Glossary and explanations

These explanations are listed to help the reader of the European Science Foundation Syllabus for Clinical Investigator Training. For a complete glossary list, see e.g. ICH-GCP.

ICH: International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use. A set of scientific and regulatory standards in clinical research on medicinal products agreed between EU, Japan and USA.

IB: Investigator's Brochure. A compilation of the clinical and non-clinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects.

CRF: Case Report Form. A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

GCP: Good Clinical Practice. 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.

GLP: Good Laboratory Practice. Principles for quality conduct of laboratory testing.

GMP: Good Manufacturing Practice. Principles for quality manufacturing conduct in producing drugs for human use.

SOPs: Standard Operating Procedures. Detailed, written instructions to achieve uniformity of the performance of a specific function.

Sponsor: An individual, company, institution, or organisation which takes responsibility for the initiation, management, and/or financing of a clinical trial.

The EC Clinical Trials Directive:
The European Union published in April 2001 a European Parliament and Council Directive 2001/20/EC regulating clinical trials with medicinal products. By May 2004, all Member States should have the Directive implemented in national regulations.

The Helsinki Declaration:
The basic ethics document which underpins human research. It is upheld by the World Medical Association and derives from the Code of Nuremberg. The last version (Edinburgh) is dated October 2000.

The investigators' responsibilities:
These are outlined in the Helsinki Declaration, the ICH-GCP, the EC Directive and in national regulations.

The Advisory Group

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Clinical Investigator Training

In 2001, as one development of its action in relation to clinical trials, the European Science Foundation (ESF) and its European Medical Research Councils (EMRC) Standing Committee set up an Advisory Group on Clinical Research Training to investigate the opportunity and feasibility of developing a European basic education and training programme on the conduct of clinical trials.

This programme should include all types of intervention in any therapeutic area, in private practice as well as in public sector. It should also be based on the ethical principles stated in the Declaration of Helsinki and the Good Clinical Practice principles as defined by the International Conference on Harmonisation (ICH-GCP) and the EC Clinical Trials Directive (2001/20/EC)).

The ESF Advisory Group decided first to carry out a European survey of training in clinical research to evaluate the current level of teaching and need for further education of clinical investigators.

The responses to the questionnaire, which was sent to ESF Member Organisations, identified a major need for training courses in clinical research. According to the result of this questionnaire, such courses should preferably be organised at the national level and lead ultimately to certification, so that this training can be recognised as an essential step in ensuring qualification of clinical investigators. The optimal duration should be 3 to 5 days.

Taking these findings into account, the Advisory Group decided to move forward in establishing a syllabus for a common basic training course for clinical investigators and ethics committee members, to be promoted by ESF as a guide for its Member Organisations. It also decided to further investigate the e-based learning approach as one powerful tool to provide such training with the ultimate goal to develop a European certification process.

In autumn 2002, the Advisory Group proposed a final draft of an ESF European Syllabus for Clinical Investigator Training that was then approved by the EMRC Standing Committee and the ESF Executive Board. This syllabus covers seven areas. The intention is to define a common ground of ethical values, scientific and quality assurance principles covering all types of clinical trials, from which countries and universities can build individualised courses.

A European Syllabus for Training Clinical Investigators

Section 1
A critical review of the trial concept

- The rationale of the trial
- Stages and milestones
- Clinical / public health importance

The rationale of the trial must be detailed, and the design must address the specific question according to present state of knowledge. The study should be put into a clinical practice context, and its hypothesis carefully defined.

Section 2
Clinical trial design

General issues

- Type of design and rationale
- Protocol and Case Report Form (CRF)
- Use of control groups / active substance and placebo
- Inclusion / exclusion criteria
- Efficacy and choice of endpoints
- Safety outcomes
- Quality of life / health economics, if appropriate

Statistical issues

- Fundamentals of statistical testing
- Power & sample size determination
- Superiority or equivalence

Special populations

- Children / elderly
- Pregnant women / foetuses
- Renal / liver failure
- Ethnic factors
- Gender

The design should be outlined. What control groups are appropriate, what type of statistical testing is planned, and is the sample size adequate? What are the differences between superiority, equivalence and non-inferiority studies? What safety issues should be identified? The course must help the investigator to identify general and specific issues for trial design.

Section 3
Ethical issues

- Values and principles in clinical investigations
- International guidelines
- Patient care in clinical research
- Responsibilities in research
- Conflict of interest
- Ethical review
- Informed consent
- Vulnerable populations
- Biological samples
- Genetic research
- Databases and confidentiality
- Fraud & misconduct

Depending on the population studied and the type of study, the clinical trial may need to address different ethical issues, e.g. in genetic research, when taking / storing biological samples, or in exportation of data outside the EU.

Section 4
Study organisation

- Clinical trial registration
- Selection of investigators
- Organisation and delegation in the investigation team
- Flow chart
- Internal and external communication
- Contracts and agreement
- Liability and insurance
- Essential and other required documents
- Logistics
- Responsibilities for the development of the intervention (medicinal products, medical device, etc.)
- Data management
- Clinical trial committees

The success of a trial is largely dependent on its organisation. There must be an organised flow of information between the principal investigator and the sponsor, the Ethics Committee, the national regulatory authority, if appropriate, other investigators and participants. Logistics including handling of informed consent procedures, eligibility, randomisation, drug accountability and data flow should be established before the study starts. Involvement of other parties (e.g. pharmacies) should be considered.

Section 5
Legal, regulatory and good practice framework

- Regulatory and legal frameworks
- Good Clinical Practice according to ICH and EU Clinical Trials Directive
- National regulations
- Application to Regulatory Agency, if appropriate
- Quality assurance systems
- Standard Operating Procedures (SOPs)
- Audits and inspections

Established quality assurance systems are crucial for the integrity of the study. They should adhere to national and international regulations and cover, when appropriate, GLP – good laboratory practice, GMP – good manufacturing practice, GCP – good clinical practice.

Section 6
Study conduct

- Investigator's brochure or equivalent
- Study monitoring
- Safety monitoring and reporting
- End-of-trial issues

The successful conduct of the study depends on all team members, their competence and understanding of the intervention. An appropriate level of quality assurance and monitoring is essential to ensure high quality of data and procedures in the study. This is based on an on-going and continuous review of the accuracy and completeness of the data.

Section 7
Reporting clinical trials

- Completeness of follow-up
- Data analysis issues
- Primary outcome analysis
- Exploratory analysis
- Clinical study report
- Communication & publication of study results

Reporting of the study must be agreed beforehand in writing with investigators and sponsors. The report should address the question in the primary hypothesis and include exploratory analyses only as hypothesis generating. Missing data and incomplete follow-up should be reported. Negative results should be made public.