16 February 2015

Submission of comments on Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited (EMA/42176/2014)

Comments from:

Name of organisation or individual
ACRO (Association of Clinical Research Organizations)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	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 post-approval and pharmacovigilance research. Each year, ACRO member companies conduct more than 11,000 clinical trials involving nearly two million research participants in 115 countries. ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Representing global CROs with more than 100,000 employees engaged in research activities around the world (including 30,000 employees in Europe), the competitiveness of the European Union as a location for clinical research is a key priority for ACRO. ACRO is pleased to provide comment on the EMA's Draft proposal for an addendum, on transparency, to the "Functional specifications for the EU portal and EU database to be audited (EMA/42176/2014). Because ACRO member companies collect and process clinical trial data on behalf of sponsors, ACRO believes that sponsors and their associations (EFPIA and	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	EuropaBio) have a principal interest in issues of clinical trial data transparency and publication. On Questions 6 – 11 (which address data publication and CCI), ACRO supports the positions of our customers and their associations. ACRO is pleased to offer comment on other key issues discussed in this draft proposal – such as inspection reports, serious breaches, and unexpected events.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
363-366		Where a particular piece of information is superseded because it was factually incorrect and submitted in error then either it should not remain in the public domain or there should be a mechanism available whereby the reason for the change is also in the public domain. Proposed change: The text should be revised to reflect either option, as appropriate.	
382-410 Question 1		ACRO agrees that the Regulation requires submission of the details listed and that it is acceptable to publish information that meets the requirements of the Regulation. However, we understand that some investigators will not want to see their detailed information in the public domain and we are concerned that the publication requirements should not be such as to discourage any EU investigator from participating in clinical research. We therefore recommend that the EMA should produce a specific template, which should be subject to further consultation with stakeholders, for the collection and submission of the minimum information required to comply with Annex I.M of the Regulation.	
411-416 Question 2		ACRO does not agree that the proposal not to publish details of Member State experts meets the requirements of the Regulation. Article 9(1) of the Regulation requires Member States to ensure that “the persons validating and assessing the application do not have conflicts of interest, are	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		independent of the sponsor, of the clinical trial site and the investigators involved and of persons financing the clinical trial, as well as free of any undue influence". Member State experts play a key role in ensuring that the potential benefits to subjects participating in a clinical trial exceed the potential risks, and, through inspection, by providing assurance that the data and conclusions generated in a clinical trial can be relied upon for future regulatory decision making, including exposure of a larger patient population to the product following marketing authorisation approval. We consider that, in order for the public to have confidence that Member States comply with Article 9(1), information on the relevant Member State experts should be published. Further, since the information on Member State experts required by Article 9(1) is essentially the same as that required under Annex I.M for investigators, we recommend the use of a similar template to collect and publish the same level of minimum information.	
417-425 Question 3		ACRO agrees that the proposal meets the requirements and objectives of the Regulation.	
426-436 Question 4		ACRO agrees that the proposal meets the requirements and objectives of the Regulation. However, we recommend that the final text of the addendum states clearly that, with the exception of the signatories of the clinical study report and the investigators who conducted the trial, the marketing authorisation holder may redact personal information within the clinical study report that identifies other personnel involved.	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
437-446 Question 5		ACRO agrees that the proposal meets the requirements and objectives of the Regulation.	
584-609 Question 6		We consider that proposal 1.3 is the only option that meets the requirements and objectives of the Regulation. This is the only option that recognises fully the requirement of Article 81.4(b) that protection of CCI will take into account the status of the marketing authorisation for the product, unless there is an overriding public interest in disclosure. The marketing authorisation applies to a specific medicinal product that is characterised in terms of the active substance, indication, formulation and route(s) of administration. Only information associated with the specific approved indication and formulation of the product should be published at the time of the product's marketing authorisation. Information related to line extensions and/or new indications will be included in additional marketing authorisation applications and therefore should be made public when the relevant additional marketing authorisation is issued.	
610-642 Question 7		We support the proposal that, regardless of marketing authorisation status, the IMPD-Q section on IMP quality and the related lists of questions, responses and assessment report sections should be considered as commercially confidential and not made public for any trial at any time, as this deals with the manufacturing and related pharmaceutical development information which continues to be CCI, indefinitely, post-marketing authorisation.	
643-654		We support the proposal to allow the sponsor to defer	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Question 8		publication of information on a clinical trial on a product with a marketing authorisation until the time that the summary of trial results is loaded into the database and made public. While information on the product will be in the public domain following approval of the marketing authorisation, the specific design of an individual post-authorisation trial may include elements of CCI that must be protected.	
655-708 Question 9		We consider that Proposal Two best meets the requirements and objectives of the Regulation. Proposal One would result in publication of more detailed information on the clinical trial at a much earlier stage than required in any other regulatory jurisdiction – we anticipate that this will be of significant concern to sponsors with regard to publication of CCI and would significantly damage the attractiveness of the EU for clinical research. We consider that Proposals Three and Four would be too complicated to administer and subject to error. We see Proposal Three as problematic because judgement as to which phase a clinical trial falls under may be subjective and open to interpretation, and an adaptive clinical trial may span more than one phase. Similarly, in relation to Proposal Four, we consider that the distinction between a therapeutic and a non-therapeutic trial can be open to interpretation.	
709-725 Question 10		ACRO agrees that the proposed time points meet the requirements and objectives of the Regulation, and support the proposal, which provides clear and objective triggers for the timing of publication.	
726-746		We have reservations about the proposal regarding publication	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
Question 11		of information on Phase I trials, which would result in publication of information on these trials at a much earlier stage than required in any other regulatory jurisdiction – we anticipate that this will be of significant concern to sponsors and would significantly damage the attractiveness of the EU for Phase I clinical research.	
747-752 Question 12		ACRO agrees that the proposal meets the requirements and objectives of the Regulation.	
753-762 Question 13		ACRO agrees that the proposal meets the requirements and objectives of the Regulation.	
763-796 Question 14		ACRO does not agree that the proposals meet the requirements and objectives of the Regulation. Inspection reports contain detailed information and findings that, taken out of context, would be misleading to the public. We are concerned that only the inspection report would be published and not the inspectee's response, which explains how they plan to correct inspection findings and prevent future occurrences. Additionally, inspection reports sometimes show that, during the limited time available for an inspection, the inspector failed to understand a situation fully. Publication of the inspection report alone would therefore give a biased and potentially (and unnecessarily) damaging view of how the trial was conducted. Often, too, inspection reports may contain detailed information about the trial design that would be considered CCI and while we note the proposal to redact inspection reports, we are concerned that there may be a failure to recognise fully the elements that constitute CCI. We	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		recommend that, rather than publishing the complete (redacted) inspection report, the responsible inspectorate should, after the evaluation of the inspectee's responses is complete, prepare a summary report for publication which gives brief details of the trial and the inspectee, together with the conclusions arising from the inspection. We also recommend that suitable arrangements are put in place for the preparation of similar summaries of inspection reports of third country authorities submitted under Article 53.2. One of the key purposes of inspection is to provide assurance that the data and conclusions generated in a clinical trial can be relied upon for future regulatory decision making, especially at the time of marketing authorisation approval. In order to achieve this aim, the EMA has recognized that individual inspection reports have to be viewed in the overall context of the marketing authorisation application and has established criteria for reviewing the impact of inspection findings on the benefit-risk assessment undertaken during evaluation of the marketing authorisation application (Points to consider on GCP inspection findings and the benefit-risk balance. EMA/868942/2011, 19 September 2012). We consider that this represents a valuable approach to place inspection findings in the overall context of the marketing authorisation application. We therefore recommend that the conclusions of this review of inspection reports is published, together with the proposed summary reports of the	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		inspections on which it is based, at the time of marketing authorisation approval.	
797-802 Question 15		ACRO agrees that the proposal meets the requirements and objectives of the Regulation.	
803-843 Question 16		ACRO agrees for the most part that the proposals meet the requirements and objectives of the Regulation, but have reservations about the proposed timing of publication of information on serious breaches and corrective measures. We are concerned that the draft addendum section on serious breaches and corrective measures does not refer to Article 81.4(d) of the Regulation, which allows for information not to be published should doing so compromise the ability to ensure effective supervision of the conduct of a clinical trial by Member States. Additionally, there are cases (e.g., fraud) where a serious breach could lead to criminal charges and legal action undertaken outside of medicines law and regulation. Such legal action could be compromised by premature publication of the serious breach (even if it is in accordance with arrangements implemented under Regulation 536/2014) and we strongly recommend that this should be recognized in the addendum.	
844-857 Question 17		ACRO agrees for the most part that the proposals meet the requirements and objectives of the Regulation, but have reservations about the proposed timing of publication of information on reporting of unexpected events and urgent safety amendments. In such cases, it is very likely that the unexpected event or urgent safety amendment will ultimately	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		result in an application for substantial modification of the clinical trial authorisation. We therefore recommend that details of the unexpected event or urgent safety modification (redacted to protect CCI) are published at the same time as information on the resulting substantial modification.	
859-872 Question 18		ACRO does not agree that the proposals as written meet the requirements and objectives of the Regulation. With regard to submission of the clinical study report (CSR) for publication, there are discrepancies between the appendices required by the text of the draft addendum, by Appendix 7 of the draft addendum, and by EMA Policy 0070 on publication of clinical data for medicinal products for human use (EMA/240810/2013, 2 October 2014). We recommend that the requirements for publication of CSRs under the Regulation are aligned with EMA Policy 0070. We also recommend that, for clinical trials authorised under the Regulation, there should be inter-operability between the database and the publication system established under Policy 0070 so that a sponsor need submit an individual CSR for publication on one occasion only.	
894-898 Question 19		ACRO does not agree that the proposed Table 2 Section 4.3 to be added to the functional specification document as an addendum meets the requirements and objectives of the Regulation. Specifically, it does not address which functionalities will be audited, and we question the need to include some (but not all) of the questions in the application form that will provide data points on which to base certain of the publication rules. We also note that the draft addendum	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		states that the “system should identify all data and documents in the EU database regarding their public or non-public status and any timeframe/event to trigger that publication, and include the necessary rules to ensure their availability at the required time.” We recommend that all of the details of this arrangement are published so that they are clearly available to users of the portal and database.	
Appendix I A.5.3		The WHO Universal Trial Reference Number (WHO UTN) is required by Annex 1(B.6) of the Regulation but is not required by Article 25.6, which simply requires that a trial should be registered in a public register which is a primary or partner registry of, or a data provider to, the WHO International Clinical Trials Registry Platform. The ClinicalTrials.gov number is also required by Annex 1(B.6) but not by Article 25.6. ClinicalTrials.gov is not a data provider to the WHO registry, so there would need to be an additional request for the WHO UTN, if this were to be mandatory. The additional administrative burden that this could create has been raised by several sponsors. We therefore recommend that the request for the EU Clinical Trial Number should trigger the automatic creation of both the WHO UTN and the EU CTN.	
Appendix I Page 47		A field is proposed for the ethics committee opinion (per Member State). This is not a requirement of the Regulation, which requires a single approval covering both regulatory and ethical aspects of the clinical trial by each Member State. We recommend that this field is deleted as it is already covered by the Conclusion on Part I of the assessment and the Decision	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
		on the trial (per Member State), which are required by the Regulation.	
Appendix 1, C.1.4.3 C.1.4.3.1 C.1.4.3.3 C.1.4.3.4		The draft proposal states that the application address will not be in the public domain at any time. However, the components of this will be published -- i.e. street address, post code and country. Proposed change: The text should be revised to state that C.1.4.3.1,3,4 will not be published.	
Appendix 1, N		While the regulation requires a positive EC opinion on a trial, there is no requirement for this to be included in the database. Proposed change: Delete text to reflect the regulation.	
Thank you and conclusion		ACRO thanks the Agency for the opportunity to comment on this draft proposal public consultation and looks forward to continued dialogue on the EU portal and EU database.	

Please add more rows if needed.