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
Daft Revision 3, […] 2009

Comments submitted by

Road Map Initiative for Clinical Research in Europe

List of content:

"The list of content of this revised version does not include anymore Attachment 1: "Information required by Member States' Competent Authorities".

Comment:

1) Despite the fact that this list was incomplete and not fully up-to-date in Revision 2 it was very helpful to prepare the CTAs for the different Member States. It should be maintained and updated. Ideally, there should be only ONE centrally submitted dossier accepted by all Member States. The list of content of this central dossier should be attached as Attachment 1. There should be a list of content for clinical trials with unauthorized IMPs, with authorized IMPs and for non-interventional studies.

   Alternatively there should be a single, central website where this detailed information is kept and maintained and the guideline should direct the reader to this.

2) "The list of content of this revised version does not include anymore Attachment 5: "Headings for aspects of a trial that might involve a substantial amendment ".

   Comment: The inclusion of this section into the main body of the text makes sense.

3) "The list of content of this revised version does not include anymore Annexes 1-3: "Application Form, Substantial Amendment Form, Declaration of End of Trial Form".

   Comment: These annexes should be maintained as they are helpful to better understand the main text.

1. Introduction
   1.1 Legal Basis

Comment: There is an error in the second bullet point:

- *Notifications of substantial proposed amendments; and*
  Correctly it should say: Notifications of proposed substantial amendments; and

Comment: There is an error in the text beneath the bullet points:

- …,and declaring the end of a clinical trials shall consider this guidance when applying Directive 2001/20/EC and its implementing acts and guidance.
  Correctly it should say: and declaring the end of a clinical trial~~s~~ shall consider…..

General comment: This section refers strongly to the completeness of the CTD's requirements. Which "power" does this request in a guidance have to ensure that the Member States adapt their national legislation after release of this guidance to adhere to this strict request?

1.2 Scope

No comments.

1.3 Definitions

As reference (13) for the definition of "non-interventional study" the "Guidelines on Pharmacovigilance for Medicinal Products for Human Use" in Volume 9 of "Notice to Applicants" is provided on page 90:

This Chapter of Volume 9A applies to the conduct of studies sponsored by the pharmaceutical industry, which evaluate the safety of products with a marketing authorisation for human use. They encompass all studies carried out to evaluate the safety of authorised medicinal products and for which a Marketing Authorisation Holder takes responsibility for their initiation, management and/or financing. This includes studies where the medicine is provided by the Marketing Authorisation Holder and those where it is prescribed in the normal way both in general practice and in the hospital setting. A study follows a protocol, which defines the study population and the design for its conduct and analysis. Therefore, in this context, databases searches to count e.g. number of adverse events or number of prescriptions are not considered studies.

The present guidance provides a framework whereby a variety of data collection methods may be used to evaluate the safety of authorised medicinal products. Whilst it is recognised that the study design used needs to be tailored to particular products and safety concerns, this guidance defines the essential principles to be applied in a variety of situations. The study methods in this field continue to develop and therefore there will be a need for regulatory review guidance to ensure that it reflects advances made in the assessment of product safety.

A post-authorisation safety study is defined in Article 1 (15) of Directive 2001/83/EC as a pharmacoepidemiological study or a clinical trial carried out in accordance with the terms of marketing authorization, conducted with the aim of identifying or qualifying a safety hazard relate to an authorised medicinal product". The definition of non-interventional trial is provided in Article 21 of Directive 2001/20/EC: "A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorisation. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within the current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of the collected data".

In this context it is considered important to clarify that interviews, questionnaires and blood samples may be considered as normal clinical practice. Based on these definitions a fundamental distinction can be made between non-interventional (observational) and interventional post-authorisation safety studies. The latter are considered clinical trials falling under the scope of the Directive 2001/20/EC.

If the definition of non-interventional is not met, the study should be considered as interventional. "

Comment: the definition should be described in this CTA guidance document – sharp and to the point – and not referenced in total to this Volume 9 guidance.

2. Request for a Clinical Trial Authorisation
   2.1 Procedural Aspects

General comment:

1) It is very good that this revision states clearly that the 60 days time frame starts with the submission of a valid request and not after review, independent of its result. However, it is not clear, how much time the NCA has for the review of the dossier and that, if the dossier was not complete, the clock starts only with confirmation of receipt of the complete dossier.

2) The VHP should be explained here.

3) This guidance should define clearly the responsibilities of the competent authority versus the ethics committee concerning aspects to be reviewed by the one or other party. This would avoid lots of delays through back and forth of requests from NCAs and ECs.

2.1.2: Applicable delays for authorisation, tacit authorisation

Comment: There is an error in the first paragraph:

In accordance with Article 9(4) of Directive 2001/20/EC, consideration of a valid request for authorisation by the national competent authority shall be carried out as rapidly as possibly and may not exceed 60 days, subject to exceptions set out in this Article

Correctly it should say: …as rapidly as possible…

2.1.3: Scope

1) The conditions for validity of the authorisation within the VHP should be defined.

2.1.4: Follow-up to request for authorization

2.1.5: Interface with other authorization requirements
(only added this here as Ingrid has listed all headers, however, I have no comment about this section)

2.1.6: Other issues

1) Only English submissions should be acceptable in all MS. This should also be the case for the cover letter and the application form.

2.2 Covering Letter

Comments:

1) The headline should say "cover" letter as this is the term used during the rest of the text

2) *"Its heading should contain the EudraCT number and the sponsor protocol number with a title of the trial."*

   Comment: As it is nowadays required for most studies to be registered in an international publicly accessible registry, the registry information should also be in the cover letter. Alternatively, the registry number should at least be provided in the Application Form.
   The Application form gives opportunity to list the registry number for only one Registry (A.6 ISRCTN number3, if available:). This should be amended on the Application form since trials may also be listed in other Registries, including *ClinicalTrials.gov* or those approved by the WHO ICTR Platform.

3) "*Moreover, the covering letter should highlight if the trial involves a first administration of a new active substance to humans."*

   Comment: According to the FiM guideline the cover letter in these cases should also contain a high-level analysis of potential risks and the most relevant elements of the plan to mitigate these risks, reference to the details in the protocol.

2.3 Allocation of the EudraCT number

No comments.

2.4 Application form

No comments.

2.5 Protocol

Comment: The protocol should contain the registry number on the cover page
Comment: A repetition of the elements to cover in FiM trials is not necessary here. Reference to this guideline would be sufficient. Especially the last paragraph in this section is not relevant for this CTA guidance.

2.6 Investigator's Brochure

No comments.

2.7 Investigational Medicinal Product Dossier

No comments.

2.8 Simplified IMPD

Comments:

1) The headline in 2.8.3 contains two times the same words “Possibility to refer to the”
2) The SmPC should not need translation

2.9 Non-investigational products used in the trial

No comments.

2.10 Other documents to be submitted

Comment: use the term “cover” letter instead of “covering” letter for consistency.

3. Notification of amendments

3.1 Legal basis and scope

No comments.

3.2 The notion of “amendment”

Comment:

1) This section introduces a new approach. It makes sense but how it should be defined how to call a change to the protocol during the approval process, e.g., “Request for change of the submitted CTA dossier”?

2) For consistency, replace: “Article 10(a) of Directive 2001/20/EC refers only to “amendments to the protocol”. This is to be understood as encompassing all documentation submitted in the context of the submitted protocol”
with approved protocol.

3) Please rephrase this sentence: “Changes of the contact details of the sponsor or any (e.g. a change of email or postal address) are not considered as amendment, if the sponsor remains identical.”
By
“Any changes of contact details of any person or organisation mentioned in the dossier are not considered as substantial amendment as long as the sponsor can be identified.” This would help to avoid a lot of substantial amendments.

4) I do not understand the sentence: “ This information should be transmitted to the national competent authority of the Member State concerned as soon as possible.” Does this mean that any change of address should be provided to the competent authority in form of a “Letter with administrative information”? What is then the difference in the administrative burden?

3.3 The notion of "substantial"

Comments:

1) Not all substantial amendments need full review. There should be a category of "administrative substantial amendments" which could be subject to implicit approval within 7 days.
2) Different Member States have compiled lists of examples for "substantial". These lists should be compiled into one exhaustive list here.
3) Alternatively, at least the following situations should be added:

Additional examples of "substantial" amendments:

- a change of sponsor or sponsor's legal representative;
- changes to study documentation such as participant information sheets, consent forms, questionnaires, letters of invitation, letters to GPs or other clinicians, information sheets for relatives or carers
- a change to the insurance or indemnity arrangements for the study

Additional examples of "non-substantial" amendments:

- minor clarifications of the protocol
- changes in funding arrangements
- changes in the logistical arrangements for storing or transporting samples;

3.4 Procedure of notification - Who should be notified?

Comment: here should be specified that a substantial amendment can only be implemented/become active, once approval has been achieved. In the meantime the trial can continue under the original conditions as long as the substantial amendment does not refer to an "urgent safety measure" that would require a temporary halt of the trial.

3.5 Format and content of notification

3.5 (f) in case of changes to the entries of the EudraCT application form, the guideline asks for a print out of this form, with the amended fields highlighted, to be submitted alongside of the amendment notification. The MHRA, for example, now only accepts electronic documents on disc. Clarification would be appreciated whether this requires a scanned, electronic, copy of the printout to be submitted.

3.6 Time for response, implementation

No comments.

3.7 Ex post notification of urgent safety measures

No comments.

3.8 Temporary halt of a trial

No comments.

3.9 Suspension/prohibition of a clinical trial by the national competent authority in case of doubts about safety or scientific validity

No comments.

3.10 Non-compliance with the applicable rules on clinical trials

No comments.

3.11 Non-substantial amendments

No comments.

4. Declaration of the End of a Clinical Trial

4.1 Legal basis and Scope

No comments.

4.2 Procedure for declaring the end of the clinical trial

No comments.

4.3 Clinical trial summary report

Comment: Please replace “can” with “usually will” in the following sentence as a report summary cannot be produced within 90 days after last patient out: “?the clinical trial summary report can be submitted subsequently to the end of trials notification.”

4.4 Follow-up

No comments.