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Revision 1

**Detailed guidance on the application format and
documentation to be submitted in an application
for an Ethics Committee opinion on the clinical
trial on medicinal products for human use**

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1. Introduction

According to Article 9 of Directive 2001/20/EC¹, a clinical trial on a medicinal product for human use may not start until the appropriate Ethics Committee has issued a favourable opinion.

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.

According Article 10 (a) of Directive 2001/20/EC the sponsor shall notify the Ethics Committees of any substantial amendments to the protocol after commencement of the clinical trial.

According to Article 10(c) of Directive 2001/20/EC the sponsor shall notify to the Ethics Committees the end of the clinical trial or an early termination of the clinical trial.

In the detailed guidance for the application form to the Ethics Committees references are given to 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 the declaration of the end of a clinical trial’², in several cases.

The application form for the request for the start of the clinical trials, the notification of the amendments and the notification for the end of the trials are of the same format as for the competent authorities but with different tick boxes.

This detailed guidance should be read in conjunction with Directive 2001/20/EC and Commission Directive 2005/28/EC³,

2. Scope

This detailed guidance is intended to fulfil the obligations laid down in Article 8 of Directive 2001/20/EC, including the requirements of Article 10 (a) and (c) of Directive 2001/20/EC.

This detailed guidance is intended to provide advice on the format and content of the information to be submitted to an Ethics Committee in any EU Member State for:

- a request for an Ethics Committee opinion on a proposal to undertake a trial on a medicinal product for human use,
- notification of a substantial amendment and the request for an Ethics Committee opinion on a substantial amendment,
- notification of the Ethics Committee on the end of the trial or an early termination of the trial.

¹ OJ L 121, 1.5.2001 p.24

² 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 the declaration of the end of a clinical trial. <http://pharmacos.eudra.org/F2/pharmacos/dir200120ec.htm>

³ OJ L 91, 9.4.2005, p.13

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. It 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 Good Clinical Practice (GCP).

The required exchange of information between the competent authority and the Ethics Committee according to Directive 2001/20/EC is also outlined.

3. Definitions

The definitions which are provided in Directive 2001/20/EC are applicable. For additional terms used in this guideline the definitions provided in Community guideline ICH/CPMP/135/95⁴ apply.

4. Format and content of an application to the Ethics Committee before commencement of a clinical trial: request for the opinion of the Ethics Committee

The applicant must submit a valid request for an opinion to the Ethics Committee. The application is considered to be valid if all required documents are complete. If that is the case the applicant will be informed and the review period starts. If an application is not valid the Ethics Committee will inform the applicant of the deficiencies. The list in attachment 1 indicates the core information and Member State specific information to be submitted as part of a valid application, and the language requirements. When relevant, the sponsor should check the language requirements with the concerned Ethics Committee before preparing the application. If a document has been omitted by the applicant, this must be specifically justified.

All documents should carry the trial identification (EudraCT number, sponsor's protocol code number, date and/or version) as well as the version and/or date of the particular document (e.g. when there have only been revisions of the subject information sheet).

Under certain circumstances and according to national requirements an abridged application might be sufficient. For example, if an Ethics Committee already has substantial information from a previous related application from the same applicant, cross-reference can be made. The application should state the EudraCT number obtained for that clinical trial. The procedure for allocating this number is described in the detailed guidance on the European clinical trials database⁵

4.1. Covering letter

The applicant should submit and sign a covering letter with the application. Its heading should contain the EudraCT number and the sponsor protocol number with a title of the trial. The text

⁴ Note for guidance on Good Clinical Practice CPMP/ICH/135/95. www.emea.eu.int/pdfs/human/ich/013595en.pdf

⁵ Detailed guidance on the European clinical trials database (EUDRACT Database).
<http://pharmacos.eudra.org/F2/pharmacos/dir200120ec.htm>

should draw attention to any special issues related to the application such as special trial populations, first administration of a new active substance to humans, unusual investigational medicinal products (IMPs), unusual trial designs, sub-studies etc. and indicate where the relevant information is in the application.

The covering letter should specify, for each IMP, the reference document(s) chosen by the sponsor to identify the unexpectedness of a serious adverse reaction in accordance with the appropriate detailed guidance⁶. In addition, it should draw attention to any scientific advice or opinion related to the trial or IMP given by the EMEA or concerned MS or the competent authority or Ethics Committee of any other country and indicate where in the application an assessor can find a copy of the advice.

4. 2. The application form

For research at a single site, the application form should be signed by the sponsor or the sponsor's legal representative and/or by the principal investigator responsible for the conduct of the trial at the site, according to regulations in each Member State⁷. In multi-centre trials the application form should be signed by the sponsor or the sponsor's legal representative and/or by the co-ordinating investigator, who is responsible for co-ordinating the work of the principal investigators at the different sites in that Member State, according to national regulations⁸.

The application form to the Ethics Committee might be composed of two modules. Module 1 is compulsory and is common for all Member States. This module is the application form as described in the detailed guidance on the submission to the competent authority and contains information on the administration of the trial, trial site(s) with principal investigator(s), the trial design and on the investigational medicinal products. This will allow the Ethics Committee an easy overview of the trial design and an evaluation of the expertise needed for the review.

Module 2 is optional and might consist of a national or local Ethics Committee application form. An example is given in attachment 4 of this guideline.

This second module can contain headings that might be helpful for the ethical review by the Ethics Committee. The aim of the example given in attachment 4 of this guideline is to provide guidance on how trial and site specific information might be presented to identify the ethical issues and describe the trial in lay language. The list of items addressed is not complete and can be modified according to the responsibilities assigned to the Ethics Committee in the Member State.

4.3. The clinical trial protocol

The content and format of the protocol should comply with the guidance in the Community guideline on Good Clinical Practice CPMP/ICH/135/95. It should be identified by the title, a sponsor's protocol code number specific for all versions of it, a number and date of version that will be updated when it is amended, and by any short title or name assigned to it. It

⁶ Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use. <http://pharmacos.eudra.org/F2/pharmacos/dir200120ec.htm>

⁷ See attachement 1 Nr 1.7 and for further information attachement 3

⁸ See attachement 1 Nr 1.7 and for further information attachement 3

should be signed by the sponsor and principal investigator (or co-ordinating investigator for multicentre trials of the sponsor).

The version submitted should include all currently authorised amendments and a definition of the end of the trial. If this is not the last visit of the last subject undergoing the trial in the Member State, the reason should be given.

Among other things, the clinical trial protocol should include:

- the evaluation of the anticipated benefits and risks as required in Article 3(2)(a) of Directive 2001/20/EC;
- a justification for the selection of trial subjects, especially when including subjects who are incapable of giving informed consent or other special populations;
- a description of the recruitment and informed consent procedures, especially when subjects who are (temporarily or permanently) incapable of giving informed consent are included or when a procedure with witnessed consent is to be used;
- 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 what is normally expected according to the subject's medical condition;
- a summary of the protocol in the national language should be submitted when required according to national provisions.

A protocol may include a sub-study to be conducted at all trial sites or only at specific sites. The covering letter should draw attention to any sub-studies and information should be provided in Section E.2 of the application form of the detailed guidance for the request for authorisation of a clinical trial, and all other applicable sections and supporting documents.

Some arrangements specific for the Member State or site might be described in separate documents. For example, the financial agreements between the sponsor and principal investigator or site, the publication policy and the investigators' access to the data might be in an agreement separate from the protocol. Copies of these agreements should be included in the application.

4. 4. Information on the investigational medicinal product

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

More information on the investigational medicinal product(s) is provided in the Investigator's Brochure (IB⁹). The Investigator's Brochure should reflect all the clinical and non-clinical data on the investigational medicinal product(s) which is relevant for the trial and provide evidence that supports the rationale for the proposed clinical trial and the safe use of the product(s) in the trial.

If the investigational medicinal product has a marketing authorisation in any Member State in the Community and the product is to be used as authorised, the Investigator's Brochure could be substituted by the authorised Summary of Products Characteristics (SmPC).

In some Member States the Ethics Committee is responsible for the review of the more extensive quality aspects and pre-clinical documentation included in the Investigational Medicinal Product Dossier (IMPD). The information that should be included in the IMPD is described in the detailed guidance on the application to the competent authority. Attachment 1

⁹ Article 8 Directive 2005/28/EC

shows which Member States require the IMPD to be included in the submission to the Ethics Committee.

4. 5. Recruitment arrangements

The procedures for enrolment of subjects should be described in detail in the trial protocol or in a separate document if it varies between sites. 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, copies of the material to be used should be appended, including any printed materials, recordings or videotapes. The procedures proposed for handling the responses to the advertisement(s) should be outlined. This includes the planned arrangements for information and/or advice to the respondents found not to be suitable for inclusion in the trial. Further guidance and information on issues that might be relevant to consider depending on the type of trial and advertisement are given in attachment 5.

4. 6. Subject information and the informed consent procedure

Article 2(j) of Directive 2001/20/EC defines the information to be provided for the informed consent.

All information to be provided to the subjects (and/or, where appropriate, the parent(s)/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 set out in the Community guideline 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 there is additional care necessary because of the subjects' participation in the trial and where it differs from that normally expected according to the medical condition.

The information sheets given to the subject and/or the parent(s)/legal representative should be kept short, clear, relevant, and understandable to a lay person. They should be in a language the subject knows.

The measures taken to safeguard the subject's privacy and the protection of personal data should be described as is required according to Directive 95/46/EC¹⁰. There should be 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 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/EC.

¹⁰ Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995, as amended by Regulation (EC) No 1882/2003

The subject should be informed of the possibility to withdraw consent without giving any reason and to require that all previously retained identifiable samples will be destroyed to prevent future analyses, according to national provisions. 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.

Information should be provided on a contact point where additional information can be obtained about the trial and the right of the trial subjects and whom to contact in the event of trial related injury, according to the system in the Member State.

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(s) or legal representative should be described. The notion of legal representative refers back to national legislation.

In those cases, two sets of information sheets might be needed according to national regulations¹¹. In addition to the information given to the subject's parent(s) or legal representative, the subject should be given information according to his/her capacity to understand. This information should include, where appropriate, a statement that the subject's decision not to participate or to withdraw from a trial will be respected, even if consent is given by the parent/legal representative. The plan for taking care of such a situation should be outlined in the protocol.

If a procedure with witnessed consent is to be used, relevant information on the reason for using a witness, on the selection of the witness and on the procedure for obtaining consent should be provided to the subject.

In case of temporarily incapacitated patients the procedure for obtaining the consent of the legal representative should be described. The procedure should be outlined that will be used to obtain/confirm consent if/when the patient regains the capacity to consent and the information to be given to the patient in that case. The detailed rules adopted by the Member States to protect individuals who are not capable of giving their consent should also be followed.

The form to be used to verify that information has been given and that the trial subject has consented (the informed consent form) 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 authorities/institutions assigned this task in the Member State or, if applicable, the Ethics Committee;
- consent to archive coded information, and for its transmission outside the Community if applicable.

Attachment 6 provides more guidance and gives examples of items that might be addressed in the subject information leaflet depending on the type of trial.

4. 7. Suitability of the investigator and quality of the facilities

¹¹ For further information see attachment 3

The qualification of the principal investigator should be described in a current curriculum vitae and/or other relevant documents. Any previous training in the principles of GCP or experience obtained from work with clinical trials and patient care should be described. Any conditions, such as economic interests, that might be suspected to influence the impartiality of the investigator should be presented.

The Ethics Committee should give an opinion on the quality of the facilities (including the availability of adequate resources, personnel and laboratory facilities). The evaluation of the quality of the facilities might be based on a written statement 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.

For multi-centre trials a list should be provided on the planned locations of the sites, the name and position of the principal investigators and the number of subjects to be included in the Member State. The Ethics Committee should consider the suitability of the principal investigator and the quality of the facilities of each site in the Member State concerned in a multi-centre trial.

4. 8. Insurance and indemnity

Unless a Member State, as this having of Article 6(4) of Directive 2001/20/EC, has made the competent authority responsible the provisions for indemnity or compensation in case of injury or death of a trial subject should be described in the application to the Ethics Committee. Also the insurance or indemnity arrangements to cover the liability of the sponsor and investigator should be stated.

4.9. Financial arrangements

The application shall include information on financial transactions and compensation to subjects and investigator/site.

It might be the responsibility of either the Ethics Committee or the competent authority to review the arrangements for rewarding or compensating investigator(s) / sites and trial subjects as well as the relevant aspects of any agreement between the sponsor and the site according to national provisions.

4. 10. Proposed other sites and/or countries involved

Brief information should be given on any plans to include sites in other Member States or non EU countries.

5 . Notification of substantial amendments after commencement of a clinical trial and opinion given by the Ethics Committees

Article 10 (a) and 10(b) of 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 product where that event is likely to affect the safety of the subjects,

reports of adverse reactions, and when the trial is halted or terminated early by the sponsor. If the competent authority suspends or prohibits a clinical trial, the Ethics Committee should also be informed. The procedures should be followed as outlined in other detailed guidances¹²

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 according to the Community guideline on Good Clinical Practice (CPMP/ICH/135/95).

5.1. Amendments

The sponsor is obliged by Article 10 (a) of Directive 2001/20/EC to inform the Ethics Committee about substantial amendments to the protocol and to submit all relevant documents in support of such amendments. The procedures described in the detailed guidance on the application to the competent authority section 4.2. should be followed.

The sponsor may not implement such amendments without a favourable opinion of the Ethics Committee, unless the changes consist of urgent safety measures to protect the trial subjects. In case these urgent measures are taken, the sponsor should as soon as possible inform the Ethics Committee of the new event, the measures taken and any plan for further action. This should be done at the same time as the competent authority is informed as described in the relevant guidance.

Criteria for considering an amendment as substantial, the format and content of the application to make such an amendment are given in the above mentioned guidance. An application of amendments identified as substantial should be submitted to both the Ethics Committee and the competent authority.

The application form, that should be used, is common to both the Ethics Committee and the competent authority. The EudraCT number of the trial should be on the application form.

In the case of substantial amendments that affect information submitted to both the competent authority and the Ethics Committee, the sponsor should make the notifications in parallel. For substantial amendments to information that only the Ethics Committee assesses (e.g. changes in an advertisement for subjects to participate in the trial or changes in facilities for the trial), the sponsor should not only submit the amendment to the Ethics Committee but also inform the CA that they have made the application. Similarly, the sponsor should inform the Ethics Committees of any substantial amendment to information for which only the competent authority is responsible (e.g. quality data in most member states). To provide this information it should be sufficient to submit the amendment notification form (Detailed guidance for the request for authorisation of a clinical trial on medicinal products for human use to the competent authorities in the European Union, Annex 2, Section A) indicating that it is “for information only”. In these cases, the notification “for information only” should be submitted to the competent authority or Ethics Committee, as applicable, once the decision on the amendment has taken place, indicating in the substantial amendment form what decision has been taken and the date of the decision.

The notification of a substantial amendment should include the following information:

- a) covering letter, including reason for qualification as a substantial amendment.
- b) application form that contains:
 - identification of CT (title, EudraCT number, sponsor’s protocol code number);

¹² Detailed guidance on the European database of Suspected Unexpected Serious Adverse Reactions (Eudravigilance-Clinical Trial Module)

- identification of applicant;
 - identification of the amendment (sponsor's amendment number and date). One amendment could refer to several changes in the protocol or scientific supporting documents;
 - a description of the amendment and the reason for it.
- c) an extract of the modified documents showing previous and new wording, where applicable
- d) the new version of modified documents where the changes are so widespread and/or substantial that they justify a new version, identified with updated number of version and date.
- e) supporting information including, where applicable:
- summaries of data;
 - an updated overall risk benefit assessment;
 - possible consequences for subjects already included in the trial;
 - possible consequences for the evaluation of the results.

The substantial amendment should be signed by the sponsor or the legal representative of the sponsor, and/or the principal investigator in single-centre trials, or co-ordinating investigator in multi-centre trials, according to national regulations¹³.

Changes to the protocol might lead to a modification of the subject information sheet and any new subject information should be appended. If there is a need to obtain new consent from the subjects, 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.

When additional sites are recruited in a multi-centre trial after the Ethics Committee has given its favourable opinion on the trial, the Ethics Committee should review and give an opinion on the qualification of the new principal investigator(s), provisions for insurance, the quality of the facilities and, according to national provisions, on the indemnity and financial agreements. The application form for substantial amendments that is common for competent authority and Ethics Committee should be used.

The sponsor may implement a substantial amendment if the Ethics Committee opinion is favourable and the competent authority has raised no grounds for non-acceptance. For amendments submitted to either the Ethics Committee alone or the competent authority alone, the sponsor may implement the amendment if the Ethics Committee opinion is favourable or the competent authority has raised no grounds for non-acceptance respectively.

Article 10(a) of Directive 2001/20/EC requires an Ethics Committee to give an opinion on a proposed substantial amendment within 35 days.

The non-substantial amendments should be handled as outlined in the 'Detailed guidance for the request for authorisation of a clinical trials on medicinal products for human use to the competent authorities in the European Union'. Documentation of the changes should be kept at the sponsor and at the site and be made available on request and for inspection.

5.2. Safety measures and adverse events

A sponsor or investigator might have to take appropriate urgent safety measures to protect subjects against any immediate hazard where new events relating to the conduct of the trial or

¹³ Attachment 1 Nr 1.7 or for further information see attachment 3

the development of the investigational medicinal product are likely to affect the safety of the subjects. These safety measures such as temporarily halting of the trial may be taken without prior favourable opinion from the Ethics Committee. The sponsor must inform the competent authority and the Ethics Committee concerned of the new events, the measures taken and their plan for further action as soon as possible. When the sponsor halts a clinical trial (stops recruitment of new subjects and/or interrupts the treatment of subjects already included in the trial), they should notify the competent authority and Ethics Committee concerned as soon as possible but at least within 15 days from the halt of the trial. They may not recommence the trial in that MS until the Ethics Committee has given a favourable opinion and the competent authority has not raised grounds for non-acceptance of the recommencement.

The sponsor shall ensure that all relevant information about serious adverse reactions and new events likely to affect the safety of the subjects are reported to the Ethics Committee in accordance with the obligations outlined in the ‘Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use’.

6. Notification after end or on an early termination of the clinical trial

According to Article 10 (c) of Directive 2001/20/EC at the end of the trial in the Member State, as defined in the protocol, the sponsor should notify the Ethics Committees within 90 days..

In case of an early termination (premature end) of the trial or temporary halt by the sponsor the Ethics Committee should be notified as soon as possible but at least within 15 days of the termination or halt, and a detailed written explanation of the reasons for the termination/halt should be given.

The same procedures should be followed as outlined and the notification form to be used as described in ‘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 the declaration of the end of a clinical trial’.

At the end of the trial (on all sites in a multi-centre trial) the sponsor should provide the Ethics Committee with a summary of the clinical trial report. To be responsible for his/her part in the report writing, the investigator should have access to the recorded and reported data to ensure accuracy, completeness and timeliness. This report should be the same as the one forwarded to the competent authority according to the Commission guideline⁵.

If after the termination of a trial the risk/ benefit analyses have changed, the new evaluation should be provided in case it will have an impact on the planned follow up of the subjects who have participated in the trial. If so, the actions needed to protect the subjects should be described.

7. Procedure

According to Article 7 of Directive 2001/20/EC Member States shall adopt procedures to reach one single Ethics Committee opinion per Member State on a proposed multi-centre trial without excluding the possibility of rejecting it at specific sites. The procedures established to reach this single opinion are outside the scope of this guideline.

The applicant for an Ethics Committee opinion is not defined in Directive 2001/20/EC and can thus be either the sponsor or the principal investigator (multi-centre trials: co-ordinating investigator) according to national provisions.

The Ethics Committee shall give its opinion within the scope of its responsibilities and within the timeframe as defined in the Directive and in accordance with national regulations.

The review by the Ethics Committee may take place sequentially or in parallel with the review by the competent authority, according to the choice of the applicant.

When information is submitted both to the Ethics Committee and the competent authority, the Ethics Committee shall give its opinion based on the same version of the documents that have been or will be submitted to the competent authority.

Attachment 1 to this guideline lists the addresses in each Member State where further information on the national systems and procedures of the Ethics Committees can be obtained.

Attachment 1: old member states

INFORMATION REQUIRED BY MEMBER STATES' ETHICS COMMITTEES

MS SPECIFIC INFORMATION FOR ETHICS COMMITTEES		AT	BE	DK	FI	FR	DE	EL	IT	IE	LU	NL	PT	ES	SE	UK
1	General															
1.1	Receipt of confirmation of the EUDRACT number	Yes							Yes			Yes	Yes	Yes	No	
1.2	Covering letter	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
1.3	Application form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
1.4	List of Competent Authorities to which the application has been submitted and details of decisions, if available	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes A	Yes	Yes	Yes	Yes
1.5	Copy of Ethics Committee opinion in the MS concerned when available	-	-	-	-	-	-	-	-	-	-	-	Yes	-	-	-
1.6	Summary of any scientific advice	Yes							No			Yes	Yes			
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor	Yes							Yes			Yes	Yes	Yes		
1.8	Will accept application to EC in English	Yes ^A			No				No			Yes	Yes			
2	Subject related															
2.1	Informed consent form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.2	Subject information leaflet	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2.3	Arrangements for recruitment of subjects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3	Protocol related															
3.1	Clinical trial protocol with all current amendments	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3.2	Summary of the protocol in the national language	Yes	Yes	Yes	Yes	Yes	Yes		Yes	Yes	No	Yes	Yes	Yes	Yes	Yes
3.3	Peer review of the scientific value of the trial, when available, not compulsory	Yes	No	No	No	Yes	No	Yes	No	Yes	No	Yes	Yes	Yes	No	Yes
3.4	Ethical assessment made by the principal/coordinating investigator, if not given in the application form or protocol	No	No	Yes	Yes	Yes	No		No	No	No	Yes	Yes	Yes	Yes	Yes
4	IMP related															
4.1	Investigator's brochure	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4.2	Investigational Medicinal Product Dossier (IMPD)	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
4.3	Simplified IMPD for known products. See table 1 in application to competent authorities	No	No	No	No	No	No	Yes	No	No	No	Yes	No	No	No	No
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community)	Yes	No	No	No	No	No		Yes	Yes	Yes	Yes	Yes	Yes	Yes	No
4.5	Outline of all active trials with the same IMP	Yes	A	No	No	No	No	Yes	Yes	Yes	No	Yes	Yes	No	No	No

	MS SPECIFIC INFORMATION FOR ETHICS COMMITTEES	AT	BE	DK	FI	FR	DE	EL	IT	IE	LU	NL	PT	ES	SE	UK
4.6	If IMP manufactured in E.U. and if no marketing authorisation in EU:															
	4.6.1 Copy of the manufacturer authorization referred to in Art. 13.1. of the Directive stating the scope of this authorization	Yes	No	No	No	No	No		Yes	No	No	Yes	No	No	No	No
4.7	If IMP not manufactured in E.U. and if no marketing authorisation in EU:															
	4.7.1 Declaration of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP	No	No	No	No	No	No		Yes	No	No	Yes	No	No	No	No
	4.7.2 Declaration of GMP status of active biological substance	Yes	No	No	No	No	No		No	No	No	Yes	No	No	No	No
	4.7.3 Copy of the importer authorization as referred to in Art. 13.1. of the Directive	No	No	No	No	No	No		Yes	No	No	Yes	No	No	No	No
4.8	Certificate of analysis for test product in exceptional cases:												No			
	4.8.1 Where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	No	No	No	No	No		No	No	No	Yes	No	No	No	No
4.9	Viral safety information and data	Yes	A	No	No	No	No		No	No	No	Yes	Yes	No	No	No
4.10	Applicable authorizations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	No	No	No	No	No		Yes	No	No	Yes	No	No	No	No
4.11	TSE certificate when applicable	Yes	No	No	No	No	No		Yes	No	No	Yes	No	No	No	No
4.12	Examples of the label in the national language	No	No	No	No	No	Yes		Yes	No	No	Yes	No	No	No	No
5	Facilities & staff related															
5.1	Facilities for the trial	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5.3	CV of each investigator responsible for the conduct of the trial in a site in the MS concerned (principal investigator)	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
5.4	Information on supporting staff in each site	Yes				Yes			No			No	Yes			
6	Finance related															
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6.3	Compensation to investigators	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
6.4	Compensation to subjects	Yes		Yes	Yes	Yes			Yes	Yes		Yes	Yes	Yes	Yes	
6.5	Agreement between the sponsor and the trial site	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	B	Yes	Yes	Yes	Yes
6.6	Agreement between the investigators and the trial sites	Yes	Yes	No	No	No	Yes		No	Yes		B	No	Yes	No	
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	No	Yes	No	No	No	No	Yes	A	Yes		B	Yes	Yes	No	No

MEMBER STATES' ADDITIONAL EXPLANATION

The symbol # means that the issue is being discussed in the MS.

The letter A preceding information below refer to letter under the MS column in the table above and provide additional explanation about the information to be provided.

Austria: A: the Ethics Committees have not found an agreement concerning the language. The leading Ethics Committees, who deal with multicenter clinical trials in Austria, have to accept documents in English

Belgium: A: Yes, but the protocol or the investigator's brochure can include this information. There is no need for a separate document.

Italy: A: If this agreement is a financial contract, this is not allowed in Italy. If this is only a confidential agreement it is not necessary to provide it to the EC.

Ireland : A

Netherlands: A: Advisable, but not obligatory
B: Should be available on request

Sweden: A: Sponsor can not be the applicant

Attachment 1: new member states

INFORMATION REQUIRED BY MEMBER STATES' ETHICS COMMITTEES

	MS SPECIFIC INFORMATION FOR ETHICS COMMITTEES	CY	CZ	EE	HU	LV	LT	MT	PL	SK	SI		NO	IS
1	General													
1.1	Receipt of confirmation of the EUDRACT number		Yes		Yes	Yes	Yes	Yes ^A	Yes				Yes	
1.2	Covering letter	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes	
1.3	Application form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes				Yes	
1.4	List of Competent Authorities to which the application has been submitted and details of decisions, if available	No	Yes	No	No	No	Yes	Yes	Yes		Yes			
1.5	Copy of Ethics Committee opinion in the MS concerned when available	-	-	-	-	-	-	-	-	-	-	-	-	-
1.6	Copy of any scientific advice													
1.7	If the applicant is not the sponsor, a letter of authorisation enabling the applicant to act on behalf of the sponsor					Yes	Yes	Yes	Yes					
1.8	Will accept application to EC in English			Yes	Yes	Yes	Yes ^A	Yes ^B	No					
2	Subject related													
2.1	Informed consent form	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes	
2.2	Subject information leaflet	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes	
2.3	Arrangements for recruitment of subjects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes	
3	Protocol related													
3.1	Clinical trial protocol with all current amendments	Yes	Yes	Yes	Yes	Yes	Yes	Yes ^C	Yes		Yes		Yes	
3.2	Summary of the protocol in the national language	Yes	Yes	Yes	Yes	No A	Yes	No	Yes		Yes		No	
3.3	Peer review of the scientific value of the trial, when available, not compulsory	No	No	No	Yes	No	Yes	Yes	No		Yes		Yes	
3.4	Ethical assessment made by the principal/coordinating investigator, if not given in the application form or protocol	Yes	No	Yes	No	No	Yes	Yes			Yes		Yes	
4	IMP related													
4.1	Investigator's brochure	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes	
4.2	Investigational Medicinal Product Dossier (IMPD)	No	No	No	No	No	Yes	No	Yes					
4.3	Simplified IMPD for known products. See table 1 in application to competent authorities	No	No	No	No	No	Yes	No	Yes		Yes		No	
4.4	Summary of Product Characteristics (SmPC) (for products with marketing authorisation in the Community)	No	No	Yes	No	No	Yes	Yes	Yes		Yes			
4.5	Outline of all active trials with the same IMP	No	No	No	No	No	No	Yes	Yes				Yes	

	MS SPECIFIC INFORMATION FOR ETHICS COMMITTEES	CY	CZ	EE	HU	LV	LT	MT	PL	SK	SI		NO	IS
4.6	If IMP manufactured in E.U., and if no marketing authorisation in EU:													
	4.6.1 Copy of the manufacturer authorization referred to in Art. 13.1. of the Directive stating the scope of this authorization	No	No	No	No	No	No	No	Yes		No		No	
4.7	If IMP not manufactured in E.U., and if no marketing authorisation in EU:													
	4.7.1 Declaration of the QP that the manufacturing site works in compliance with GMP at least equivalent to EU GMP	Yes	No	No	No	No	No	No	Yes		No		No	
	4.7.2 Declaration of GMP status of active biological substance	No	No	No	No	No	No	No	Yes		No		No	
	4.7.3 Copy of the importer authorization as referred to in Art. 13.1. of the Directive	Yes	No	No	No	No	No	No	Yes		No		No	
4.8	Certificate of analysis for test product in exceptional cases:													
	4.8.1 Where impurities are not justified by the specification or when unexpected impurities (not covered by specification) are detected	No	No	No	No	No	No	No	Yes		No		No	
4.9	Viral safety information and data	No	No	No	No	No	No	Yes ^D	Yes		No		No	
4.10	Applicable authorizations to cover trials or products with special characteristics (if available) e.g. GMOs, radiopharmaceuticals	No	No	No	No	No	Yes	No	Yes		No		No	
4.11	TSE certificate when applicable	No	No	No	No	No	No	Yes	Yes		No		No	
4.12	Examples of the label in the national language	No	No	No	No	No	Yes ^B	Yes ^E	Yes		No		No	
5	Facilities & staff related													
5.1	Facilities for the trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		No	
5.2	CV of the coordinating investigator in the MS concerned (for multicentre trials)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes	
5.3	CV of each investigator responsible for the conduct of the trial in a site in the MS concerned (principal investigator)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes	
5.4	Information about supporting staff in each site					B		Yes	Yes					
6	Finance related													
6.1	Provision for indemnity or compensation in the event of injury or death attributable to the clinical trial	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes	
6.2	Any insurance or indemnity to cover the liability of the investigator and sponsor	Yes	Yes	Yes	Yes	Yes ^C	Yes	Yes	Yes		Yes		Yes	
6.3	Compensation to investigators	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes		No		Yes	
6.4	Compensation to subjects	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes		Yes		Yes	
6.5	Agreement between the sponsor and the trial site	Yes	Yes	No	Yes	No ^D	Yes	Yes	Yes		Yes		Yes	
6.6	Agreement between the investigators and the trial sites	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes		No		Yes	
6.7	Certificate of agreement between sponsor and investigator when not in the protocol	Yes	Yes	No	No	No	Yes	Yes	Yes		No		Yes	

MEMBER STATES' ADDITIONAL EXPLANATION

- Lithuania:** A: Application form in English as well as in Lithuanian is required
B: For authorized products in Lithuania, for other –according to Directive 2001/20/EC
- Malta:** A: A copy of the email containing the notification of the EudraCT number which was received by the applicant
B: Application form has to be filled in in English, other documentation might be in English or Maltese
C: Clinical trial protocol with all current amendments (if any) and summary in English
D: Viral safety studies, if applicable
E: Examples of the label should be in one of the official languages, i.e. Maltese and/or English
- Latvia:** A: Only if available
B: It depends on the protocol
C: If available
D: Should be available on request

Attachment 2:

INFORMATION REQUIRED FOR ETHICS COMMITTEE APPLICATION: MODULE 2 AND LANGUAGE

LANGUAGE OF APPLICATION DOCUMENTS	AT	BE	DK	FI	FR	DE	EL	IT	IE	LU	NL	PT	ES	SE	UK
Application form: format in English accepted								No			Yes				
Application form: answers in English accepted				No				No			Yes				
Application form: answers in local language accepted				Yes				Yes			Yes				
Module 2 required				No				A			No				
Module 2 (if applicable): questions in English accepted				n.a.							n.a.				
Module 2 (if applicable): answers in English accepted				n.a.							n.a.				
Module 2 (if applicable): answers in local language accepted				n.a.							n.a.				

LANGUAGE OF APPLICATION DOCUMENTS	CY	CZ	EE	HU	LV	LT	MT	PL	SK	SI		NO	IS
Application form: format in English accepted			Yes	Yes	Yes	Yes ^A	Yes						
Application form: answers in English accepted			Yes	Yes	Yes	Yes	Yes						
Application form: answers in local language accepted			Yes	Yes	Yes	Yes	No ^A						
Module 2 required			No	No	No	No	Yes						
Module 2 (if applicable): questions in English accepted			n.a.	n.a.	n.a.	n.a.	Yes						
Module 2 (if applicable): answers in English accepted			n.a.	n.a.	n.a.	n.a.	Yes						
Module 2 (if applicable): answers in local language accepted			n.a.	n.a.	n.a.	n.a.	No						

Italy: Not decided yet if Module 2 is necessary for Italy

Lithuania: A: Application form in English as well as in Lithuanian is required

Malta: A: Application form has to be filled in in English, other documentation might be in English or Maltese

Attachment 3

Addresses to the competent authorities and/or where information on the Ethics Committee system in the Member States in the European Union can be obtained

Old member states

AUSTRIA

Ständiges Beratungsgremium
Österreichischer Ethikkommissionen
c/o Ethik-Kommission der Medizinischen Fakultät der Universität
Wien und des AKH-Wien
Borschkegasse 8b/E 06
A-1090 Wien
Österreich
Tel.: + 43 1 40400 2248
Fax: +43 1 40400 1690

Bundesministerium für Gesundheit und Frauen
Abteilung III/A/1
Radetzkystrasse 2
A-1031 Wien
Österreich
Tel: +43 1 71100-0
Fax: +43 1 71100 14760
<http://www.bmgf.gv.at>

BELGIUM

Federal of Public Service Health, Food Chain Security and
Environment
Directorate-General for Medicinal Products
Department Research and Development
Av. Bischoffsheim 33
B – 1000 Brussels
Tel.: +32 2 227 55 00
Fax: +32 2 227 55 55
E-mail: CT.RD@afigp.fgov.be
<http://www.afigp.gov.be>

DENMARK

The Danish National Committee on Biomedical Research Ethics
Slotholmsgade 12
DK-1216 København K
Denmark
E-mail: cvk@im.dk
<http://www.cvk.im.dk>

FINLAND

Clinical trials
Enforcement & Inspection
National Agency for Medicines
PO Box 55
FIN-00301 Helsinki
Finland
Tel: + 358 9 473341
Fax: + 358 9 47334 323
<http://www.nam.fi>

Ethics Committee information:
The National Advisory Board on Health Care Ethics (ETENE)
The Sub-Committee on Medical Research Ethics (TUKIJA)
Ministry of Social Affairs and Health
PO Box 33
(Kirkkokatu 14)
Helsinki
00023 Government
Tel.: + 358 9 16001 (switch board)
Fax : +358 9 160 74312
E-mail: etene@stm.fi
<http://www.etene.org>

FRANCE

Direction Générale de la Santé
Sous direction des Politiques de santé et stratégies, SDIC
8, avenue de Ségur,
753 50 Paris 07 SP
Tel.: +33 1 40 56 60 00
Fax: +33 1 40 56 67 69

GERMANY

Permanent Working Group of German Ethics Committees
Ottostrasse 12
D-50859 Köln
Tel.: +49 2234 7011 570
Fax: +49 2234 7011 140
E-mail: doppelfeld@aerzteblatt.de
<http://www.ak-me-ethik-komm.de>

ITALY

Clinical Trials and Research
Italian Medicines Agency – AIFA
Via della Sierra Nevada, 60
00144 Rome
Italy
E-mail: sperimentazione.clinica@sanita.it
http://oss-sper-clin.sanita.it/consultazione_ce_pub.htm

LUXEMBOURG CNER
CRP-Sante
B.P. 2021
L-1020 Luxembourg

NETHERLANDS Central Committee on Research Involving Human Subjects (CCMO)
PO Box 16302
7500 BH The Hague
The Netherlands
Tel: + 31 70 3406700
Fax: + 31 70 3406737
E-mail: ccmo@ccmo.nl
<http://www.ccmo.nl>

PORTUGAL Comissão de Ética para a Investigação Clínica
Parvilhão 17A
Parque da Saúde de Lisboa
Avenida do Brasil, 53,
1749-004 Lisboa
Tel: +35 121 7985340
Fax: +35 121 7987209

SPAIN Coordinating Center for Research Ethics Committees
Paseo del Prado, 18 – 20
28071 Madrid
Spain
E-mail: cc-ceics@msc.es
<http://www.msc.es>

SWEDEN Clinical Trial Unit
Medical Products Agency
PO Box 26
S- 751 03 Uppsala
Sweden
Tel.: + 46 18 17 46 00
Fax: + 46 18 54 85 66
E-mail: clintrial@mpa.se
<http://www.mpa.se>

Ethics Committee information:
Scientific Research Council
S- 103 78 Stockholm
Sweden
Tel.: + 46 8 546 44 000
Fax: + 46 8 546 44 180
<http://www.vr.se>

UNITED KINGDOM Central Office for Research Ethics Committees (COREC)
50 Eastbourne Terrace
London W2 3 QR
UK
Tel.: + 44 20 7725 3431
Fax: + 44 20 7725 3465
<http://www.corec.org.uk>

New member states

CYPRUS

Cyprus National Bioethics Committee
1 Apellis st.
1403 Lefkosia
Cyprus
Tel.: +357 22 889 100 or 103
Fax: +357 22 665080
E-mail: roc-law@cytanet.com.cy

CZECH REPUBLIC

State Institute for Drug Control –
Branch of Clinical Trials and Pharmacovigilance
Šrobárova 48
100 41 Praha 10
Czech Republic
Tel.: +420 272 185 817
Fax: +420 272 185 816
E-mail: klin.sekret@sukl.cz
<http://www.sukl.cz>

ESTONIA

Ethics Review Committee on Human Research of the University of
Tartu
19 Ravila Street
51014 Tartu
Estonia
Tel.: +372 7 374 350
Fax: +372 7 374 352

Tallinn Medical Research Ethics Committee
Hiiu 42
11619 Tallinn
Estonia
Tel.: +372 6 593 924
Fax: +372 6 593 901

HUNGARY

National Institute of Pharmacy
Budapest
Zrínyi u. 3
Hungary
H-1051
P.O.Box 450
Tel.: + 36 1 266 28 74
Fax: + 36 1 266 28 74
E-mail: eggenhofer.judit@ogyi.hu

Medical Research Council
Ethics Committee for Clinical Pharmacology
Budapest
Arany János u. 6.-8.
Hungary
H-1051
Tel.: +36 1 301 78 71
Fax: +36 1 331 17 85
E-mail: magyari.ilona@eum.hu

LATVIA

Ministry of Health
Department of Pharmacy
72 Brivibas Street
Riga, LV-1011
Latvia
Tel.: +371 7876110
Fax: +371 7876111
E-mail: Kristine_Pavlovska@vm.gov.lv

LITHUANIA

Lithuanian Bioethics Committee
Vilniaus str. 33-230
LT-01119 Vilnius
Lithuania
Tel./fax: +370 5 212 45 65
E-mail: lbek@sam.lt
<http://bioetika.sam.lt>

MALTA

Competent authority:
Clinical Trials Unit
Licensing Directorate
Medicines Authority
198, Rue D'Argens,
Gzira, GZR 03
Malta
Tel.: +356 23439000
Fax: +356 23439161
E-mail: prelicensing.mru@gov.mt
<http://www.health.gov.mt/mru>

Ethics Committee:
Health Ethics Committee
Castellania Palace
Merchant's Street
Valletta CMR02
Malta
Tel.: +356 25599000

Fax: +356 25599385
E-mail: hec@gov.mt

POLAND

Office for Medicinal Products, Medical Devices and Biocides
Central Register of Clinical Trials
30/34 Chelmska Str
00-725 Warsaw
Poland
Tel.: +48 22 841 67 42 ext 335
Fax: +48 22 851 43 66
<http://www.urpl.gov.pl>

SLOVAKIA

State Institute for Drug Control
Section of drug safety and clinical trials
Kvetná 11
825 08 Bratislava 26
Slovak Republic
Tel.: +421 2 5293 17 34
Fax: +421 2 5293 17 34
E-mail: trial-sukl@sukl.sk
<http://www.sukl.sk>

SLOVENIA

Agency for Medicinal Products and Medical Devices
Mali trg 6
1000 Ljubljana
Slovenia
Tel.: +386 1 47 86 240
Fax : +386 1 47 86 260

Clinical Centre,
Institute for Clinical Neurophysiology (Ethics Committee)
Zaloska 7
1525 Ljubljana
Slovenia
Tel.: +386 1 522 15 00
Fax: +386 1 522 15 33

EFTA

NORWAY

Norwegian Medicines Agency
Sven Oftedalsvei 6
NO-0950 OSLO
Norway
Tel.: +47 22 89 77 00
Fax: +47 22 89 77 99
E-mail: post@noma.no
<http://www.noma.no>

The National Committees for Research Ethics
Street address: Prinsensgate 18
Postal address: P.O. Box 522, Sentrum
N-0105 Oslo
Norway
Tel.: +47 23 31 83 00
Fax: +47 23 31 83 01
E-mail: post@etikkom.no
<http://www.etikkom.no>

Attachment 4

Information on the application form for the Ethics Committee

Module 1

This first module of the application form to be used to the Ethics Committee is the same as the form used in the submission to the competent authority.

To be found in ‘Detailed guidance for the request for authorisation of a clinical trial on a medicinal product for human use to the competent authorities, notification of substantial amendments and declaration of the end of the trial’ Annex 1.

Module 2

Module 2 is optional and represents a national or local Ethics Committee application form. This second module can contain headings that might be helpful for the ethical review by the Ethics Committee. The aim of the example given in this section is to provide guidance on how trial and site specific information might be presented to present the ethical issues and describe the trial in lay language. The list of items addressed is not complete and can be modified according to the responsibilities assigned to the Ethics Committee in the Member State.

1.	EudraCT trial number Ethics Committee trial ID
2.	Title of the project (understandable for lay persons)
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 possible gain 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, temporarily 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 unforeseen / 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. Procedures of the site to check if the subject participates simultaneously in other research or if a required period has elapsed 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 the investigator(s).

**NAME AND SIGNATURE OF APPLICANT - CO-ORDINATING
INVESTIGATOR/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:

Attachment 5

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 and national recommendations.

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 should be provided to the Ethics Committee on the procedures to handle the answers to the advertisement. This might contain information on the qualifications of the person who will be responsible for the first contact with the subjects, e.g. a nurse. This is especially important when patients and not healthy volunteers 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. There might be a description of how the patient will be given advice or help to contact a relevant institution/clinic not related to the planned trial.

All information to be provided to the respondent should be submitted to the Ethics Committee for approval. If there is a screening procedure to evaluate the suitability of the respondent a separate information letter might be used, giving information on the procedure and the reasons for screening. It should be explained what the consequences might be in case of a certain outcome of the screening. For example if a biopsy shows pathological changes the patient will be asked if he/she is willing to participate in a trial and a brief overview of the trial is given. For the trial itself, a more extensive information letter could provide the detailed information on the trial. This letter 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 subject 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.

Attachment 6

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. Subject information, general aspects.

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).

In addition, written information should be provided on:

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. The names and addresses of the investigator, study nurse etc who are responsible for taking care of the included subjects.
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 additional care that might be needed due to findings during follow up.
4. Any financial or other ties to the sponsor as well as institutional affiliations of the investigator as well as the name and address of sponsor /sources of funding.
5. The Ethics Committee positive opinion.
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 person responsible for keeping the key and who will have access
 - in the case of retention of subject samples and information:
 - to 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
7. The subject's right to obtain updated information about what data is recorded as well as the right to require corrections of errors

8. The right of the subject (or parent or legal representative) to withdraw consent to participate in the trial.
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.
10. The right of the subject (parent or legal representative) to be informed of any plans for new analyses on retained identifiable material that were not foreseen when the subject consented to participate in the study. The investigator might have to ask for new consent and the subject has the right to refuse further analyses, according to national rules.

2. Information in pharmacogenetic trials

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. Subjects should be informed of the possible consequences of genetic testing, e.g. for obtaining insurance policies etcetera. When applicable, the information on the genetic part of the trial might be separate from the information on the other part. Information should be provided on the possibility for the subject to abstain from the genetic testing but still be able to participate in the non-genetic part of the trial, according to national recommendations. Further information on pharmacogenetic trials can be obtained from the position paper from the Committee for proprietary medicinal Products¹⁴.

3. Trial specific and general explanatory information to subjects.

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 reasons for quality control and quality assurance and the need for Source Data Verification (SDV) as well as measures to protect the confidentiality of personal information, systems for labelling, analysing and publishing data and availability of insurance/indemnity systems could be explained. This general second part, once approved by the Ethics Committee, could be used where appropriate in similar trials in that Member State.

¹⁴ Position paper on terminology in pharmacogenetics, EMEA/CPMP/3070/01