

29 August 2016

Directorate General for Health and Food Safety DG SANTE  
Unit B4 "Medical products – Quality, Safety and Innovation"  
European Commission  
F101 08/058  
B-1049 Brussels

**RE: Public consultation on “Risk proportionate approaches in clinical trials”**

Dear Sir/Madam:

The Association of Clinical Research Organizations (ACRO) represents the world's leading, global 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 discovery, pre-clinical, proof of concept and first-in-man studies through pivotal studies assessing the safety and effectiveness of new products – as well as post-approval and pharmacovigilance research. With over 33,000 employees engaged in research activities in Europe, and more than 120,000 worldwide, ACRO member companies advance clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 9,000 clinical trials involving nearly two million research participants in 142 countries. On average, each of our member companies works with more than 500 pharmaceutical, biotech, and medical device sponsors of clinical trials each year.

ACRO’s comments are organized into 3 sections:

- general comments
- suggested revisions to specific line numbers in the consultation document
- topics omitted from the consultation document and recommended for inclusion in the final document

**I. General comments**

ACRO welcomes and supports the draft recommendations on Risk Proportionate Approaches in Clinical Trials developed by the European Commission’s expert group on clinical trials for the implementation of Regulation (EU) No 536/2014. ACRO strongly supports the concept of a risk-proportionate approach to clinical trial management. ACRO finds especially helpful the guidance on the level of additional risk or burden to the safety of the trial subjects posed by additional diagnostic or monitoring procedures as compared to normal clinical practice in the Member State concerned (lines 128 – 141), and hopes that this guidance will diminish the current lack of harmonization between Member States on this issue.

ACRO fully supports the introductory statement (lines 56 – 57) that a risk proportionate approach should be adapted to the risk to the subject of the research carried out, but was surprised to note that here and elsewhere in the document (with limited exceptions) the importance of a risk proportionate approach to ensuring data integrity and the quality of the clinical trial is not equally stressed. The ICH E6 Good Clinical Practice (GCP) Integrated Addendum, which is nearing finalization and is referenced in the consultation document, specifically requires that sponsors establish a quality management system that focuses on trial activities essential to ensuring human subject protection and the reliability of trial results. ACRO therefore considers that this is a significant omission from the consultation document and urges the European Commission to ensure that the subject is adequately addressed in the final guidance document.

While *not* requesting amendment of the proposed text, ACRO also wishes to draw attention to the current wording of lines 189 – 191 of the proposed guidance: “The risk evaluation should commence prior to the finalisation of the protocol as the risk assessment and mitigation may influence the trial design and procedures, as well as the financing or funding of the clinical trial or development project.” ACRO completely supports this position. However, it is the experience of ACRO member companies that CROs are often not involved prior to the finalization of the protocol. Risk evaluation may therefore be conducted by a CRO only after the protocol is finalized (or nearly finalized). ACRO is therefore concerned that the expectation of the European Commission that the risk evaluation be completed before the protocol is final may not be realistic in the short term given the industry’s current reality.

**II. Suggested revisions to specific line numbers**

Line Numbers	Current text	Issue/question	Suggested language
54 - 57	“Many clinical trials, however, pose only a minimal additional risk to subject safety compared to normal clinical practice. A proportionate approach to the design and conduct of clinical trials is therefore supported by the Regulation. This approach should be adapted to the risk to the subject of the research carried out.”	As noted above, GCP is concerned with providing assurance that the results of clinical trials are credible, in addition to protecting the trial subject. This should be reflected in these introductory statements.	“Many clinical trials, however, pose only a minimal additional risk to subject safety <b>and trial integrity</b> compared to normal clinical practice. A proportionate approach to the design and conduct of clinical trials is therefore supported by the Regulation. This approach should be adapted to the risk to the subject <b>and/or trial integrity</b> of the research carried out.”

60	“the risk posed to a subject”	As above.	“the risk posed to a subject <b>and/or trial integrity</b> ”
82 - 84	“In this document, more explanations and examples of the areas for potential adaptation are provided, when sponsors follow a risk proportionate approach in the design and conduct of clinical trials.”	The word “when” in this statement implies that a sponsor need not necessarily follow a risk proportionate approach in the design and conduct of clinical trials. This is not consistent with lines 96 – 98 (“In practice all clinical trials determine procedures which are in various respects risk adapted and therefore these considerations are relevant in all cases”). Also, this is contrary to the aims of Regulation (EU) No. 536/2014, and the ICH E6 GCP Integrated Addendum, which is nearing finalization and is specifically referenced in the consultation document, to require proportionate risk adaptation in clinical trials. Consequently, the statement should be reworded to reflect the expectation that sponsors will follow a risk proportionate approach.	“In this document, more explanations and examples of the areas for potential adaptation are provided <b>to support</b> sponsors <b>as they implement</b> a risk proportionate approach in the design and conduct of clinical trials.”
109 - 156	“Low intervention Clinical Trials”	Two frameworks are described, viz Article 2(3) of the regulation and the OECD recommendations. Whilst similar, Article	Additional text should be added to clarify the role of OECD recommendations relative to Article 2(3) of the Regulation.

		<p>2(3) is based primarily on IMP status and diagnostic monitoring procedures whereas OECD recommendations are based on a stratified approach including the IMP marketing authorization as well as other aspects such as patient population, informed consent document, etc. It is not clear if the intent of this section is to recommend that the requirements of both frameworks are consolidated into a single approach, or if the reference to OECD recommendations is simply to support the statement in lines 147 – 149 that “Low intervention clinical trials, as defined in the Regulation correspond to the OECD categories A and B(1).”</p>	
<p>168 - 174</p>	<p>“A risk based quality management system for clinical trials should include the following steps:</p> <ul style="list-style-type: none"> <li>• risk identification</li> <li>• risk evaluation</li> <li>• risk control</li> <li>• risk review</li> <li>• risk communication</li> <li>• risk reporting”</li> </ul>	<p><i>Please see also Lines 181-182 re: importance of including “risk avoidance.”</i></p> <p>A risk-based quality management system for clinical trials should include an important and additional first step as described in the ICH E6 GCP Integrated Addendum (ICH E6 R2), which is nearing</p>	<p>“A risk based quality management system for clinical trials should include the following steps:</p> <ul style="list-style-type: none"> <li>• <b>critical process and data identification</b></li> <li>• risk identification</li> <li>• risk evaluation</li> <li>• risk control</li> <li>• <b>risk communication</b></li> <li>• <b>risk review</b></li> <li>• risk reporting”</li> </ul>

		<p>finalization: critical process and data identification. The steps as listed in lines 168 - 174 can then be performed relative to critical processes and data, as well as to the protection of trial subjects. However, risk review and communication are listed in the opposite order to that of ICH E6 R2; ACRO recommends that the order in the final guideline should be fully aligned with ICH E6 R2.</p>	<p>Recommended text for an additional subsection on Critical Process and Data Identification is as follows: “Sponsors should prospectively identify critical data and processes that if inaccurate, not performed, or performed incorrectly, would threaten the protection of human subjects or the integrity of the study results.” (see also Section 3 on omitted issues below).</p>
181 - 182	<p>“For each risk identified, an appropriate mitigation strategy (for monitoring) should be implemented or a determination made that the risk can be accepted.”</p>	<p>Mitigation is not the only strategy for addressing an identified risk; avoidance is equally appropriate and should be referenced in the document.</p>	<p>“For each risk identified, an appropriate mitigation strategy (for monitoring) <b>or avoidance strategy</b> should be implemented or a determination made that the risk can be accepted.”</p> <p>ACRO recommends that this is followed by the additional text: “For risk avoidance, the results of data and statistical analysis of results, and results from inspections and audits, etc. from prior similar or comparable clinical trials should be considered. To avoid “re-inventing the wheel” for risk evaluation of a new trial, already known risks, and statistical frequency should be considered in the risk evaluation of a new trial.”</p>
224	Table 1	<p>Data management should be included as an additional area where a risk proportionate</p>	<p>Add data management to Table 1, and include text as in the current 2013 Reflection Paper on risk based quality management in clinical</p>

		approach may be applied.	trials: “Consider the precision, the accuracy and the timing of clinical measurements. In particular in relation to the importance of the variable in terms of the trial objectives, including safety monitoring (e.g. the occasional omission of some measurements, or early or late performance of some study visits may be in some cases less critical than in others).”
325 – 369	“IMP Management”	The European Commission consultation document on definition of investigational medicinal products (IMPs) and use of auxiliary medicinal products (AMPs) proposes the application to the management of both IMPs and AMPs of the same risk-proportionate requirements. This section of the current consultation document is therefore equally applicable to AMPs and, for consistency, both the section heading and the text should reflect this.	Wherever the term “IMP” appears in this section, it should be replaced with “IMP or AMP”. Wherever the term “investigational medicinal product” appears in this section, it should be replaced with “investigational medicinal product or auxiliary medicinal product”.
411-413	“Centralised monitoring enables the review of reported data / information, remote contact, communication and training where relevant and can be used to set certain actions in motion when pre-determined	ACRO fully supports this position and recommends that the text should make clear that decisions and actions resulting from centralized monitoring, and the basis for them, must be documented.	Add text: “Decisions and actions, and the basis for them, must be documented.”

	tolerance limits for processes or data have been exceeded.”		
421 - 428	“A risk adaptive approach to monitoring should include utilisation of one of or a combination of approaches listed below”	ACRO considers that monitoring of pre-defined operational metrics critical to quality is also a suitable subject for centralized monitoring in a risk-adapted approach, and recommends that this is stated in the text.	Add the following to the list of approaches: “centralized monitoring of pre-defined operational metrics critical to quality.”
449	“Objectives achieved by other means”	The meaning of this statement is unclear. ACRO therefore recommends that more explanatory text is added.	Revise text to clarify its meaning.
455 - 465	“IMP related documentation”	As above for lines 325 - 369, this text is applicable to AMPs as well as IMPs and should reflect this.	Wherever the term “IMP” appears in this section, it should be replaced with “IMP or AMP”.
466 - 469	“Hospital laboratory accreditation certificates and reference ranges (when these laboratories are not providing information that is critical to the reliability of the trial results) or where the data values are used in their own right, where accreditation certificates are not applicable (or not available) and other measures such as population statistics in large trials account for divergences;”	It is not clear what is meant by “data values used in their own right”, or what “accreditation certificates are not applicable”. Additionally, it is ACRO’s view that a single example of divergences is not sufficient to explain the intent of this statement. Consequently, ACRO recommends that more detail is added to this paragraph to provide greater clarity.	Add more explanatory detail to this paragraph to provide greater clarity of the intent.

### III. Omissions in consultation document recommended for inclusion in final document

#### Preserving 2013 Reflection Paper content on issue of quality

Although the consultation document states that it is based on the 2013 Reflection Paper on risk based quality management in clinical trials, some important information and guidance included in the Reflection Paper is missing from the consultation document. Specifically, ACRO recommends that text should be added to the consultation document to address the following points referenced in both the Reflection Paper and the ICH E6 GCP Integrated Addendum (ICH E6 R2), which is nearing finalization : (1) use of pre-defined quality tolerance limits and (2) reporting quality. ACRO recommends three new sections. First, we ask that the Commission consider adding the text from section 5.2 (Quality tolerance limits) of the Reflection Paper. Second, ACRO recommends expanding the section on Risk Reporting (lines 239 – 242 of the consultation document) by adding the text from section 6.2 (Reporting quality) of the Reflection Paper. Finally, ACRO recommends that risk reporting should not only be included in the clinical study report but also in in public databases for clinical trials.

#### Source Data Verification

There is now considerable published evidence showing that the still common practice of 100% source data verification is a resource-intensive exercise that adds little to the overall quality and integrity of a clinical trial. It is therefore surprising that the consultation document does not specifically refer to the use of a risk proportionate approach to source data verification, as promoted in the FDA's 2013 guidance on a risk-based approach to monitoring. ACRO recommends that this should be specifically addressed in the final guidance. ACRO recommends that the new subsection on Critical Process and Data Identification proposed by ACRO (lines 168 – 174, above) should include the text: *"The sponsor should consider the quantity and types of source data that need to be verified against CRFs or corroborated against other records during the sponsor's identification of critical data and processes, or in the risk assessment, or both."*

#### Risk-based monitoring

Section 4.4 (Monitoring), does not describe the important aspects of a "risk based monitoring" approach, nor does it explain that monitoring plans should be adapted during the course of a clinical trial in response to changing events. ACRO believes that these are important omissions and recommends that the text, such as the following, be added to this section of the guidance document. ACRO therefore asks the Commission to consider adding the following text to section 4.4:

*"Monitoring activities should focus on preventing or mitigating important and likely sources of error in the conduct, collection, and reporting of critical data and processes necessary for human subject protection and trial integrity. For each clinical trial, the sponsor should develop a monitoring plan that describes the monitoring methods, responsibilities, and requirements for the trial. The monitoring plan should include a brief description of the study, its objectives, and the critical data and study procedures, with particular attention to*



*data and procedures that are unusual in relation to clinical routine and require training of study site staff. The plan should also communicate the specific risks to be addressed by monitoring and should provide those involved in monitoring with adequate information to effectively carry out their duties. A monitoring plan may reference existing policies and procedures (e.g., standard operating procedure describing general monitoring processes or issue investigation and resolution). All sponsor and CRO personnel involved with monitoring, including those who review or determine appropriate action regarding potential issues identified through monitoring, should review the monitoring plan and associated documents (e.g., standard operating procedures or other documents referenced in the monitoring plan). Sponsors should consider what events would indicate a need for review and revision of the monitoring plan and establish processes to permit timely updates where necessary. For example, a protocol amendment, change in the definition of significant protocol deviations, or identification of new risks to study integrity could result in a change to the monitoring plan.”*

ACRO thanks the Commission for the opportunity to comment on this public consultation on “Risk proportionate approaches in clinical trials.”

Please contact ACRO if we can provide additional information or answer any questions ([knoonan@acrohealth.org](mailto:knoonan@acrohealth.org)).

Respectfully submitted,



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EU Transparency Register information:

ACRO's public ID number in the Transparency Register is: **150920420956-26**