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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

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1. Introduction

This detailed guidance should be read in the light of the requirements of Directive 2001/20/EC[1]. It is a requirement of the Directive that a clinical trial on a medicinal product for human use may not start until the appropriate Ethics Committee has issued a favourable opinion. This detailed guidance is intended to provide advice on the documents that should be submitted in an application for an ethics committee opinion on a proposal to undertake such a trial. It is intended to form the basis for the format and content of a submission for an Ethics Committee opinion, and should be followed unless otherwise justified.
The Community guideline on Good Clinical Practice (CPMP/ICH/135/95) as adopted by the Committee for Proprietary Medicinal Products and published by the Agency provides useful additional guidance on Ethics Committees and other relevant issues.

2. Legal Basis

Article 8 of Directive 2001/20/EC requires the Commission, in consultation with Member States and interested parties, to draw up and publish 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, in particular regarding the information that is given to subjects, and on the appropriate safeguards for the protection of personal data. This detailed guidance is intended to fulfil the obligations laid down in this article.

The Directive also requires certain documents to be submitted to the Ethics Committee for consideration or information during the conduct of and at the termination of the trial.

3. Scope

This detailed guidance applies to the format and accompanying documentation of the application for an Ethics Committee opinion on a clinical trial on a medicinal product for human use before commencing a trial.
If substantial amendments to the protocol are requested after the start of the trial the Ethics Committee is required to give its opinion on the proposed changes. The documentation to be submitted to the Ethics Committee in such cases is also described in this guidance.
This detailed guidance also covers the documentation to be forwarded to the Ethics Committee during the conduct and at the termination of the trial to allow the Ethics Committee to fulfil its obligations according to the Directive and the principles of GCP.
The documentation that the competent authority should forward to the Ethics Committee according to Directive 2001/20/EC is also outlined.

4. Definitions

The definitions which are provided in Directive 2001/20/EC are applicable.

5. Contacts with the Ethics Committee.

The documentation to be submitted to the Ethics Committee is outlined in this detailed guidance. However, the Ethics Committee may request any additional documentation or

[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

information that it may need to fulfil its responsibilities according to the principles of Good Clinical Practice.

When there is more than one trial site in a Member State, the relevant procedure established in the Member State should be followed to obtain a single Ethics Committee opinion for that Member State.

Attachment 1 to this detailed guidance lists contact points in the different Member States where information can be obtained on the national systems and procedures in the different Member States.

5.1. Before commencement of a clinical trial.
The applicant shall submit a valid application to the Ethics Committee. The applicant may be the sponsor or his legal representative in the EU and/or the investigator as defined in national regulations.

For research at a single site, the application may be signed either by the sponsor or by the principal investigator responsible for the conduct of the trial at the site according to regulations in each Member State. In the case of multi-centre trials in a Member State the application may be signed either by the sponsor or by the investigator responsible for co-ordinating the conduct of the trial in that Member State according to national or local regulations.

The Ethics Committee shall give its opinion within the scope of its responsibilities as defined in the Directive and in accordance with national regulations, having reviewed the same version of the documents that is reviewed by the competent authority In some Member States the Ethics Committee reviews the Investigational Medicinal Product Dossier while in others this task is undertaken by the competent authority.

5.2. During conduct of a clinical trial.
The sponsor is obliged by Directive 2001/20/EC to inform the Ethics Committee of substantial amendments to the protocol and to submit scientific documents in support of such amendments. The Ethics Committee shall give its opinion after review of the same version of the documentation that is reviewed by the competent authority.

According to Directive 2001/20/EC and the principles of Good Clinical Practice, the Ethics Committee should have established procedures for conducting further review of the trial . Depending on the national regulations this might include requesting and reviewing reports on the conduct and outcome of the trial, to be submitted at defined intervals based on the complexity and type of trial.

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5.3. After termination or end of the trial.
According to Directive 2001/20/EC, the Ethics Committee should receive a detailed written explanation of the reasons for an early termination of a trial. In any event, at the end of the trial as defined in the protocol, the Ethics Committees should be notified in accordance with Directive 2001/20/EC. The same procedures and format/content should be followed as are outlined in the detailed guidance for a request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities in the European Union ENTR/6303/02.

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6. Documentation to be supplied.

A valid application must contain the documents listed in table 1, unless otherwise justified with a reason(s) acceptable to the Ethics Committee. When an application is not valid the Ethics Committee will inform the applicant and give the reasons.

Table 1. Documentation to be supplied to request an Ethics Committee opinion on a clinical trial

- ❑ Covering letter
- ❑ Application form (including EUDRACT clinical trial number)
- ❑ Clinical trial dossier
  - – Investigator's Brochure
  - – Complete protocol with amendments to date
  - – Protocol summary
  - – Informed consent form
  - – Subject information leaflet
  - – Provision for indemnity or compensation to trial subjects (according to national requirements)
  - – Insurance or indemnity for liability of sponsor and investigator (according to national requirements).
  - – Financial arrangements: compensations to investigators and subjects and agreement sponsor/site (according to national requirements)
  - – Documentation on subject recruitment procedures, including
    - o advertisements, video tapes, etc. to be used for recruitment,
    - o procedure for obtaining informed consent
  - – Questionnaires/diaries etc. to be handed out to subjects. Sample case report forms (CRF)
  - – Documentation on suitability of investigator and supporting staff, including
    - o Curriculum Vitae of investigator and key personnel
    - o declaration of sources of funding and possible conflicts of interest
  - – Publication policy and investigators access to data, if the agreement is not in the protocol
  - – Documentation on suitability of site and adequacy of facilities
  - – Copy of competent authority authorisation, if available
  - – Previous peer review, when applicable
- ❑ Investigational medicinal product dossier (IMPD), if not considered by the Competent Authority

Under certain circumstances and according to national requirements an abridged application might be sufficient. If an Ethics Committee already has substantial information from a previous related application from the same applicant, to which cross-reference can be made, an abridged application might be sufficient, according to national requirements.

6.1. Submission before the commencement of the trial.

A. The application form

An application form may be composed of modules, some of which may be common for all Member States according to national regulations.
Before submitting the application to the ethics committee, the applicant should obtain the EUDRACT identification number for the clinical trial. The procedure for allocating this number is described in the detailed guidance on the European clinical trials database (ENTR/6421/01). This number is also required for the submission of the application to the competent authority.

Four modules are proposed.

Module 1 contains administrative information about the trial, the investigational medicinal product(s) and the sponsor. This module contains the same information as is required in the request for authorisation by the competent authority in each Member State. It is suggested that an identical module should be used by Ethics Committees, to ensure consistency of information across Member States, and between the competent authority and Ethics Committee within each Member State.

Module 2 contains details about the design of the trial as required by the competent authority. All the required information and documents listed here should form the basis of a module in the application form for submission to the Ethics Committee.

Module 3 and 4 are tentative and presented only to provide guidance on possible ways to present trial and site specific information from the applicant to the Ethics Committee and from the Ethics Committee to the competent authority.

Module 3 gives a list of examples of topics and issues on which the Ethics Committee might require information from the applicant before reaching its opinion. The list is intended to provide guidance only, is not complete and should be modified by Member States according to the trial protocol and the responsibilities assigned by them to their Ethics Committees.

Module 4 provides a tentative format for the Ethics Committee decisions. This module might also be sent to the competent authority to inform them of the Ethics Committee opinion. It might also be used for entry of this opinion into the European database by the competent authority.

The proposed system is further outlined in Attachment 2.

In some Member States, the national regulations may require that the Ethics Committee should be informed that the project has been submitted to and/or reviewed and approved by other parties. This might be the case when for example X-rays, isotopes, xeno-transplants or stem cells are to be used, or when a scientific review board of a funding institution or other body has to review the protocol.

B. The investigational medicinal product

The application form contains the information required to identify the investigational medicinal product(s), the formulation(s) and strength(s), dose(s) and treatment period(s).

Information on the investigational medicinal product is also provided in the Investigator's Brochure. This should be prepared from all the available information and evidence that supports the rationale for the proposed clinical trial and the safe use of the investigational medicinal product in the trial. When the investigational medicinal product has a marketing authorisation in the EU and the product is to be used in the same authorised conditions, the Investigator's brochure could be the authorised SPC.

According to national requirements, the Ethics Committee might additionally have to request and review the more extensive pharmaceutical and pre-clinical documentation included in the Investigational Medicinal Product Dossier (described in the detailed guidance on the submission to the competent authorities of a request for authorisation of a clinical trial ENTR/6418/01) when this information is not reviewed by the Competent Authority.

C. The clinical trial protocol

The trial protocol should be identified by: the title, a sponsor's code unique for all versions of it, a number and date of version that will be updated with the inclusion of amendments, and, if available, by a short title or name. It should be dated and signed by the sponsor and principal investigator at the site. In multi-centre trials the co-ordinating investigator responsible for the application to the Ethics Committee should be the investigator who signs the protocol submitted according to the national system.

The protocol should contain the information outlined in the detailed guidelines on GCP (ENTR/ 6416/01). There should also be a description of the plan for the provision of any additional care of the subjects once their participation in the trial has ended, where it differs from that normally expected according to their medical condition.

In those cases where the publication policy and the investigators' access to the data is declared in an agreement separate from the protocol, this agreement should be made available to the Ethics Committee for review.

The review of information on financial transactions, insurance, indemnity and compensation, might be the responsibility of the competent authority, according to national provisions.

D. Recruitment arrangements.

The procedures for enrolment of subjects should be described in detail in the study protocol. This description as well as the reasons for selection of the subject group is of special importance in studies where subjects are included who are not able to give their informed consent.

When recruitment of subjects is planned to be by advertisement, the procedure(s) should be described in the submission. Copies of the material to be used should be appended, including any printed materials, recordings or videotapes. The procedures proposed for taking care of subjects responding to advertisements should be stated, including arrangements for the subjects found not to be suitable for inclusion in the planned trial. Further guidance and information on issues that might be relevant to consider depending on the type of trial and advertisement are given in Appendix1.

E. Information to be provided to potential trial subjects and the informed consent procedure.

All information to be provided to the subjects (and/or, where appropriate, the parents/guardian/legal representative) before their decision to participate or abstain from participation should be submitted together with the form for written informed consent. The information should be based on the elements sets out in the Community guideline on Good Clinical Practice (CPMP/ICH/135/95). There should also be a description of the arrangements for taking care of the subjects after their participation in the trial has ended, where it differs from that normally expected according to their medical condition. All documents should carry the trial identification (protocol identity and date and/or version).

The information sheets given to the subject and/or the parent/guardian/legal representative should be kept short, clear, relevant, and understandable to a lay person. They should be in a language the subject knows. It might sometimes be useful to divide the information to be provided in two parts. One part should contain the information necessary for the subject to decide whether or not to participate in the planned trial. It could focus on the information specific for the planned trial and only contain information related to general issues and systems such as protection of privacy, insurance etc. as is relevant to the trial in question. The second part should contain general information common to trials in the Member State. It might address and explain in more detail the national systems for the protection of the rights, welfare and safety of the subjects, the need for Source Data Verification (SDV) and measures to protect the confidentiality of personal information, systems for labelling, analysing and publishing data and availability of insurance/indemnity systems. This general second part, once approved by the Ethics Committee, could be used where appropriate in similar trials in that Member State.

In cases where minors or incapacitated subjects are to be included, two sets of information sheets might be needed according to national regulations. In addition to the information given to the subject's parent, guardian or legal representative, the subject should be given information according to his/her capacity to understand, including where appropriate a statement that the subject's decision to withdraw from a trial will be respected, even if consent is given by the parent/guardian/legal representative.

The measures taken to safeguard the subject's privacy and the protection of personal data should be described. This includes information on how the identity of the subject, biological material obtained from the subject and any recorded data will be coded, stored and protected. Information should be given about the person(s) who will have access to the code list, where the list will be kept and for how long and who will be responsible for keeping and destroying it. The information should address the right of the subject to ask for updated information on what data are recorded, to require corrections of errors, and to know who will be responsible for keeping the data and who will have access to them in keeping with Directive 95/46/EEC[2]. The information should include a statement that the consequence of the subject's withdrawal of consent will be that no new information will be collected from the subject and added to existing data or a database. The subject should be informed of the possibility to withdraw consent and to require that all previously retained identifiable samples will be destroyed to prevent future analyses, according to national provisions.

[2] Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data

In clinical trials where genetic testing is included, this should be clearly explained to the subject. The information should give the background and purpose of the genetic tests, the planned analyses and whether the samples will be kept to make future analyses possible in conjunction with the planned project. When applicable the information on the genetic part of the trial might be separate and contain information about the possibility for the subject to abstain from the genetic testing but still participate in the clinical part of the trial, according to national recommendations.

When analyses are planned for research on new aspects/genes, information should be provided that the investigator might have to ask for a new consent and that the subject has the right to refuse further analyses, according to national rules.

Information should be provided on the contact point where additional information about the trial can be obtained, according to the system in the Member State. In addition the procedures at the research site for giving information to potential subjects and for obtaining their informed consent should be described.

The form to be used to verify that information has been given and that the trial subject has consented should contain at least three elements.

- Consent to participate in the trial,
- Consent to make confidential personal information available (direct access) for quality control and quality assurance by relevant personnel from the sponsor, a nominated research organisation on behalf of the sponsor, and inspection by the competent authority or, if applicable, the Ethics Committee.
- Consent to archive coded information, and for its transmission outside the EU if applicable.

In trials with minors or incapacitated subjects the procedures to obtain assent/consent from the minor or incapacitated subject, where appropriate, as well as from the parent, guardian or legal representative should be described. When a procedure with witnessed consent is to be used, the procedure for the selection of witness and the procedure to be used for information and consent should be stated. When unconscious or temporarily incapacitated patients are included, the information to be given and the procedure to be used to obtain consent if/when the patients regain the capacity to consent should be outlined.

Appendix 2 provides more guidance and gives examples of possible items that might be addressed in the subject information leaflet depending on the type of trial.

F. Investigator qualifications, suitability and facilities at the site

The qualification of the principal investigator, investigator(s) and co-/sub-investigators should be described in current curriculum vitae and/or other relevant documents. Any previous training in or experience obtained from work with clinical trials and in the principles of GCP should be stated.

The amounts and arrangements for reimbursing or compensating investigator(s) or the site should be presented. Any condition that might be suspected to influence the impartiality of the investigator should be presented. In some Member States this information will be evaluated by the competent authority.

The availability of adequate resources, including personnel and laboratory facilities should be evaluated. This suitability might for example be confirmed in writing by the head of the clinic/institution at the trial site or by some other responsible person, according to the system in the Member State.

G. Proposed other sites and/or countries involved

For multi-centre trials a listing should be provided with information on the locations of the sites, the name and position of the principal investigators and the number of subjects to be included per site in the Member State. Information should be given on any plans to include sites in other Member States or 3rd countries.

H. Ethics Committees concerned in this Member State and/or other countries

Information should be given if another Ethics Committee has already reviewed the protocol in the Member State and the reasoned outcome. When the opinion of the concerned Ethics Committees in other Member States or in 3rd countries has been not favourable the reasoned opinion of the Ethics Committee should be stated.

I. Documents appended to the application to commence a trial.

To constitute a valid application the following documents should be submitted together with the application form, unless otherwise stipulated in national regulations. Depending on the type of trial, not all documents on the list will be relevant and in case this is not obvious the reasons for not submitting a document should be stated.

The application should contain information on the EUDRACT identification number for the clinical trial. The detailed procedure for allocating this number is described in the detailed guidance on the European clinical trials database (ENTR/6421/01).

- ❑ Covering letter, including EUDRACT clinical trial number
- ❑ Clinical trial dossier
  - Investigator's Brochure or SPC
  - Complete protocol with amendments to date
  - Protocol summary
  - Informed consent form
  - Subject information leaflet
  - Provision for indemnity or compensation to trial subjects (according to national requirements)
  - Insurance or indemnity for liability of sponsor and investigator (according to national requirements).
  - Financial arrangements: compensations to investigators and subjects and agreement sponsor/site (according to national requirements)
  - Documentation on subject recruitment procedures, including
    - Printed materials, advertisements, video tapes, etc. to be used for recruitment,
    - procedure for obtaining informed consent
  - Questionnaires/diaries etc. to be handed out to subjects. Sample case report forms (CRF) might have to be submitted according to national provisions.
  - Documentation on suitability of investigator and supporting staff, including
    - Curriculum Vitae of investigator and key personnel
    - declaration of sources of funding and possible conflicts of interest

- Publication policy and investigators access to data, if the agreement is not in the protocol
- Documentation on suitability of site and adequacy of facilities
- Copy of competent authority authorisation, if available
- Previous peer review, when applicable

- Investigational medicinal product dossier (IMPD), if not considered by the Competent Authority

6.2. Substantial amendments to the protocol

Directive 2001/20/EC requires that all substantial amendments or changes in supporting documents must be reviewed and a favourable opinion obtained from the Ethics Committee before implementation. Examples of such amendments and the format and content of the application are given in the detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities in the European Union, notification of substantial amendments and declaration of the end of a clinical trial (ENTR/6418/02).

If after the trial has commenced the applicant proposes to advertise for subjects this will also be regarded as a significant amendment to the protocol. In this case the requirements in section 6.1.D of this document apply.

As described for the initial submission the amendment should be signed and the appropriate application form for amendments used, see appendix 3.

If up-dated, the new version of the Investigator's Brochure or Summary of Product Characteristics should be submitted.

The reasons for the amendment should be stated and a new risk benefit analysis presented.

Any new subject information should be appended and if there is a need to obtain new consent from the participants, the procedure should be described. Possible consequences for the evaluation of the results for the subjects already included and for the usefulness of data recorded and stored should be discussed.

Information should be presented on when the amendment was submitted to the competent authority, and if not run in parallel, if/when it was approved/ given no grounds for non-acceptance by the competent authority.

6.3. Information to the Ethics Committee during the conduct of the trial

Directive 2001/20/EC describes the information arising during the conduct of a trial that must be submitted to the Ethics Committee for review or information. This includes new events relating to the conduct of the trial or the development of the investigational medicinal where that event is likely to affect the safety of the subjects, early termination or suspension of the trial, and reports of suspected serious adverse reactions (whether unexpected or not). In addition, the Ethics Committee may request the investigator and/or sponsor to submit any other information necessary to fulfil the requirement of continuing review of the trial.

When a change of principal investigator or significant changes of key personnel in the trial team occurs, information should be sent to the Ethics Committee for re-consideration of the

opinion. There might also be a need for a new evaluation of suitability of the site and a new statement by the head of the clinic/institution, according to national requirements.

The sponsor is obliged to notify the Ethics Committee on the occurrence of any new event relating to the conduct of the trial or the development of the investigational medicinal product and of the appropriate safety measures taken.

The sponsor is obliged to inform the Ethics Committee about deaths and life-threatening events and suspected serious unexpected adverse reactions. The reported death of a subject may lead to a request from the sponsor for additional information which should be forwarded to the Ethics Committee.

The sponsor must provide the Ethics Committee with an annual listing of all suspected serious adverse reactions. The birth date for this annual listing of all suspected serious adverse reactions is the time of the first authorisation by a competent authority to conduct a clinical trial on that investigational medicinal product in a Member State. Guidance to the sponsor on the presentation of annual listings is provided in the 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.)

The information provided should be sufficient to allow the Ethics Committee to decide if it is necessary and appropriate to reconsider its opinion. In such a case the Ethics Committee should inform the competent authority, which should respond appropriately.

6.4. Declaration of end of trial

The sponsor must notify the Ethics Committee at the end of the trial. If the trial has terminated prematurely the reasons for the termination must be given. The detailed guidance on the declaration of the end of the trial as given in ENTR/6418/02 should be followed.

If after the termination of a trial the risk benefit analyses have changed, the new evaluation should be provided and any actions described that will be needed to protect the subjects who have taken part in the trial.

If there are grounds to consider that the conditions in the request for authorisation of the trial are no longer met and the competent authority decides to suspend or prohibit the trial, the competent authority must inform the Ethics Committee and give the reasons for the decision.

If the competent authority finds that the obligations for the conduct of the trial are no longer met by one or more persons involved in the conduct of the trial, it must inform those responsible of the action to be taken to remedy the situation. The competent authority must also inform the Ethics Committee of the necessary course of action.

6.5. Progress and final reports.

The investigator should, where applicable, provide the Ethics Committee with a summary of the outcome of the trial after the trial is completed.

6.6. Trials with medicinal products with special characteristics and for products for gene therapy, somatic or xenogeneic cell therapy and genetically modified organisms).

A written authorisation is required from the competent authority before the start of the trial. Thus the investigator and/or sponsor should provide information on when such an application was submitted to the competent authority and if it is already approved.

7. Appended documents

Attachment 1.	Information on Ethics Committees in the Member States of the European Union.
Attachment 2	Application form for ethics committee opinion
Attachment 3	Application form for substantial amendment to the conduct of a clinical trial
Appendix 1.	Advertising for trial subjects.
Appendix 2.	Content of subject information

Attachment 1 (to be completed)

Attachment 2.

Module 1 and module 2 might be used for requests for the opinion of the Ethics Committee in a Member State in EU. In principle they have the same lay out as the forms the sponsor should use for the application to the competent authority in the Member State. Modules 3 and 4 are only presented for information and to provide guidance on and examples of items that might be useful for the evaluation by the Ethics Committees.

MODULE 1

REQUEST FOR OPINION OF THE ETHICS COMMITTEE ON A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE

A. TRIAL IDENTIFICATION

For official use

Date of receipt of request:	Date of request for additional information:
Ethics Committee Registration number:	

To be completed by the applicant

EUDRACT clinical trial number :

Full title of the trial :

Code of the protocol or other identifier (version and date):

B. APPLICANT IDENTIFICATION

Sponsor
Name :
Status : academic ❑ pharmaceutical industry ❑ other ❑ : Specify :
Address :
Telephone number :
Fax number :
e-Mail :

Legal representative* of the sponsor in the EU for the purpose of this trial (if different from the sponsor)
Name :
Address :
Telephone number :
Fax number :
e-mail :

* as stated in article 19 of Directive 2001/20/EC

Representative of the sponsor in this Member State:
Name :
Address :
Telephone number :
Fax number :
e-Mail :

C. TYPE OF APPLICATION

Please tick in the appropriate box:
❑ clinical trial on a non-authorised investigational medicinal product
❑ clinical trial on an authorised medicinal product on a new indication, i.e. not in the authorised Summary of Products Characteristics, (SPC)
❑ clinical trial with an authorised medicinal product in new conditions of use (different from in the authorised SPC, i.e. new target population, new dosage schemes, new administration route etc.)
❑ clinical trial with an authorised medicinal products used according to the SPC
❑ other Specify:

D. TRIAL MONITORING (Repeat as necessary for multiple organisations)

Has the sponsor has transferred any (or all) the sponsor's trial-related duties and functions to a contract research organisation (CRO) or other agent : yes ❑ no ❑
If yes, specify, Name : Address : Telephone number : Duties / functions subcontracted :

E. INFORMATION ON INVESTIGATIONAL MEDICINAL PRODUCT(S) BEING USED IN THE TRIAL : MEDICINAL PRODUCT BEING TESTED OR USED AS A REFERENCE

If the trial is performed with several medicinal products, use extra pages ; information should be given for each product, likewise if the product is a combination product information should be given for each active substance.

Indicate which of the following is described below, then repeat as necessary for each:	
Investigational medicinal product being tested	❑
Investigational medicinal product used as a reference	❑

E.1. STATUS OF THE INVESTIGATIONAL MEDICINAL PRODUCT

TO BE COMPLETED ONLY FOR THE INVESTIGATIONAL MEDICINAL PRODUCT TO BE TESTED

Have you made any other submission to the Member state for a clinical trial authorisation request relating to the investigational medicinal product to be tested? yes ❑ no ❑ If yes, give the EUDRACT number (s) :

E.2 DESCRIPTION OF THE INVESTIGATIONAL MEDICINAL PRODUCT

Product name :

Name of each active substance :

Code name, if given :

Pharmaceutical form (use allowed terms) :

Qualitative and quantitative composition *of active and inactive substances (to be completed only if the investigational product has no marketing authorisation) :

Principal pharmacological characteristic :

Route of administration :

Strength :

** Information to fill in the composition of active and inactive substances*

1. Enter constituent(s) as actual substances included in the formulation, eg as salt and then base equivalent where applicable
2. Use INN or european or MS pharmacopoeia
3. In the case of liquid preparations: all quantities for oral preparations should relate to a 5 ml dosage. Please state in dosage information any deviation from this rule. Quantity should be expressed as a percentage for other liquid preparations, including parenterals; please insert WW, WV etc. as appropriate. DO NOT INSERT a percentage sign.
4. The following abbreviations for units are recommended:-
   ng - nanograms; µg - micrograms; mg - milligrams; g - grams; kg - kilograms; µl - microlitres; ml - millilitres; l - litres; U - units; KU - kilounits (1,000 U); MU - megaunits (1,000,000 U); IU - International Units; µCi - microcuries; Bq - becquerels.
5. After each substance, state a functional code for the identification of the type of substance. Use the following letters :
   A: Active substances, C: Colouring matters, F: Aroma and flavour additives, I: Other inactive substances, P: Preservatives
6. Trailing zeros following the decimal point may be omitted.

Type of product	
- Is the active substance of chemical origin?	no ❑
- Is the active substance of biological / biotechnological origin **?	no ❑
- Is this a cell therapy product **?	no ❑
- Is this a gene therapy product ** ?	no ❑
- Is this a radiopharmaceutical product ?	no ❑
- Is this an immunological medicinal product (such as vaccine, allergen, immune serum)**?	no ❑
- Is this a herbal medicinal product?	no ❑
- Is this a homeopathic medicinal product?	no ❑
- Is this a product containing genetically modified organisms ?	no ❑
- Is it another product? If yes, specify :	no ❑

*** Please, complete E2, E3 or E4 form*

E.3. BIOLOGICAL/BIOTECHNOLOGICAL PRODUCTS INCLUDING VACCINES

Type of product
❑ extractive
❑ recombinant
❑ vaccine
❑ plasma derived products
❑ others specify :

E.4. CELL THERAPY PRODUCT (no genetic modification)

Origin of cells :
❑ autologous
❑ allogeneic
❑ xenogeneic Specify species of origin :

Type of cells :
❑ stem cells
❑ cells of the immune system
❑ keratinocytes
❑ fibroblasts
❑ chondrocytes
❑ others Specify :

E.4. GENE THERAPY PRODUCTS

Gene of interest :	
In vivo gene therapy : ❑ yes ❑ no	**Ex vivo gene therapy :** ❑ yes ❑ no

Type of gene transfer product :	
❑ plasmid	Specify if naked or complexed :
❑ virus	Specify if adenovirus, retrovirus, AAV, …:
❑ others	Specify :

Genetically modified cells : ❑ yes ❑ no
If yes, specify : - origin of the cells (autologous, allogeneic, xenogeneic) : - type of cells (hematopoietic stem cells, …) :

F. INFORMATION ON PLACEBO (IF RELEVANT)

Manufacturer
Name : Address :
Product name :

Pharmaceutical form (use standard terms): **Route of administration:** **Qualitative and quantitative composition :**

MODULE 2

G. GENERAL CONSIDERATIONS ON THE TRIAL

(A summary of the essentials of the trial allowing a classification of the type of trial. It might be used for statistical purposes.)

Medical condition or disease under investigation :
Specify, please: ICD10 classification code : MEDRA classification code, if available :

Objective :
Main objective : Secondary objectives :

Scope of the trial

Is the research potentially of direct benefit for the subject ?	yes ❑ no ❑
Therapeutic	yes ❑ no ❑
Prophylactic	yes ❑ no ❑
Diagnostic	yes ❑ no ❑
Other:	yes ❑ no ❑ If yes, specify :
Indicate each of the following which apply:	yes ❑ no ❑
- Safety	yes ❑ no ❑
- Efficacy	yes ❑ no ❑
- Pharmacokinetic	yes ❑ no ❑
- Pharmacodynamic	yes ❑ no ❑
- Bioequivalence	yes ❑ no ❑
- Dose Response	yes ❑ no ❑
- Pharmacogenomic	yes ❑ no ❑
- Pharmacoeconomic	yes ❑ no ❑

Trial type* and phase			
❑ Human pharmacology (Phase I) ❑ Bioequivalence study	❑ Therapeutic exploratory (Phase II) ❑ Other :	❑ Therapeutic confirmatory (Phase III)	❑ Standard conditions of use (Phase IV)

**according to Community guideline CPMP/ICH/291/95*

Design of the trial					
Randomised :	yes ❑ no ❑				
Controlled :	yes ❑ no ❑	If yes, specifiy :			
		Open :	yes ❑ no ❑		
		Single blind :	yes ❑ no ❑	Double blind :	yes ❑ no ❑
		Parallel group :	yes ❑ no ❑	Cross over :	yes ❑ no ❑
		Other :	yes ❑ no ❑	If yes, specify :	
		and specify the comparator :			
		(An) Other medicinal product(s) as comparator:			yes ❑ no ❑
		Placebo as comparator:			yes ❑ no ❑
		Other:			yes ❑ no ❑
		If other, specify (e.g. no treatment , best standard of care, surgery, local treatment protocol etc) :			
Multiple site :	yes ❑ no ❑				
Multiple state :	yes ❑ no ❑	If yes, specify other countries involved in the trial : - EU countries : - Third countries :			
Primary end point:					
Description of the treatment groups, if relevant :					
Maximum duration of treatment of a subject according to the protocol :					

Estimated starting date of the trial * (DD/MM/YYYY) **:**

Estimated finishing date of the trial (DD/MM/YYYY) **:**

Definition of the end of trial given in the protocol :

Estimated total duration of the trial (day or month) **:**

* please, declare the real start date as soon as available (date of inclusion of the 1st patient in the Member State)

G. POPULATION OF TRIAL SUBJECTS

Age :
Age span:

	❑ Preterm Newborn Infants	❑ Adult	❑ Elderly
❑In utero	❑ Newborn (0 – 27 days)	(18-65)	(> 65)
	❑ Infant and Toddler (28days – 24 months)		
	❑Children (2 – 11 years)		
	❑Adolescent (12 – 18 years)		

Gender:
❑ Female ❑ Male
Planned ratio:

Special population of trial subjects :

- women of child bearing potential	yes ❑	no ❑
- pregnant	yes ❑	no ❑
- nursing woman	yes ❑	no ❑
- emergency situation	yes ❑	no ❑
- subject incapable of giving consent personally	yes ❑	no ❑

If yes, specify :

Principal inclusion criteria *(list the most important, maximum 3)***:**

Principal exclusion criteria *(list the most important, maximum 3)***:**

Number of subjects to be included :
- in the Member State :
- in each Member State trial centre:
- in the EU :
- in the whole clinical trial :

Plans for treatment after the subject has ended participation in the trial : Please specify

Insurance or indemnity to cover liability of sponsor and investigator :
Name of the company/organisation : Address : Contract number/reference :

Subject recruitment procedure

❑ from list or log at clinic/institute
❑ advertisement
❑ other

Please specify and provide documentation :

H. PROPOSED CLINICAL TRIAL SITES

Coordinating investigator (for multicenter trial) or Principal investigator (monosite trial)			
Name	Surname	Qualification	Address of the investigator site
Other principal investigators for sites in the Member State			
Name	Surname	Qualification	Address of the investigator site

I. OTHER ETHICS COMMITTEE(S) OR AUTHORITIES CONCERNED IN THIS MEMBER STATE (*IF APPLICABLE)* :

Name and address of other Ethics Committees concerned in this Member State (if applicable):			
Date of submission :			
Opinion :	❑ to be requested	❑ submitted	❑ given
If given, specify :	Date of opinion:		
	❑ favourable:		
	❑ not favourable . Please give the reasons :		

H. DOCUMENTS APPENDED TO THE APPLICATION FORM

- ❑ Covering letter
- ❑ Complete protocol with amendments to date
- ❑ Protocol summary
- ❑ Investigator's Brochure
- ❑ Informed consent form
- ❑ Subject information leaflet
- ❑ Provision for indemnity or compensation to trial subjects (according to national requirements)
- ❑ Insurance or indemnity for liability of sponsor and investigator (according to national requirements)
- ❑ Financial arrangements: compensations to investigators and subjects and agreement sponsor/site (according to national requirements)
- ❑ Documentation on subject recruitment procedures, including
  - ❑ advertisements, video tapes, etc. to be used for recruitment
  - ❑ procedure for obtaining informed consent
- ❑ Questionnaires/diaries etc. to be handed out to subjects. Sample case report forms (CRF)
- ❑ Documentation on suitability of investigator and supporting staff, including
  - ❑ Curriculum Vitae of investigator and key personnel
  - ❑ declaration of sources of funding and possible conflicts of interest
- ❑ Publication policy and investigators access to data, if the agreement is not in the protocol
- ❑ Documentation on suitability of site and adequacy of facilities
- ❑ Copy of competent authority authorisation, if available
- ❑ Previous peer review, when applicable
- ❑ Investigational medicinal product dossier (IMPD), if not considered by the Competent Authority

MODULE 3

The module 3 is intended to be comprehensible for all members of the Ethics Committee and provide enough detailed information to help the Ethics Committee to reach its reasoned opinion. The list provided below is intended to provide guidance on aspects that might be addressed when relevant. It is not intended to be a complete listing of all elements necessary for the Ethics Committee to consider during its work, but to indicate some and give examples that might have to be considered in some trials.

1. ID of trial according to EUDRACT Ethics Committee trial ID
2.Title of the project (*This should be understandable for laypersons*)
3. Summary of the project. (*justification and relevance*)
4. Results of pre-clinical tests or reasons for not doing pre-clinical tests
5. Primary hypothesis in this trial *(if relevant, also secondary hypotheses)*
6. Research ethical considerations *(Identify and state any possible problems that might occur. Present possiblegain in knowledge to be obtained in the trial and its importance, possible risks for injuries or distress for the participants. Present your own evaluation of the risk-benefit ratio)*.
7. Reason for including persons from vulnerable groups, i.e. minors, temporaily or permanently incapacitated subjects.
8. Description of the recruitment procedure *(all material to be used should be appended)*
9. Procedure at the site to provide information and obtain consent from the subjects , or parents or legal representatives if applicable *(who will give the information and when, need for legal representatives, witness etc)*.

10. Investigational procedures and any deviations necessary from the routine treatment
11. Risk assessment, foreseeable risks of treatment and procedures to be used (*incl. pain, discomfort, violation of integrity and means to avoid and/or take care of unforseen/unwanted events)*
12. Previous experience of the conduct of similar research procedures at this site.
13. Any foreseeable benefit for included subjects
14. Relation between subject and investigator (*patient-physician, student – teacher etc)*
15. Simultaneous participation in other research or required period since previous participation in research *(of special importance when healthy subjects are included in pharmacology trials).*
16. Requirements and methods for recording health control for healthy subjects *(i.e. hospital files or other national requirements*)
17. Methods for searching, recording and reporting adverse effects *(describe when, by whom and how, i.e. open questions and/or according to lists)*
18. Procedures used to protect the privacy of recorded data, source documents and samples *(if applicable).*
19. Plan for treatment or care after the subject has ended the participation in the trial *(who will be responsible and where)*
20. Statistical consideration and reasons for the number of subjects to be included in the trial.
21. Amount and procedure for remuneration or compensation of subjects *(description of amount paid, during the participation in the trial and for what, i.e. travel cost, loss of earning, pain and discomfort etc)* .
22. Rules for stopping or prematurely ending the trial at the site(s) in this Member State or as a whole
23. Agreement on investigator´s access to data, publication policy etc. *(if not available in the protocol)*

24. Sources of funding *(if not available in the protocol)* and information on financial or other interests of theinvestigator(s).

NAME AND SIGNATURE OF APPLICANT - PRINCIPAL INVESTIGATOR (and/or sponsor, if applicable)	
I hereby confirm that the information given in this application is correct and that I am of the opinion that it will be possible to conduct the trial in accordance with the protocol, national regulations and principles of Good Clinical Practice.	
Name : Surname : Address : Position: :	
Date :	Signature:

MODULE 4.

This module is intended to provide guidance on a possible format for documenting the opinion of the Ethics Committee and to recall the need to provide the competent authority with information on the opinion of the Ethics Committee. The form is not intended to be obligatory. It might also be used to provide the opinion of the Ethics Committee on other information submitted during the conduct of the trial such as significant amendments.

OPINION OF ETHICS COMMITTEE ON AN APPLICATION FOR A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE

TRIAL IDENTIFICATION

Date of receipt of request:	Date of opinion:
EUDRACT clinical trial number :	
Ethics Committee trial ID:	

Title of the trial :

Code of the protocol or other identifier (date, version):

Person responsible for the request: *(name and address)*
(Investigator/Sponsor/Sponsor's legal representative – delete as applicable)

Opinion of the Ethics Committee:

Favourable/ not favourable opinion/ amendment needed
Reason(s) for opinion:

Date: Signature:

Information sent to competent authority: Date:

Date of receipt of requested amendment:

Favourable/ not favourable opinion:
Reason(s) for opinion:

Date: Signature:

Information sent to competent authority: Date:

Re-evaluation (protocol amendment, safety concern, interim results):
Date of reciept:

Favourable/not favourable opinion:
Reason(s) for opinion:

Date: Signature:

Information sent to competent authority: Date:

ATTACHMENT 3.

APPLICATION FOR APPROVAL BY ETHICS COMMITTEE OF AN AMENDMENT TO THE PROTOCOL FOR A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE

TRIAL IDENTIFICATION

Date of receipt :	Date of first opinion:
EUDRACT clinical trial number :	
Ethics Committee trial ID:	

Title of the trial :

Code of the protocol or other identifier (date, version):

Code of the amendment or other identifier (date, version):

Person responsible for the submission: *(name and address)*
(Investigator/sponsor/sponsor's legal representative -delete as applicable)

SECTIONS OF THE INITIAL / PREVIOUS APPLICATION FORM MODIFIED BY THE AMENDMENT

DOCUMENTS APPENDED TO THE APPLICATION FORM FOR AMENDMENT
Please submit only relevant documents and, when necessary, make clear referrals to ones already submitted.

❑ Covering letter stating reasons for the amendment

❑ Updated complete protocol (if applicable) and amendment

❑ Summary of protocol and summary of amendment
❑ Updated Investigator's brochure or SPC (date, version)
❑ Updated Investigational Medicinal Product Dossier, *if not considered by CA*

❑ Updated Subject information leaflet (date, version)
❑ Updated Informed consent form (date, version)

❑ Provision for indemnity or compensation in the event of injury or death attributable to a clinical trial*
❑ Insurance and indemnity for liability of sponsor and investigator*
❑ Reimbursement to investigator/institution/site/subjects*

❑ Copy of competent authority decision, if available

❑ Documentation on subject recruitment procedures
❑ Advertisement/ video tapes etc to be used for recruitment
❑ Questionnaires/ diaries etc. to be handed out to subjects. Sample Case Record Forms, *when applicable.*

❑ CV of investigator and key personnel
❑ Declaration of sources of funding and possible conflicts of interest
❑ Statement on suitability of site and adequacy of facilities
❑ Previous peer review (when applicable)

* Directive 2001/20/EC allows Member States to delegate consideration of these issues to the competent authority

NAME AND SIGNATURE OF APPLICANT (PRINCIPAL INVESTIGATOR AND/OR SPONSOR)

I hereby confirm that the information given in this application is correct and that I am of the opinion that it will be possible to conduct the trail in accordance with the protocol, national regulations and principles of Good Clinical Practice.

Name :
Surname :
Address :
Position: :

Date : Signature :

APPENDIX 1.

Advertising for trial subjects.

This appendix is intended to provide guidance on items that might be relevant to consider when advertising for subjects who will be asked to participate in a clinical trial. The items listed do not comprise a complete list and should be modified according to the type of trial.

All advertisements for trial subjects should be included in the submission for approval by the Ethics Committee. The review by the Ethics Committee might also include the procedures to take care of subjects responding to the advertisement.

The advertisement might contain information on the following points:

1. The research nature of the project
2. The scope of the trial
3. Which type/group of subjects might be included
4. The investigator clinically/scientifically responsible for the trial, if possible or if required by local regulations.
5. The person, name, address, organisation, to contact for information
6. That the subject responding will be registered
7. The procedure to contact the interested subjects
8. Any compensation for expenses
9. That a response on the part of a potential subject only signifies interest to obtain further information

Information concerning the procedures might include the qualifications of the person who is responsible for the first contact with the subjects. This is especially important when patients are replying to an advertisement. In addition, resources/procedures should be in place to provide information to and take care of patients not suitable for inclusion in the planned trial. Lack of suitability might be obvious at the first contact or after screening of the subjects who responded.

All information to be provided to the subjects relating to steps taken subsequent to the placing of the advertisement should be submitted to the Ethics Committee for approval. If there is a screening procedure to evaluate the suitability of the respondent two sets of information sheets might be used, according to local regulations. One set could provide information on the screening procedure and the reasons for it. The second more extensive information could provide the information on the trial and should follow the usual requirements.

Potential subjects should be informed that personal information might be recorded and will be protected according to national requirements. The procedure for giving the participating subjects compensation or rewards and the amount(s) should be outlined. The applicant should also describe the procedure for informing the subject on how he/she may be eliminated from the register.

APPENDIX 2.

Content of subject information

This appendix is intended to provide further guidance on items that might be of relevance for the subject information leaflet. It is not intended to provide a complete list of items which should be included, but to give some examples of items that might have to be considered if relevant to the particular trial.

1. The information sheet should state clearly the justification for the trial, its relevance and objective and should contain at least all the items listed in the relevant section of the Community guideline on Good Clinical Practice (CPMP/ICH/135/95).

2. In addition written information should be provided on:

2.1 the contact point from which further information may be obtained relating to the trial and in case of injury, according to national requirements.

2.2 the names and addresses of the investigator, study nurse etc who are responsible for taking care of the included subjects.

2.3 any planned procedures for follow up after the end of the trial (for example for trials involving gene transfer medicinal products) and/or plans for treatment that might be needed after the subject has completed trial participation.

2.4 any financial or other ties to the sponsor as well as institutional affiliations of the researcher well as the name and address of sponsor /sources of funding

2.5 the Ethics Committee positive opinion.

2.6 the subject's rights to privacy and the means taken to ensure protection of personal data.
This might include information on:

- procedures for coding,
- the arrangement with code-keys: the name of the responsible person who will have access
- in the case of retention of subject samples and information,
  - from whom the data and samples are accessible
  - the location and duration of retention
  - name of the person who will be responsible for keeping the samples and the results
  - procedure for handling any retained identifiable samples
  - plans to anonymise or destroy samples after analysis

2.7 the subject's right to obtain updated information about what data is recorded as well as the right to require corrections of errors

2.8 the right of the subject (or parent, guardian or legal representative) to withdraw consent to participate in the trial

2.9 the fact that in the event of the withdrawal of consent to participate in the trial, no new data will be added to the database and that, according to national provisions, the subject (or parent, guardian or legal representative) may require all previously retained identifiable samples to be destroyed to prevent further analysis.

Information in Pharmacogenetic trials

The subjects should, when relevant, be informed of their right to abstain from the genetic part of such a trial but to be able to participate in the non-genetic part. Information should also be given regarding the subject's right to know of and abstain from possible new analyses not directly related to the initially planned trial.