given.

Payments Payment for participation in a trial is a potentially problematic issue and the IEC must ensure that the amount and method of any payment agreed with participants is acceptable and reasonable. The payment also needs to be divided such that receiving the expected fee is not entirely dependent upon completion of the trial by the subject.

Membership of the IEC There must be a range of expertise present within the membership of the IEC that possesses the ability to assess the scientific, medical and ethical aspects of a trial. There should be at least five members, one of whom should have a primary interest in a non-scientific specialty, and one of whom must be independent of the trial site and organisation.

Operating procedures Organised and run like any well-constituted committee, the IEC must have written operating procedures, keep written minutes of meetings and decisions and comply with GCP and relevant regulatory requirements. A quorum must be present for any decisions taken, and only those who have been present and participated in the deliberations of the IEC can vote on any issues.

Written operating procedures should include details of the scheduling of meetings and the conduct and timing of trial reviews. The IEC must also determine that no modifications should be made to the trial protocol without its approval, other than when necessary to eliminate immediate dangers to the trial subjects or to make minor logistical changes (eg, an amendment to a telephone number). The IEC also defines what issues the investigator needs to report: these may include all adverse drug reactions (ADRs) and changes that need to be made to the conduct of the trial.

Records All relevant records must be kept by the IEC for at least three years after completion of the trial. The documentation must also be available to be reviewed by regulatory authorities.

THE INVESTIGATOR

The investigator must be adequately and appropriately qualified to be in charge of the trial, and be able to provide documentation to the sponsor, the IEC, and the regulatory authority, that supports this. He or she must also be thoroughly familiar with all aspects of the actions and effects of the investigational product being used in the trial. An awareness of GCP, and an ability to enforce it, is necessary; this includes allowing monitoring and auditing of the trial to take place.

Resources The resources available to the investigator must allow demonstration that sufficient subjects can be recruited into the trial within the agreed time, and that there is adequate time allowed for the effective con-

duct of the trial. A full range of support staff must be available, each of whom is fully trained and briefed on the protocol, the investigational product, and his or her duties.

Medical care of the subjects It is necessary for a qualified physician to be an investigator or sub-investigator for the trial and who can take all the trial-related medical decisions. There must also be adequate medical facilities to be able to deal with any adverse events. It is also normally expected that the trial physician will notify the subject's physician about the subject's participation in the trial (if the subject agrees and has a primary physician).

The investigator is responsible for regular communications with the IEC and for informing them of any untoward changes in the conduct of the trial. He or she is also responsible for ensuring that there is compliance with the approved protocol, and for ensuring that there are no deviations from it unless there is an urgent clinical need to do so, and the changes are approved retrospectively by the IEC.

Investigational product In theory, the investigator is also responsible for the investigational product and its accountability throughout the trial. In practice, this is usually delegated to a trial pharmacist. The pharmacist should keep records of the delivery of the product to the trial site, the stocks held at the site, the usage by each subject, and the return to the sponsor of any unused product. Safe and secure storage of the product is essential. The investigator, usually through the trial pharmacist, is also aware of the degree of randomisation of the trial and the procedures for "unblinding" the trial (eg, in the event of an adverse event or accidental revealing of the randomisation process).

Informed consent All ethical guidelines (eg, appropriate regulatory guidelines and the Declaration of Helsinki) must be followed in obtaining a subject's informed consent. There must be written procedures for a subject to give consent, which have been approved by the IEC. There must also not be undue coercion for a subject to participate in a trial.

Full information about the trial, and the approval given for it by the IEC, must be communicated to the subject before giving consent. This information should be presented in non-technical language, and any questions that the subject may have must be answered fully.

If the subject cannot give informed consent personally (eg, due to their medical condition or age), a legally acceptable representative can do so, accompanied by an impartial witness to the signing of the consent form if the legally acceptable representative cannot read the form.

Information that must be provided to a subject giving informed consent includes:

- Confirmation that the trial involves research

- The purpose of the trial and how a subject will be assigned to a group during the trial
- Those aspects of the trial that are experimental
- Those risks and benefits that can be reasonably foreseen in participating in the trial
- Compensation or treatment available should a trial-related injury arise
- Payments (and their interval) and expenses to be paid
- Confirmation that the participation in the trial is voluntary
- Recognition that the monitor, auditors, IEC and the regulatory authority will be given access to the subject's original medical records without violating their confidentiality
- The expected duration of the trial

In an emergency, where it is not possible to obtain the prior consent of the subject, that of the legally acceptable representative can be sought. When neither of these options is available, the subject can be enrolled in the trial following procedures laid down in the protocol that have been agreed by the IEC. In all cases, the safety and well-being of the subject are paramount, and there must be compliance with all regulatory requirements. Consent should be sought from either the subject or his or her legally acceptable representative at the earliest subsequent opportunity.

Records and reports Data are reported to the sponsor by the investigator using case report forms (CRFs), whose content must be consistent with the source documents. CRFs should be retained for future reference and measures taken to prevent their accidental destruction. They must be retained for at least two years after the last approval of a marketing authorisation application or at least two years after completion of clinical development of the investigational product. (They may need to be held for longer under the requirements of some national regulatory authorities.) All reports and records must be held available for inspection by the monitor, auditor, IEC, and regulatory authority.

Safety reporting The investigator must report all serious adverse events to the sponsor immediately, and follow up a verbal report with a written report. Adverse events must be reported using the unique code number assigned to a subject, maintaining confidentiality. In the event of death of a subject, further information (eg, autopsy reports) must also be forwarded by the investigator.

Premature termination or suspension of a trial If a trial is terminated, the investigator must notify the trial subjects and ensure that their continued medical treatment is appropriate; he must also inform the regulatory authorities concerned. Whether it is the investigator or sponsor that stops the trial, a detailed explanation must be given to the IEC.

THE SPONSOR

Quality assurance and quality control Written SOPs are required to ensure that trials are conducted in compliance with the protocol, GCP, and appropriate regulatory requirements. Similar constraints apply to the data generated, documented and recorded. Monitoring and auditing by the sponsor must be carried out at trial sites and all documentation must be made directly available to the sponsor. All interested parties must also allow inspections by their national and foreign regulatory authorities.

Contract research organisation Companies may delegate, under written agreements, some or all trial-related activities to a contract research organisation. Nevertheless, the ultimate responsibility for the trial and its conduct lies with the sponsor.

Medical expertise Appropriately qualified medical personnel, either employed directly by the sponsor or on a consultancy basis, must be made available by the sponsor to advise on trial-related medical problems.

Trial design The design of the trial, its conduct, and the protocol must be prepared under the guidance of the sponsor by appropriately qualified staff.

Trial management, data handling and record-keeping The conduct of the trial, and the preparation, verification and statistical analysis of the data, must be carried out by appropriately qualified staff. An independent data-monitoring committee may assess the trial's progress and offer advice to the sponsor on whether a trial should continue.

Trial data are increasingly being developed electronically, for which appropriate written safeguards and protocols must be generated. An audit trail must be achieved, especially to identify changes to the data, and there must be an adequate security system that controls and monitors personnel making changes.

If the sponsor discontinues a trial, all relevant documentation must be retained for at least two years after termination and the sponsor must notify the appropriate regulatory authorities of the decision. Documentation must also be retained for at least two years after the last approval of a marketing authorisation in an ICH region or until there are no pending or contemplated marketing authorisation applications in an ICH region.

Investigator selection Suitably qualified and trained investigators are selected by the sponsor under a written agreement. The investigator must agree to conduct the trial according to GCP and the relevant regulatory requirements, and using the written protocol approved by the sponsor and the IEC. There must be compliance with record-keeping requirements, and the investigator must permit monitoring, auditing and inspection.

Compensation to subjects and investigators Insurance or indemnity should be provided

by the sponsor against potential claims arising from the trial or from related activities. Any compensation payments made must be made in accordance with regulatory requirements.

Notification to regulatory authorities The sponsor is responsible for submitting the required applications to regulatory authorities before the trial starts.

Confirmation of review by the IEC The investigator must supply to the sponsor his name and address, written confirmation that operations are carried out according to GCP standards, and written proof of approval having been obtained from the IEC.

Manufacturing and packaging of the investigational product All investigational products used in the trial must be manufactured to GMP standards and coded to protect the blinding of the trial. Transport and storage conditions may need to be carefully controlled to prevent product deterioration, depending upon its physical characteristics. Should a medical emergency warrant it, the coding should be organised to allow rapid identification of the product's identity by an authorised person.

Supplying and handling the investigational product It is the sponsor's responsibility to supply the investigators with the trial product once all the preliminary documentation has been satisfactorily completed. Full details of the optimal transport and storage conditions must be explained by the sponsor to the investigator. All shipments must be fully documented and that documentation retained as one of the trial's essential documents.

Access to records The investigator must allow the sponsor direct access to the all documents needed to monitor the trial, audit, review by the IEC, and regulatory inspection.

Adverse drug reaction reporting Serious and unexpected ADRs must be notified by the sponsor to the investigator, the IEC, and where required, to the regulatory authority. Safety updates and periodic reports may also need to be submitted by the sponsor to the regulatory authority.

Monitoring Monitoring helps ensure that the rights and well-being of trial subjects are protected, that the data generated in the trial are valid and accurate, and that the trial is being conducted according to GCP requirements. Monitors must be appropriately qualified and be made fully aware of all aspects of the investigational product and the conduct of the trial. They are appointed by the sponsor in numbers that reflect the complexity and size of the trial and its endpoints. Monitors in effect act as liaison channels between the investigator and the sponsor, and ensure that the trial is carried out according to the sponsor's written instructions. The range of their functions may vary between trials but, in essence, they are responsible for verifying that:

- The investigator's qualifications and resources are adequate throughout the trial
- The trial product is stored and handled appropriately
- The protocol is being followed
- Informed consent has been obtained from all subjects
- The investigator has all documentation needed to carry out the trial in compliance with regulatory requirements
- Only eligible subjects are recruited into the trial and that sufficient numbers are available for the trial
- The accuracy and completeness of the CRFs for each subject
- All ADR reports and adverse event reports are fully documented
- All essential documentation is completed

Monitors have to prepare a written report for the sponsor after each trial site visit which outlines the significant facts and findings from the visit, any deficiencies and deviations from the protocol identified and any action that is required for the investigator to carry out.

Audit The process of audit carried out for the sponsor is independent of the trial's quality control procedures. The primary purpose of an audit is to evaluate the conduct of the trial and to ensure compliance with the protocol and all other written and regulatory procedures. It is the sponsor's responsibility to detail what is to be audited, how the audit is to be carried out, how frequently, and the structure and content of the audit report. These issues will be determined by the complexity of the trial, its size, and the potential risk to participants. Unless there is a problem of non-compliance with GCP, or legal proceedings require their release, it is usual for regulatory authorities not to request access regularly to audit reports. Not doing so helps maintain the independence and value of the audit function.

Non-compliance A sponsor must take prompt action to redress failure to comply with the protocol, SOPs, GCP and regulatory requirements by the investigator or institution. Should this non-compliance be persistent, their involvement in the trial must be terminated by the sponsor and this action reported to the regulatory authority.

Premature suspension or termination of a trial If for whatever reason a trial is suspended or terminated, the sponsor must notify those involved: the institution, investigator, regulatory authority and the IEC. It is still necessary for the sponsor to supply to the regulatory authority all the clinical trial reports.

Multicentre trials A sponsor of any trial that is carried out in a number of different locations, which may be spread over several countries or continents, has to ensure that all locations comply with all the above requirements.

CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENTS

The trial protocol is a crucial document, outlining all aspects of the trial and its performance. If any information is contained in other trial documents, these further documents must be cross-referenced to the trial protocol. The core information must include the following:

- General information
- Background information
- Trial objectives and purpose
- Trial design
- Selection and withdrawal of subjects
- Treatment of subjects
- Assessment of efficacy
- Assessment of safety
- Statistics
- Direct access to source data/documents
- Quality control and quality assurance
- Ethics
- Data handling and record keeping
- Financing and insurance
- Publication policy
- Supplements

More detailed information on the data required under each heading is given in Panel 1 opposite.

THE INVESTIGATOR'S BROCHURE

The investigator's brochure comprises a summary of the clinical and non-clinical data on the investigational product for the clinical trial. It is provided to the investigators, who are responsible for it being forwarded to the IEC. In essence, the brochure explains why the trial is taking place and why various critical aspects of the trial (eg, dose, methods of administration and safety monitoring procedures) have been selected. The brochure also details how the subjects enrolled in the trial should be managed clinically. When prepared in a simple and non-promotional way, it allows the investigating clinician to assess the potential risk/benefit of the trial.

The amount of information provided in the investigator's brochure will vary depending upon the stage of the development of the trial product. For a previously marketed and well-established product, there is usually need only for a brochure of limited scope and size. The brochure should also be updated at least once a year, or more frequently if new relevant information becomes available before annual updating.

The content of most sections of the investigator's brochure is self-explanatory. The summary should preferably not exceed two pages, but should cover all information available at the particular stage of development. The introduction should give the names of the product (chemical, generic, and trade), its pharmacological class, the potential advantages of the new product over existing therapies, why the research is being conducted and the product's likely indications.

Details of the formulation, including

excipients, are necessary to permit action in the event of a safety problem. Appropriate storage and handling guidelines should also be provided.

Studies carried out on non-clinical pharmacology, toxicology, pharmacokinetics and metabolism should be summarised. Data should include the species tested and the dose interval and duration. The finding should be evaluated.

Human studies already carried out should be explained and include information on pharmacodynamics, dose response, safety and efficacy. Countries in which the investigational product has already been marketed should be listed and any relevant findings from previous marketing explained.

Panel 1: Clinical trial protocol requirements

GENERAL INFORMATION

- Protocol title, identifying number, and date. Any amendments should also bear the amendment number and date
- Name and address of sponsor and monitor
- Name and title of the person(s) authorised to sign the protocol and any amendments for the sponsor
- Name, title, address and telephone number of the sponsor's medical expert for the trial
- Name and title of the investigator(s) who is/are responsible for conducting the trial and the address and telephone number(s) of the trial site(s)
- Name, title, address and telephone number of the qualified physician responsible for all trial-related medical decisions
- Name and address of the clinical laboratory and other medical and/or technical departments/institutions involved in the trial

BACKGROUND INFORMATION

- Name and description of the investigational product
- Summary of findings from non-clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial
- Summary of known and potential risks and benefits, if any, to human subjects
- Description of and justification for the route of administration, dosage, dosage regimen and treatment periods
- A statement that the trial will be conducted in compliance with the protocol, GCP, and applicable regulatory requirements
- Description of the population to be studied
- References to literature and data that are relevant to the trial and that provide background for the trial

TRIAL OBJECTIVES AND PURPOSE

- A detailed description of the objectives and purpose of the trial

TRIAL DESIGN

- A specific statement of the primary and secondary endpoints to be measured
- A description of the type and design of the trial (eg, double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedure and stages
- A description of the measures to be taken to minimise/avoid bias, including randomisation and blinding
- The trial treatment and the dosage and dosage regimen of the investigational product. A description of the dosage form, packaging and the labelling of the investigational product should also be given
- The expected duration of subject participation and a description of the sequence and duration of all trial periods, including any follow-up
- A description of the "stopping rules" or "discontinuation criteria" of individual subjects, parts of the trial and the entire trial
- Accountability procedures for the investigational product, including the placebo and comparator (if any)
- Maintenance of the trial randomisation codes and procedures for breaking codes
- The identification of any data to be recorded directly on the case report forms and to be considered to be source data

SELECTION AND WITHDRAWAL OF SUBJECTS

- Subject inclusion and exclusion criteria
- Subject withdrawal criteria and procedures specifying when and how to withdraw subjects from the trial, the type and timing of the data to be collected for withdrawn subjects, whether and how subjects are to be replaced and the follow-up for subjects withdrawn from the trial

TREATMENT OF SUBJECTS

- The treatment to be administered, including: name of the product; dose; dosing schedule; route and mode of administration; treatment period, including the follow-up period
- Medication and treatment allowed (including rescue medication) and not allowed before and during the trial
- Procedures for monitoring compliance

ASSESSMENT OF EFFICACY

- Specification of efficacy parameters
- Methods and timing for assessing, recording and analysing efficacy parameters

ASSESSMENT OF SAFETY

- Specification of safety parameters
- Methods and timing for assessing, recording and analysing safety parameters
- Procedures for eliciting reports of and recording and reporting adverse events and intercurrent illnesses
- The type and duration of the follow-up of subjects after adverse events

STATISTICS

- A description of the statistical methods to be used, including timing of any planned interim analyses
- The number of subjects planned to be enrolled. In multicentre trials, the number of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification
- The level of significance to be used
- Criteria for termination of the trial
- Procedure for accounting for missing, unused and spurious data
- Procedures for reporting any deviations from the original statistical plan
- The selection of subjects to be included in the analyses (eg, all randomised subjects, all dosed subjects, all eligible subjects, evaluable subjects)

DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

- The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator will permit trial-related monitoring, audits, IIEC review, and regulatory inspection, providing direct access to source data and documents

QUALITY CONTROL AND QUALITY ASSURANCE

ETHICS

- Description of ethical considerations relating to the trial

DATA HANDLING AND RECORD KEEPING

FINANCING AND INSURANCE

- If not addressed in a separate agreement

PUBLICATION POLICY

- If not addressed in a separate agreement

SUPPLEMENTS