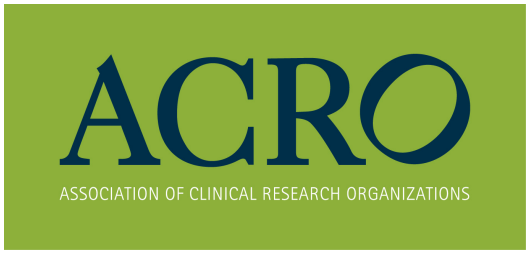
SUBMISSION OF COMMENTS ON

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

Name of Organisation	Country
ACRO (Association of Clinical Research Organizations)	ACRO member companies are located throughout the European Economic Area (EEA), Eastern Europe, the Americas, and Asia-Pacific regions.

Submitted 8 September 2009 to **entr-pharmaceuticals@ec.europa.eu**



1. GENERAL COMMENTS

The Association of Clinical Research Organizations (ACRO) represents the world's leading clinical research organizations (CROs). Our member companies provide a wide range of specialized services across the entire spectrum of development for new drugs, biologics and medical devices, from pre-clinical, proof of concept and first-in-man studies through postapproval and pharmacovigilance research. Last year, ACRO member companies conducted more than 9,000 clinical trials involving nearly 2 million participants in 115 countries. With more than 66,000 employees engaged in research activities around the world, ACRO advances clinical outsourcing to improve the quality, safety, and efficiency of biomedical research.

ACRO thanks the Commission for issuing this Guidance relating to requests for authorisation for clinical trials, notification of substantial amendments and declaration of the end of a trial. As a stakeholder in the clinical trials process, the global CRO industry is committed to assisting the Commission in the harmonisation of clinical trial conduct through the application of good clinical practice. Thus, we are pleased to submit comments on the above-referenced Draft Guidance during the public consultation.

ACRO found the updated guideline to be well written and helpful, in particular through the increased use of referenced guidance documents. In general, we understand the protocol submitted for authorization now needs to state a clear and unambiguous end of trial, and include safety strategies, particularly for first-in-man studies, both of which are positive developments. We applaud the further guidance provided on possibilities of cross-referencing between IMPD, IB and SmPC data, as well as consideration of a valid request for authorisation in which validation will not delay the consideration. While these clarifications and additions are useful, we have significant questions in regards to actions the Commission proposes to take to achieve harmonisation. Ideally, ACRO would like to see an EU Regulation that establishes unified, comprehensive and fully integrated standards for clinical trials with medicinal products for human use in the European Economic Area, and we recognize the Commission is working towards this. Further, the current 2005 guidance document includes a tabular listing of document requirements by Member States which is missing in this draft. We would request that a similar table be provided once review is complete as each Member State has their own interpretation in practice.

Thank you again for the opportunity to submit comments on the updated guidance. Please feel free to contact ACRO at any time for additional input.

Respectfully submitted,

Douglas Peddicord, Ph.D.
Executive Director

8 September 2009

2. SPECIFIC COMMENTS ON TEXT

Section # + Paragraph # + Page #	Comments	Suggestions/Proposed Changes
1.1.+2+4	The clarification that member States are not allowed to "add on" the Community Rules is very welcome, but this is exactly what happened when the Directive was originally implemented. How does the Commission plan to prevent such adding on in future and what action is the Commission planning to address adding on that occurred in the past?	ACRO believes descriptions of how to address any “add-ons” that are noticed by a CRO/Sponsor would be very useful.
1.1+Last paragraph+5	Seems reasonably clear, but could use some emphasis.	ACRO suggests changing "shall consider" to "shall follow", to emphasise need for compliance; similarly, throughout the documents, consider replacement of "should" by "must".
1.2+2+5	Paragraph 2 provides references to guidance documents to advanced cell therapies but no specific examples of the type of advanced therapies are provided.	ACRO believes a summary of the type of advanced therapies covered by references of guidance documents e.g. “gene therapy, somatic therapy, tissue engineered products etc.” would be useful.
2.1.2+2+7	Paragraph 2 states “Day 0 is the date of submission of the request. If the request is valid, on day 60 at the latest the consideration of the request has to be finalised.” While this clarification is very welcome, national laws in some Member States have incorporated in law a specific validation period. How does the Commission propose to address this to achieve harmonization? In practice, all Member States count Day 0 as the date of receipt of a valid application. What steps is the Commission taking to achieve harmonization on Day 0 as the date of submission?	In practice Day 0 is date of receipt of a submission by the CA, so this may need to be corrected.

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2.2+2+9	Topics to be listed in the cover letter have been increased e.g. description of population, design, IMPs/nIMPS, GMOs, radiopharmaceuticals, narcotics etc.	ACRO believes guidance on the length of the letter may be needed.
2.4+3+10	Text states [(c) In the sponsor's opinion, it is reasonable for the proposed clinical trial to be undertaken]. The current EudraCT form states the Applicant's opinion in section I: Is the EudraCT form going to be updated or does the guidance document need to state the Applicant's opinion?	ACRO suggests further clarification is needed re: comment.
2.4.+Last Paragraph+ 11	Text reads [Certain information contained in the application form is going to be made public, following its entry into EudraCT by the national competent authority of the Member State concerned.]	ACRO believes a description of the information to be made public would be a useful guide.
2.7.1+7+15	Text reads [-certification of the CMP compliance of the manufacturing of any biological substance]	Is this a typographical error and should read "GMP" or does this refer to a compliance monitoring program (CMP)?
2.7.2+3+16	The title of the referenced guideline is incorrect. The title is Guidance on Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals.	Correct referenced guideline title.
2.7.3+4+17		ACRO believes a definition of "third countries" would be very useful.
2.8+4+18	Text reads [the information related to the IMP is contained in the SmPC and has been assessed previously as part of a marketing authorisation in any Member State or in an ICH country]	ACRO believes a definition of "an ICH country" would be very useful.

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	This allows the use of the SmPC (or equivalent labeling) approved by an ICH country in place of the Investigator Brochure. Does "an ICH country" mean USA and Japan only or does it also include the ICH observers, Canada and Switzerland?	
2.8.3+Title+ 18	"Possibility to refer to the Possibility to refer to the SmPC" is a somewhat confusing title.	
2.9+3+21	As currently written, this could conceivably permit a competent authority to request a NIMP dossier routinely. It would be preferable to give some indication of the types of circumstances in which such a request would be justified.	ACRO believes a description of the types of circumstances which justify routine requests for a NIMP dossier would be a useful.
3.1+2+21	This clarification is welcome but is not consistent with some national laws/guidelines that, additionally, require that details of some types of amendment are submitted for information. How does the Commission propose to address this to achieve harmonisation?	
3.2+7+22	By definition, many IB updates will contain substantial new data - this is one of the reasons for producing new IBs. To classify these as substantial amendments seems overcomplicated. In addition, the process to be followed, e.g., notification to all CAs and ECs in respect of all ongoing studies, seems unclear and potentially onerous.	ACRO suggests further clarification is needed re: comment.

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3.3 + 5+23	We acknowledge that the examples given in the revised draft serve as guidance and are not an exhaustive list. We note that in practice each Member State has a different interpretation of substantial/non substantial and this leads to much confusion.	
3.3.1+10+23	Text reads [Change of the number of trial subjects per trial site as long as the total number of trial subjects is the same] This is typically not a substantial amendment. The guidance should clarify whether "total number of trial subjects" refers to the total number in the trial in the Member State concerned or in the entire trial.	ACRO suggests clarification of whether "total number of trial subjects" refers to the total number in the trial in the Member State concerned or in the entire trial.
3.3.1+14+24	Text reads [Limited lengthening of the trial time]	ACRO believes a more specific definition of "Limited lengthening of the trial time" would be very useful.
3.3.2+2+24	Given the widespread differences in the interpretation of Annexe 13, this section may increase confusion and diversity of interpretation.	ACRO believes further clarification is needed re: comment.
3.4 +4+25 3.6+5+27	Clearer guidance on whether the other body should be informed would be preferred – the word “recommended” is not definite.	Since the other body does not assess the initial document and the amendment can be implemented without the opinion/grounds for non-acceptance of the other body we find it is time consuming to notify the other body of this amendment and does not add any value/benefit. The notification is related to a change to a document they do not review, have no opinion of and increases reporting. ACRO strongly suggests that it is NOT recommended to inform the other body.

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3.5+5+26 3.5+3+27	Footer 46 states that the CTA form should contain the original protocol version and date and should not be amended. However section f states that if the substantial amendment implies changes to entities of the EudraCT form the Sponsor should submit a revised copy incorporating the changes.	ACRO suggests that the protocol version and date are amended on the EudraCT form.
3.6+4+27	Directive 2001/20/EC does not establish a legal time limit for competent authorities to deal with substantial amendments. What action will the Commission take to ensure that competent authorities respect the proposed 35 day timeline? It would also be good to clarify whether day 0 is day of submission, as is the proposed case for the initial CT Application.	ACRO suggests defining whether day 0 is date of submission or receipt of submission.
3.7+6+28	This potentially allows numerous additional tests to be introduced and recruitment to continue before the CA and/or EC has had the opportunity to consider the new information which provokes these tests; this seems unsatisfactory.	ACRO suggests the inclusion of the recommendation that recruitment should be suspended in such circumstances. ACRO also suggests the inclusion of a time limit within which the sponsor is expected to notify the competent authority and ethics committee that an urgent safety measure has been implemented.
4.2.2 +1+31	The details regarding what information is required to be provided to the Competent Authority for an early terminated/premature end trial has been removed.	ACRO suggests to keep current text

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4.3+1+31	The one year submission timeline for CSR summary submission has been removed.	ACRO suggests confirmation if there is a timeline.