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# Detailed Guidelines on the principles of good clinical practice in the conduct in the EU of clinical trials on medicinal products for human use

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**Detailed Guidelines on the principles of good clinical practice in the conduct in the EU of clinical trials on medicinal products for human use**

## 1 Introduction

All clinical trials on medicinal products for human use should be designed, conducted, recorded and reported according to the principles of good clinical practice. This guideline clarifies the principles of good clinical practice in the conduct in the European Union of clinical trials on medicinal products for human use. It should be read in conjunction with Directive 2001/20/EC[1] and its other implementing texts[2]. In conducting clinical trials in the EU, sponsors and investigators shall also take into account the Community guidelines relating to the quality, safety and efficacy of medicinal products for human use and updates as adopted by the Committee for Proprietary Medicinal Products and published by the Agency, in particular the note for guidance on Good Clinical Practice (CPMP/ICH/135/95), which contains much important detail.

## 2 Legal Basis

Article 1.3 of Directive 2001/20/EC requires that the principles of good clinical practice and detailed guidelines in line with those principles be adopted and, if necessary, revised to take account of technical and scientific progress. The Commission is required to publish these detailed guidelines.

## 3 Scope

These detailed guidelines apply to all clinical trials on investigational medicinal products for human use conducted within the EU. They do not apply to non-interventional trials**.** The guidelines apply to the design, conduct, recording and reporting of such trials, the protection of the subject and the credibility of the trial data.

## 4 Principles of GCP

These principles apply to all clinical trials, as defined by Directive 2001/20/EC, that are conducted in the EU. In relation to clinical trials involving minors or incapacitated adults not able to give informed legal consent the relevant provisions of Articles 4 and 5 of Directive 2001/20/EC also apply.

4.1 Clinical trials should be conducted in accordance with the ethical principles that for instance are reflected in the 1996 version of the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

4.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and present and future patients. A trial should be initiated only if the anticipated therapeutic and public health benefits justify the risks and continued only if compliance with this requirement is permanently monitored. Continuing review of each ongoing trial should be conducted at intervals appropriate to the degree of risk to the subjects.

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[1] Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use

[2] See Annex 1

4.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

4.4 The available nonclinical and clinical information on an investigational medicinal product should be adequate to support the proposed clinical trial.

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

4.6 A trial should be conducted in compliance with the protocol that has received a prior favourable opinion from an independent ethics committee and in respect of which the competent authority has not issued any grounds for non-acceptance.

4.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of an appropriately qualified doctor or, when appropriate, of a qualified dentist.

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

4.9 The informed consent of the trial subject or, in the case of a minor, the parents or legal representative or, in the case of an incapacitated adult not able to give informed consent, the legal representative should be obtained before that subject participates in a clinical trial.

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

4.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with Directive 95/46/EEC.

4.12 Investigational medicinal products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

4.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

## 5 Ethics Committee

Directive 2001/20/EC requires the Member States to take the measures necessary for the establishment and operation of Ethics Committees. In doing so, the responsibilities, composition, functions, and operations of the Ethics Committees and the rules for record keeping should be set out. The Ethics Committee should establish, document in writing, and follow its procedures. In the case of multi-centre clinical trials carried out in one or more Member States simultaneously, Member States shall establish a procedure for the adoption of a single Ethics Committee opinion for each Member State.

One of the responsibilities of the Ethics Committee is to safeguard the rights, safety and well-being of all trial subjects and to provide public assurance of that protection by, among other things, expressing an opinion on the trial protocol, the suitability of the investigators and the adequacy of the facilities, and on the methods and documents to be used to inform trial subjects and obtain their informed consent. Special attention should be paid to trials that may

include vulnerable subjects. Additional safeguards applicable to such trials are set out in articles 4 and 5 of Directive 2001/20/EC.

Efficient systems should be put in place for the communication of information between the Ethics Committees and the competent authorities.

## 6 Investigator

The investigator should take into account the relevant Community guidelines with respect to qualifications and agreements, adequate resources, medical care of trial subjects, communication with the Ethics Committee, compliance with the protocol, investigational medicinal product(s), randomisation procedures and unblinding, informed consent of trial subjects, records and reports, progress reports, safety reporting, premature termination or suspension of the trial, and the final report by the investigator.

With respect to informed consent, according to Directive 2001/20/EC, a clinical trial can only be undertaken if the trial subject or, when the person is not able to give informed consent, his legal representative has given his written consent after being informed of the nature, significance, implications and risks of the clinical trial. If the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation. The notion of legal representative refers back to existing national law and consequently may include natural or legal persons, an authority and/or a body provided for by national law.

## 7 Sponsor

The sponsor should take into account the relevant Community guidelines with respect to quality assurance and quality control, contract research organisations, medical expertise, trial design, trial management, data handling and record keeping, investigator selection, allocation of duties and functions, compensation to subjects and investigators, financing, submission to regulatory authorities, confirmation of review by Ethics Committees, information on the investigational medicinal product(s), manufacturing, packaging, labelling and coding of investigational medicinal products, supply and handling of investigational medicinal product(s), record access, safety information, adverse drug reaction reporting, monitoring, audit, noncompliance, premature termination or suspension of a trial, clinical trial reports and multicentre trials.

A sponsor may transfer any or all of his trial-related duties and functions to a Contract Research Organisation (CRO) or other body. In such cases the provisions of these detailed guidelines apply to the CRO or other body to which any trial-related duties or functions have been transferred. The ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor.

## 8 Clinical Trial Protocol and Protocol Amendments

The contents of a trial protocol should generally include the following topics: general information, background information, trial objective 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, financial and insurance matters, publication policy, supplements. Site specific information may be provided on separate protocol page(s), or

addressed in a separate agreement, and some of the above information may be contained in other protocol referenced documents, such as an Investigator's Brochure.

## 9 Investigators' brochure

The Investigator's Brochure is a compilation of the clinical and nonclinical data on the investigational medicinal product(s) that are relevant to the study of the product(s) in human subjects. The information should be presented in a concise, simple, objective, balanced and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her unbiased risk-benefit assessment of the appropriateness of the proposed clinical trial. A summarised style is also required for any update of this document. The following minimum information should be included in an investigator's brochure: general considerations (title page, confidentiality statement), contents of the investigator's brochure (table of contents, summary, introduction, physical, chemical and pharmaceutical properties and formulation, nonclinical studies – nonclinical pharmacology, pharmacokinetics and product metabolism in animals, toxicology [single dose, repeated dose, carcinogenicity, special studies, reproductive toxicity, genotoxicity], effects in humans- pharmacokinetics and product metabolism in humans, safety and efficacy, marketing experience, summary of data and guidance for investigator.)

## 10 Essential Documents for the Conduct of a Clinical Trial

10.1 Before the clinical phase of the trial commences the following documents should be generated and should be on file before the trial formally starts:

| Title | | Location in files of | |
|---|---|---|---|
| | | Investigator/ institution | Sponsor |
| 10.1.1 | investigator's brochure or current Summary of Product Characteristics, if product is marketed in the EU | x | x |
| 10.1.2 | signed protocol and amendments, if any, and sample case report form (CRF), | x | x |
| 10.1.3 | information given to trial subject (and/or to parent or legal representative if unable to give informed consent), | x | x |
| 10.1.4 | financial aspects of the trial, | x | x |
| 10.1.5 | insurance statement, | x | x |
| 10.1.6 | signed agreements between involved parties, | x | x |
| 10.1.7 | dated, documented favourable opinion of independent ethics committee of | x | x |
| 10.1.7.1 | the protocol and any amendments, | | |
| 10.1.7.2 | CRF (if applicable), | | |
| 10.1.7.3 | informed consent form(s), | | |
| 10.1.7.4 | any other written information to be provided to the subjects (and/or to parent or legal representative if unable to give informed consent), | | |
| 10.1.7.5 | advertising for subject recruitment (if used), | | |
| 10.1.7.6 | subject compensation (if any), | | |
| 10.1.7.7 | any other documents given | | |

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| | approval/favourable opinion, | | |
| 10.1.8 | ethics committee composition, | x | x (where required) |
| 10.1.9 | regulatory authority(ies) authorisation/ notification of clinical trial authorisation request | x | x |
| 10.1.10 | curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub-investigator(s), | x | x |
| 10.1.11 | normal value(s)/range(s) for medical/ laboratory/technical procedure(s) and/or test(s) included in the protocol, | x | x |
| 10.1.12 | medical/laboratory/technical procedures /tests, | x (where required) | x |
| 10.1.13 | sample of label(s) attached to investigational medicinal product container(s), | | x |
| 10.1.14 | instructions for handling of investigational medicinal product(s) and trial-related 10.1.17 materials (if not included in protocol or investigator's brochure), | x | x |
| 10.1.15 | shipping records for investigational medicinal product(s) and trial-related materials, | x | x |
| 10.1.16 | certificate(s) of analysis of investigational medicinal product(s) shipped, | | x |
| 10.1.17 | decoding procedures for blinded trials, | x | x |
| 10.1.18 | master randomisation list, | | x($3^{rd}$ party if applicable) |
| 10.1.19 | pre-trial monitoring report, when applicable | | x |
| 10.1.20 | trial initiation monitoring report, when applicable | x | x |
| 10.1.21 | List of appropriately qualified persons to whom the investigator has delegated significant trial-related duties | x | x |

10.2 During the clinical conduct of the trial, in addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available:

| Title | | Location in files of | |
|---|---|---|---|
| | | Investigator/ institution | Sponsor |
| 10.2.1 | investigator's brochure updates, | x | x |
| 10.2.2 | any revision to: | x | x |
| 10.2.2.1 | protocol/amendment(s) and CRF, | | |
| 10.2.2.2 | informed consent form, | | |
| 10.2.2.3 | any other written information provided to subjects (and/or to parent or legal representative if unable to give informed consent), | | |
| 10.2.2.4 | advertisement for subject recruitment (if | | |

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| used), | | |
| 10.2.3 dated, documented favourable opinion of ethics committee of the following: | x | x |
| 10.2.3.1 substantial protocol amendment(s), | | |
| 10.2.3.2 revision(s) of: | | |
| 10.2.3.2.1 informed consent form, | | |
| 10.2.3.2.2 any other written information to be provided to the subject (and/or to parent or legal representative if unable to give informed consent), | | |
| 10.2.3.2.3 advertisement for subject recruitment (if used), | | |
| 10.2.3.2.4 any other documents given approval/favourable opinion, | | |
| 10.2.3.2.5 continuing review of trial (where required), | | |
| 10.2.4 regulatory authority(ies) authorisations for: | x (where applicable) | x |
| 10.2.4.1 substantial protocol amendment(s) and other documents, | | |
| 10.2.5 curriculum vitae for new investigator(s) and/or sub-investigator(s), | x | x |
| 10.2.6 updates to normal value(s)/range(s) for medical/ laboratory/ technical procedure(s)/ test(s) included in the protocol | x | x |
| 10.2.7 updates of medical/laboratory/ technical procedures/tests, | x (where required) | x |
| 10.2.8 documentation of investigational medicinal product(s) and trial-related materials shipment, | x | x |
| 10.2.9 certificate(s) of analysis for new batches of investigational medicinal products, | | x |
| 10.2.10 monitoring visit reports, | | x |
| 10.2.11 relevant communications other than site visits, | x | x |
| 10.2.12 signed informed consent forms, | x | |
| 10.2.13 source documents, | x | |
| 10.2.14 signed, dated and completed case report forms (CRF), | x (copy) | x (original) |
| 10.2.15 documentation of CRF corrections, | x (copy) | x (original) |
| 10.2.16 notification by originating investigator to sponsor of serious adverse events and related reports, | x | x |
| 10.2.17 notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and ethics committees of unexpected serious adverse drug reactions and of other safety information, | x (where required) | x |
| 10.2.18 notification by sponsor to investigators of safety information, | x | x |
| 10.2.19 interim or annual reports to ethics committees and authority(ies), | x | x (where |

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| | | required) |
| 10.2.20 subject screening log, | x | x (where required) |
| 10.2.21 subject identification code list, | x | |
| 10.2.22 subject enrolment log, | x | |
| 10.2.23 investigational medicinal products accountability at the site, | x | x |
| 10.2.24 signature sheet, | x | x |
| 10.2.25 record of retained body fluids/ tissue samples (if any) | x | x |
| 10.2.26 any update to the list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties | x | x |

10.3 After completion or termination of the trial, all of the documents identified above should be in the file together with the following:

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|---|---|---|
| 10.3.1 investigational medicinal product(s) accountability at site, | x | x |
| 10.3.2 documentation of investigational medicinal product destruction, | x (if destroyed at site) | x |
| 10.3.3 completed subject identification code list, | x | |
| 10.3.4 audit certificate (if available), | | x |
| 10.3.5 final trial close-out monitoring report, | | x |
| 10.3.6 treatment allocation and decoding documentation, | | x |
| 10.3.7 final report by investigator to ethics committee where required, and where applicable, to the regulatory authority(ies), | x | |
| 10.3.8 clinical study report. | x (if applicable) | x |

## 11 Competent authority

It is the responsibility of the competent authorities to implement provisions for the commencement and suspension of clinical trials and for the management of any infringements, according to Article 9 of Directive 2001/20/EC. It is also their responsibility to establish their rules of operation and procedure.

The competent authorities of the Member States are responsible for conducting inspections of the sites concerned by any clinical trial conducted to verify compliance with the provisions on good clinical and manufacturing practice.

Annex 1

**List of implementing texts of Directive 2001/20/EC (in development)**

- Detailed guidance on the application format and documentation to be submitted in an application for an ethics committee opinion on a clinical trial on a medicinal product for human use ENTR/6417/01
- Detailed guidance on the submission to competent authorities of a request for authorisation of a clinical trial on a medicinal product for human use ENTR/6418/01
- Detailed guidance on the European clinical trials database ENTR/6421/01
- Detailed guidance on the database of Suspected Unexpected Serious Adverse Reactions ENTR/6101/02
- Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use ENTR/6422/01
- Detailed guidelines on the trial master file and archiving
- Detailed guidelines on the qualifications of inspectors who should verify compliance in clinical trials with the provisions of good clinical practice for an investigational medicinal product
- Detailed guidelines on inspection procedures for the verification of GCP compliance
- Detailed guidelines on the qualifications of inspectors who should verify compliance in clinical trials with the provisions of good manufacturing practice for an investigational medicinal product
- Detailed guidelines on inspection procedures for the verification of GMP compliance
- Detailed guidelines on the Community basic format and the contents of the application for a manufacturing and/or import authorisation of an investigational medicinal product for human use
- Commission Directive on the requirements to obtain an authorisation to manufacture or import an investigational medicinal product and the requirements to be met by the holder of this authorisation
- Revised Annex 13 Manufacture of investigational medicinal products, Volume 4 of the rules governing medicinal products in the European Union
- Commission Directive 91/356/EEC as amended