Association of Clinical Research Organizations
Comments in Response to
the European Commission's Public Consultation on the
Revision of the Clinical Trials Directive 2001/20/EC Concept Paper

May 13, 2011

I. Introduction

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. Annually, ACRO member companies conduct more than 9,000 clinical trials involving nearly 2 million participants in 115 countries. With more than 70,000 employees engaged in research activities around the world, of which over 24,000 are located in the European Union/European Economic Area (EEA), ACRO advances clinical outsourcing to improve the quality, safety, and efficiency of biomedical research.

The European Commission's 09/02/2011 Public Consultation on the Concept Paper regarding the revision of the "Clinical Trials Directive" (2001/20/EC) provides another welcome opportunity to provide feedback to the Commission on its current thinking for the future of the European clinical trials framework. ACRO's member companies have greatly invested in the clinical development infrastructure in the EU and are committed to assisting the Commission with the development of improvements that support the vital continuance of research in the region. With this in mind, we are pleased to submit comments on the Concept Paper during the public consultation.

II. Boxed "Consultation Item" Comments

Consultation item no. 1:

ACRO agrees that a single submission would greatly reduce the administrative work of sponsors for submission of documentation to the Member States concerned. Centralizing submissions would lend efficiency to the CTA process for all stakeholders involved.

ACRO emphasises the need to establish a single regulatory framework for clinical trials that is administratively simple and applies a risk-adapted approach to the implementation of common standards throughout the Community to ensure the quality of trials and the well-being of trial subjects.

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Consultation item no. 2:

ACRO agrees that a separate assessment would insufficiently address the issues described, as difficulties created by independent assessments would remain. A centralized review streamlines the process, and would give clearer definition to the role of individual Member States in that process.

Consultation item no. 3:

ACRO's preferred option for trials involving more than one Member State would be a central assessment, leading to a single clinical trial authorization valid throughout the Community. While this option most clearly ensures the establishment of a recognizable Community standard for clinical trial approval and regulation, ACRO understands that it may be very costly to establish a scientific committee with representatives of all Member States which places further management responsibilities on the EMA. This option would, however, allow for additional Member States to be added easily after the review has been completed.

Consultation item no. 4:

ACRO believes the 'coordinated assessment procedure' (CAP) has been thoroughly described in this catalogue.

Regarding the provision of a 'Reporting Member State" to lead the assessment, ACRO questions if all agencies truly have the capacity to function in this role given the fact that the smaller countries have only a very limited staff number working on CTA review.

Consultation item no. 5:

ACRO agrees to the inclusion of the aspects under section a) in the scope of the CAP, focusing on the risk-benefit assessment, as well as aspects related to quality of the medicines and their labelling.

Further, ACRO agrees that aspects under b) and c) relating to ethical issues and local expertise would not be suitable for the CAP and should remain within the ambit of the individual Member States, and recommends that ethics committees in the Member States take responsibility for the evaluation of these aspects of a clinical trial.

Legal clarity on the respective scope of assessment in these three areas by the designated responsible body is greatly appreciated.

Consultation item no. 6:

ACRO supports the approach to vote and decide by simple majority in cases of disagreement with the assessment report. As outlined in this concept paper, the purpose of the CAP is to allow for a joint assessment by Member States concerned, which ACRO recommends should lead to a single clinical trial authorisation that would be valid throughout the Member States involved. Divergence from this purpose and process regarding the risk-benefit assessment opens the door to revert back to the inefficient system of multiple assessments that currently exists.

The option to refer matters to the Commission or the Agency for a decision at the EU level is in line with the vision for a joint assessment and single decision, yet could easily have a negative effect on timelines and cost.

The option to 'opt out' is least preferable to ACRO as it negates the purpose of the CAP, as explained above. While the broader public health and safety of trial participants is and should always be paramount, the CAP would allow national practice to be taken into account and concerns by individual Member States to be independently addressed during the review of ethical issues and local expertise.

Consultation item no. 7:

ACRO supports the approach to make the CAP mandatory for all multinational trials, provided that arrangements are put in place to ensure that common standards are applied throughout the Community, whether the trial is single-country or multinational. We agree that it seems unnecessary for single country trials to undergo assessment through the CAP, yet common standards will strengthen the effectiveness of the system, and, in turn, the safety of trial participants and the public at large.

ACRO also recommends that all Clinical Trial Applications should be electronic, linking in with the existing EudraCT system.

Consultation item no. 8:

ACRO fully supports the concept of applying a risk-adapted approach to the application of common standards. Based on the limited information provided, the pre-assessment would be a positive step, and yet it is imperative that such a measure shortens overall timelines as opposed to extending them. ACRO further recommends that the pre-assessment should be mandatory for all clinical trials and the identification of 'type-A trials' in the pre-assessment extends uniformly to all Member States involved.

Regarding substantial amendments, ACRO agrees there should be clear rules on the timelines for approval by the national competent authority, and further suggests that greater consistency is required in the interpretation over what is 'substantial.' Mandatory use of the CAP for multinational clinical trials, together with appropriate guidelines and common standards for single-country trials, would help to ensure this consistency.

Consultation item no. 9:

ACRO believes that the divergent interpretations of the term "non-interventional", especially with respect to "no additional diagnostic or monitoring procedure and use of epidemiological methods," should be addressed as soon as possible. As such, ACRO agrees that a broader definition of 'non-interventional trial' may not be the answer, but rather a clearer, detailed definition would reduce the likelihood of inconsistent interpretation. Harmonized, proportionate requirements which would apply to all clinical trials falling within the scope of the present Clinical Trials Directive may still create confusion and divergent interpretations and do not address the urgent need for a clear definition of those trials that are subject to the Directive and those that are not..

Consultation item no. 10:

ACRO agrees that all clinical trials, regardless of the nature of the sponsor, should be regulated in the same way and in accordance with common standards to ensure the quality of clinical trials and to safeguard trial subjects.

Consultation item no. 11:

ACRO agrees this approach would assist in harmonizing rules for conducting clinical trials in the EU. Very clear guidance will be needed to ensure that all parties have a common understanding of how a risk-adapted approach to quality should be implemented.

Consultation item no. 12:

ACRO recommends the following key aspects on which more detailed rules are needed:

- Protocol deviations and protocol violations: Harmonized definitions and reporting requirements for ECs and CAs.
- Responsibilities of the ECs and CAs to patients enrolled into trials: Both have clearly defined responsibilities regarding approvals, but few relating to conduct, and to communication to patients when conduct has been inappropriate, e.g., the recruitment of ineligible subjects into trials, especially those who may have gone on to experience serious adverse reactions.

- Harmonized procedures for how to consent patients into paediatric and emergency trials.
- Acceptance of Third Country data
- Role and responsibilities of the legal representative of a sponsor that is not established in the Community. ACRO also recommends that the Commission considers replacing the term "legal representative" with one that is more descriptive of the role and responsibilities – see response to Consultation Item No. 16.
- Document requirements needed for an application to the regulatory authority and the ethics committee.
- Classification and management of substantial and non-substantial amendments.

Consultation item no. 13:

ACRO agrees that this approach would assist in the simplification, clarification and harmonization of the rules for medicinal products used in the context of a clinical trial.

Consultation item no. 14:

ACRO supports a policy option that ensures adequate protection for participants of clinical trials, and clearly states that the sponsor of a clinical trial (even when the sponsor is established outside the EU) retains the overall legal responsibility and liability for all aspects of the trial. Further, we recommend that the new legislative text, as indicated in the current text of Directive 2001/20/EC, should clarify for all parties that it is the responsibility of the ethics committee to verify sponsor insurance.

Consultation item no. 15:

ACRO supports maintaining the concept of a single sponsor (option 1), with or without the stated provisions, as the sponsor retains overall legal responsibility and liability for all aspects of the trial. Should option 2 be pursued allowing for a concept of 'multiple sponsorship'/'joint sponsorship'/'shared sponsorship'/co-sponsorship,' this fact remains unchanged but will lead to complexity and confusion relative to the transfer of trial-related duties and functions to other parties (e.g., CROs) by joint sponsors.

Consultation item no. 16:

ACRO agrees with the proposed suggestions to amend the Clinical Trials Directive to align conditions for emergency clinical trials with that of internationally-agreed texts on the topic.

In our experience, the most appropriate mechanism to reconcile patient's rights and the peculiarities of emergency trials is one where there has been prior approval from an ethics committee so that, if prior informed consent is not possible, a patient may be entered into the trial in an emergency situation prior to provision of informed consent on condition that consent from the patient or their legal representative is obtained as soon as is practical after entry. Additional safeguards can be added to enable the ethics committee to apply specific conditions to the use of such an approach.

ACRO also suggests that additional consideration might be given to defining emergency, incapacitation and legal representative in the revised text. Use of the term "legal representative" in two contexts within the text of the current Directive is confusing. We recommend that it is retained (and defined) for the legal representative of the patient and that an alternative term, which is more descriptive of the role and responsibilities, is used for the legal representative of the sponsor.

Consultation item no. 17:

ACRO agrees with the principles put forth to ensure compliance with good clinical practices in clinical trials performed in third countries. We believe that all clinical trials conducted outside the EU which are submitted to support authorisations in the EU, should be conducted scientifically and ethically in accordance with EU principles and standards. From the strict regulatory point of view of ensuring compliance with EU standards for trials that provide data used in EU applications, we urge the adoption of a risk-adapted approach to enforcement based on the contribution of the data to the EU dossier. Where these data make a significant contribution to the dossier's pivotal clinical trials on which EU regulatory decisions will be based, we agree that legally required additional information about the trials would allow for better control and enforcement. However, such detailed information may not be needed in the case of non-pivotal trials, except where the non-EU data make a significant contribution to the evaluation of the safety of the product concerned.

ACRO's member companies are greatly invested in the global clinical development infrastructure, and like all stakeholders in the clinical trial process, have an ethical, moral and legal obligation to ensure that clinical trials are conducted in accordance with appropriate ethical considerations, good clinical practice and applicable regulations. As such, we urge the Commission to utilize existing structures with a track record of quality, like global CROs, to support its goals of protecting the rights and safety of the public, as well as capacity building in third countries where the regulatory framework for clinical trials is less developed.

Finally, while supporting transparency, ACRO does not support mandatory registration of clinical trials performed in third countries in EudraCT. Sponsors applying for marketing authorisations in the EU may not always have initially planned to market within the EU, thus trials would not have been registered at the time they were being

conducted. ACRO suggests that the registration of trials in equivalent, publically available databases, e.g. ClinicalTrials.gov, should suffice.

Consultation item no. 18:

ACRO agree that the figures presented, with particular attention to sections 5-7, appear to be reasonable estimates of the time required for the various activities.

III. Conclusion

ACRO appreciates the challenge before the Commission in collecting perspectives from numerous stakeholders and working to craft a solution that that supports a robust framework for the oversight and conduct of clinical trials that holds the safety and welfare of patients at its core.

ACRO is grateful for this opportunity to provide comments in response to the Commission's Consultation, and we welcome further dialogue on these critical issues. Please feel free to contact ACRO at any time for additional input.