3 November 2015

Submission of comments on “External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA policy 0070” (EMA/471266/2015)

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).

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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. With more than 110,000 employees engaged in research activities around the world (including 30,000 in Europe), ACRO advances 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 research sponsors annually. ACRO is grateful to the EMA for this opportunity to provide comments on the EMA's draft external guidance on procedural aspects related to Policy 0070. ACRO member companies generate, analyse and report clinical data on behalf of clinical trial sponsors. ACRO's comments are focused on the procedural aspects of the draft guidance as they relate to activities that may be	

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	undertaken by ACRO member companies. ACRO believes that sponsors and their associations (EFPIA and EuropaBio) have a principal interest in issues of clinical trial data transparency and publication and supports the positions of our customers and their associations regarding the specific issues of the nature and the timing of publication of clinical data. Additionally, ACRO welcomes the fact that, in preparing the draft guidance, the EMA has taken due account of comments raised during the stakeholder meetings of 24 June and 7 September 2015. ACRO considers, however, that there remains scope for further improvement of the guidance in order to reduce the potential for duplication of information and to simplify the procedure even more. Given that the procedure will place a significant additional resourcing burden on organisations (not only marketing authorisation applicants/holders but also third party vendors, including ACRO member companies, that prepare and file submissions on behalf of applicants and holders), we recommend the EMA to ensure that the final procedure adopted is as streamlined as possible to maximise the efficient use of company resources. ACRO is also concerned that the timelines proposed for the various steps of the procedure have been specified before companies have practical experience of following	

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	the process. It is therefore not clear whether compliance with these timelines is achievable in practice without adding significantly to the resourcing burden for companies. ACRO encourages the EMA, therefore, to show flexibility around compliance with timelines in the early days of implementing the procedure and to be prepared to revise the timeline requirements of the guidance, if necessary, on the basis of actual experience.	

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)*
47 - 104		Comment: For purposes of clarity and ease of use, ACRO recommends replacing the current text with a detailed list of documents falling within the scope of the Policy. Proposed change (if any): Include a detailed list of documents falling within the scope of the Policy.	
130		Comment: There is a typographical error in that the relevant workflow is in Appendix 5.7, not 5.8 as stated. Proposed change (if any): Reference Appendix 5.7 (but see ACRO recommendation on line 718).	
144		Comment: The meaning of the sentence “Applicants should note that the clinical reports within a module need to be individual” is unclear and may lead to confusion. ACRO understands that redacted documents are to be provided in the same format as the original documents in the submission dossier, i.e. either as a single document comprising the clinical study report plus its appendices or as separate documents for the report and its appendices. We therefore assume that this sentence means that multiple study reports should not be provided within a single document, and recommend that the requirement is explained and clarified in greater detail.	

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		Proposed change (if any): Explain and clarify the requirement in greater detail.	
149 - 151		Comment: There is no value in the “Redaction Proposal Version” including documents for which no redaction is proposed. Consequently, ACRO recommends that the reference to a “Redaction Proposal Version” of “all clinical reports” is modified to make clear that only copies of documents in which redaction is proposed are required. Proposed change (if any): Make clear that only copies of documents in which redaction is proposed are required.	
155 - 157		Comment: The required file format requirements listed in this section (3.3.1.3) are presented in less detail than those in section 3.3.3.4. ACRO recommends that a new section is included in the guidance that provides a single description of format requirements for both the “Redaction Proposal Version” and the “Final Redacted Version”. Additionally, ACRO notes the statement that “the current eCTD specification applies and PDF version 1.7 onwards are currently accepted.” In fact, the current eCTD specification allows for PDF versions 1.4 – 1.7 to be used. ACRO recommends that the guidance document should not seek to apply more stringent requirements than those of the eCTD specification.	

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		Proposed change (if any): Provide a single description of format requirements for both the “Redaction Proposal Version” and the “Final Redacted Version” that is not more stringent than the current eCTD specification.	
171 - 180		Comment: Typically, clinical study reports contain little CCI but can include considerable PPD. As the EMA will assess only redaction requests based on CCI considerations, the value of marking proposed PPD redactions as such is questionable. For simplicity, ACRO therefore recommends that only redactions proposed on CCI grounds should be specifically labelled as such in the document (i.e., there is no additional need for PPD redactions to be labelled). Proposed change (if any): Make clear that only redactions proposed on CCI grounds should be specifically labelled as such in the document and there is no need to label PPD redactions.	
183 - 184		The text is not consistent with the cover letter templates presented in Appendices 5.4 and 5.5, which do not include reference to an interactive table. The link included in the draft guidance brings up a table that does not include the information shown in the examples in the draft guidance. Proposed change (if any): Ensure consistency between this	

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		section of the document, the cover letter templates, and the actual interactive table.	
186 - 188		Comment: The statement “In addition to uploading the cover letter applicants/ MAHs must confirm, in the interactive table that the cover letter including the declaration has been uploaded” is not consistent with the illustration below line 188, which refers only to the clinical reports and not to the cover letter. Proposed change (if any): Ensure consistency between text and illustration.	
191 - 192		The statement “For the redaction proposal version of each of the clinical reports applicants/MAHs must complete a justification table in Word format” implies that this is required for every clinical report. ACRO recommends that it is made clear that a justification table is required only for each clinical report containing one or more proposed CCI redactions. Proposed change (if any): Make clear that a justification table is required only for each clinical report containing one or more proposed CCI redactions.	
198 - 201		ACRO queries the value of submitting separate justification tables for the study report and for each appendix. ACRO recommends that a single justification table should be	

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		adequate for each report plus its appendices, thus reducing the administrative burden, and can just as readily identify the location of each proposed CCI redaction. Proposed change (if any): Make clear that a single justification table is required for each report plus its appendices.	
216 - 218		In ACRO's view, it is unreasonable to request separate redaction packages when multiple duplicate applications have been submitted for the same medicinal product under different invented names. This adds significantly to the administrative burden for no apparent benefit to the public who may wish to view the reports. When the reports are published, ACRO considers that the EMA should be able to make clear when multiple copies of an identical application were received and where the reports relating to all of these applications are located. Proposed change (if any): Delete the requirement for separate redaction packages.	
241 - 250		The character "." cannot be used in eCTD filenames. Additionally, eCTD mandates a 180 character path limit and a single filename limit of 64 characters. The naming conventions proposed in the draft guidance may therefore cause eCTD validation failures if the path or filename length is exceeded, which is possible in the case of study reports with long names.	

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		ACRO therefore recommends revision of this section to ensure consistency with eCTD specifications. Additionally, some documents are considered as study reports only for the purposes of Policy 0070 and are not considered study reports in eCTD (e.g., reports of data analyses from multiple studies) and so do not have a study report number. The guidance should describe the naming conventions to be applied to such studies. Proposed change (if any): Ensure consistency with eCTD specifications and describe naming conventions for non-eCTD study reports.	
311 - 312		In order to help applicants to complete the justification tables appropriately, ACRO recommends that the draft guidance should include an explanation of how to complete the tables and what is to be included in each column. Proposed change (if any): Include an explanation of how to complete the justification tables and what is to be included in each column.	
326 and 340 - 342		Until experience of following the procedure has been gained, it is not known if the timelines described in these sections are routinely achievable. ACRO encourages the EMA, therefore, to show flexibility around compliance with timelines in the early days of implementing the procedure and to be prepared to	

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		revise the timeline requirements of the guidance, if necessary, on the basis of actual experience. Proposed change (if any):	
329		Comment: The guidance allows for one round of consultation which includes separate exchanges between the applicant/MAH and EMA. It is unclear what is intended by the concept of “separate exchanges”. It is assumed that for each point of clarification requested, only one response can be given with no follow up discussion permitted. Furthermore, it is assumed that while several such requests may be made, they might be made at different times during the review time rather than being received in one list. Proposed change (if any): Clarify the meaning of “separate exchanges” within the context of one round of consultation.	
343		Comment: There is a typographical error in that the relevant workflow is in Appendix 5.8, not 5.9 as stated. Proposed change (if any): Reference Appendix 5.8 (but see ACRO recommendation on line 718).	
364 - 365		Comment: See earlier comment on lines 155 – 157 concerning consistency of format requirements with eCTD specifications.	

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		Proposed change (if any): Provide a single description of format requirements for both the “Redaction Proposal Version” and the “Final Redacted Version” that is not more stringent than the current eCTD specification.	
366		ACRO recommends that guidance is included on how to handle large study reports exceeding 100 Mbytes. Proposed change (if any): Include guidance on how to handle large study reports exceeding 100 Mbytes.	
414		ACRO recommends that the guidance explains the purpose and design of the watermark that will be applied by the EMA. Proposed change (if any): Explain the purpose and design of the watermark that will be applied by the EMA.	
597, 650 and 708		Comment: The EURS is not available to the marketing authorisation applicant/holder. ACRO recommends that the reference to EURS is changed to eCTD. Proposed change (if any): Change the reference to EURS to eCTD.	
620 – 622 and 674 - 676		The template cover letters to accompany the “Redaction Proposal Document” package and withdrawal require confirmation that “the Subsequent Submissions do not contain	

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		any redactions that were not present in the Original Submission; and (b) the Final Submission does not contain any redactions that were not explicitly agreed in writing by EMA." These Subsequent and Final submissions will not have been prepared at the time of submission of these cover letters, therefore it will not be possible for the company to give such confirmation at that time. Additionally, the sentence under (b) above is inconsistent with the fact that EMA will review and agree only redactions proposed on CCI grounds; PPD redactions will not need EMA agreement and will not be reviewed by the EMA. Proposed change (if any): ACRO recommends that these lines are deleted from the templates.	
718		The process flowchart in Appendix 5.7 is inconsistent with text in section 3.3.1 of the draft guidance, which allows for the Redaction Proposal Document to be submitted prior to the EMA opinion. Additionally, in ACRO's view, Appendices 5.7 and 5.8 add little to the more detailed information presented in Appendices 5.9 and 5.11. ACRO therefore recommends that Appendices 5.7 and 5.8 are deleted and any information in them that is not currently in 5.9 and 5.11 is added to 5.9 and 5.11, which should subsequently be reviewed carefully to ensure consistency with the text of the guidance. Proposed change (if any): Delete Appendices 5.7 and 5.8 and	

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		ensure any information in them that is not currently in Appendices 5.9 and 5.11 is added to 5.9 and 5.11, which should subsequently be reviewed carefully to ensure consistency with the text of the guidance	
724		Appendix 5.9 does not include any timeline for the “Publish” stage of the process. ACRO recommends that this is added. Also, ACRO notes that other timelines are given as “days” or “calendar days” and recommends use of consistent terminology. Additionally, until experience of following the procedure has been gained, it is not known if the timelines described in these sections are routinely achievable. ACRO encourages the EMA, therefore, to show flexibility around compliance with timelines in the early days of implementing the procedure and to be prepared to revise the timeline requirements of the guidance, if necessary, on the basis of actual experience. Under the proposed procedure, submission of the Redaction Proposal Version of the clinical study reports take place ≤ 30 days pre-opinion and ≤ 10 days post-opinion, or ≤ 30 days post-receipt by EMA of the withdrawal letter. The EMA conclusion is available within 47 days, the applicant agreement is submitted within 4 days, then the final reports are submitted within 20 days. Thus, the final reports are submitted 71 days after the procedure commences i.e. 41 to 61 days post-opinion. This may be problematic in relation to	

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		the implementation of Clinical Trial Regulation (EU) No. 536/2014. The recently finalised Appendix, on disclosure rules, to the "Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014" states that the clinical study report will be published 30 days after the marketing authorisation decision (authorisation or refusal of MA application) or 30 days after withdrawal of the application by the applicant. In practice, it is possible that the date 61 days post-opinion set by the proposed Policy 0070 procedure will occur earlier than the 30 days post-marketing authorisation set by Regulation (EU) No. 536/2014. Proposed change (if any): Add a timeline for the "Publish" stage of the process and ensure consistency in use of days or calendar days. Ensure timelines for publication of clinical study reports are aligned between the procedure for Policy 0070 and the implementation requirements of Regulation (EU) No. 536/2014.	
725		Consistent with ACRO comments on lines 311-312, ACRO recommends that it would be helpful for the justification table in Appendix 5.10 to include examples of suitable entries under each column that would or would not be acceptable to the EMA. Proposed change (if any): Add helpful examples to assist companies in completing the justification satisfactorily.	

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729		The overall timeline for the Redaction Consultation Process in Appendix 5.11 totals 47 days. This is not consistent with the 50 days shown for this part of the overall process in Appendix 5.9. Furthermore, the appendix does not include tasks (with associated timing) that take place after the EMA final conclusion is issued. Under the proposed procedure, submission of the Redaction Proposal Version of the clinical study reports take place ≤ 30 days pre-opinion and ≤ 10 days post-opinion, or ≤ 30 days post-receipt by EMA of the withdrawal letter. The EMA conclusion is available within 47 days, the applicant agreement is submitted within 4 days, then the final reports are submitted within 20 days. Thus, the final reports are submitted 71 days after the procedure commences i.e. 41 to 61 days post-opinion. This may be problematic in relation to the implementation of Clinical Trial Regulation (EU) No. 536/2014. The recently finalised Appendix, on disclosure rules, to the “Functional specifications for the EU portal and EU database to be audited - EMA/42176/2014" states that the clinical study report will be published 30 days after the marketing authorisation decision (authorisation or refusal of MA application) or 30 days after withdrawal of the application by the applicant. In practice, it is possible that the date 61 days post-opinion set by the proposed Policy 0070 procedure will occur earlier than the 30 days post-marketing	

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		authorisation set by Regulation (EU) No. 536/2014. Proposed change (if any): Ensure consistency of all timelines quoted throughout the guidance text and appendices. Ensure timelines for publication of clinical study reports are aligned between the procedure for Policy 0070 and the implementation requirements of Regulation (EU) No. 536/2014. ACRO thanks the EMA for the opportunity to submit comments on the "External guidance on the procedural aspects related to the submission of clinical reports for the purpose of publication in accordance with EMA policy 0070" (EMA/471266/2015) Please do not hesitate to contact us if we can provide additional information (knoonan@acrohealth.org or +1 202 464 9340).	

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