10 July 2017

Submission of comments on Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials (EMA/15975/2016)

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. With more than 130,000 employees engaged in research activities around the world (including 57,000 in Europe), ACRO advances clinical outsourcing to improve the quality, efficiency and safety of biomedical research. Each year, ACRO member companies conduct more than 7,000 clinical trials involving 1.3 million research participants in over 100 countries. On average, each of our member companies works with more than 700 research sponsors annually. ACRO welcomes and supports the draft guideline on GCP compliance in relation to the Trial Master File. While some specific comments are noted below, ACRO congratulates the EMA on drafting a generally comprehensive document on such a complex subject.	

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)*
116 - 118		Comment: This statement is ambiguous in that it does not make clear that the TMF comprises the documentation and/or computer systems that provide all of the data from the clinical trial and information on decision-making that will allow the trial to be reconstructed and verified without the need for additional explanation from the associated sponsor or site staff. ACRO recommends revising the statement to read in this way. Proposed change (if any): Revise the statement to read: “the TMF comprises the documentation and/or computer systems that provide all of the data from the clinical trial and information on decision-making that will allow the trial to be reconstructed and verified without the need for additional explanation from the associated sponsor or site staff.”	
133 - 135		Comment: The guideline states “The investigator/institution is responsible for and should therefore have control of all essential documents and records generated by the investigator/institution before, during and after the trial (at all times)” without clarification of the period referred to as “....after the trial.” Proposed change (if any): Add a reference to the retention times within section 6.4, to ensure clarity in relation to 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)*
		meaning.	
146 - 148		Comment: The sentence “Remote access, i.e. access to investigator documentation at the investigator site from a different location by sponsor personnel, to personal data of trial subjects in the investigator TMF, is unacceptable” is unnecessarily proscriptive. The subject can give consent to their personal information being made available to the sponsor and therefore there is no reason why sponsor personnel cannot have remote access to a trial subject’s personal data as long as it is made clear in the informed consent information that this will be the case. Centralized (i.e., remote) monitoring of clinical trials is increasingly common and is encouraged by ICH E6(R2). With appropriate subject consent, remote monitoring and auditing of informed consent forms and other documentation that may contain subject identifiers is permissible. Proposed change (if any): Add “unless the subject has consented to their personal information being sent to or accessed from outside the investigational site” to the end of the current sentence.	
161 - 167		Comment: While documents can be stored in separate locations, the concept of the “TMF” is that all essential documents are entirely available for inspection at all times (direct access). There needs to be suitable indexing so that	

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)*
		the location of all essential documents is evident. Sponsors frequently hold separately some study documentation that is not immediately accessible for a CRO who therefore are not able to provide direct access to those documents during inspection of a CRO (and *vice versa*). ACRO recommends that the guideline should include advice on this situation and recommends the addition of the following text. Proposed change: Add a new paragraph after line 167 to read as follows: “When a sponsor has delegated functions to a vendor, both the sponsor and vendor will be involved in maintaining sections of the TMF. In this situation, the sponsor and vendor are both responsible for ensuring there is a documented arrangement to make the entire TMF readily available as required for inspection, both during and after completion of the trial. It is recommended that this is contained in the contractual arrangements between the two parties.”	
165 - 166		Comment: The draft guideline states “The documentation should be filed in each appropriate section of the TMF in date sequential order as this facilitates provision of a clear audit trail.” The act of filing of documents within the TMF is not always possible within a chronological order, due to factors such as a difference between ‘date of document’/‘date of approval’ and the actual ‘date of receipt’ for a particular document. It is acknowledged that clarity of chronology is	

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)*
		very important, and we would suggest that the guideline should make reference to the option of utilising electronic TMF capabilities for sorting of the documents into a clear chronological order to aid location of documentation. Proposed change (if any): Add “or can be sorted electronically, so as to be represented in date order within an electronic TMF”.	
169 - 200		Comment: ACRO recommends that it would be helpful to include a statement in this section of the guideline to make clear that only final documents are required in the TMF and that it is not necessary to retain draft versions for inspection purposes (see also comment on lines 550 – 553 below). Proposed change (if any): Include a statement in this section of the guideline to make clear that only final documents are required in the TMF and that it is not necessary to retain draft versions for inspection purposes.	
176 - 181		Comment: ACRO strongly supports this statement, which allows for a reduction of the essential document requirements where this is justified in advance of the trial, based on a risk-proportionate approach. However, ACRO recommends that it would be very helpful to sponsors if the guideline were to include some examples of situations where the essential documents could be reduced or (as in the section referenced	

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)*
		in the following comment) include a reference to were such examples can be found. Proposed change (if any): Include examples of where the essential documents could be reduced or (as in the section referenced in the following comment) include a reference to were such examples can be found.	
183 - 187		Comment: The draft guideline states “Article 57 of the Regulation states that the trial master file essential documents content shall take into account “all characteristics of the clinical trial, including in particular whether the clinical trial is a low-intervention clinical trial” therefore for such trials, some documentation specified in the ICH-GCP E6 guideline may not be necessary due to the implementation of a risk proportionate approach (approach and examples can be seen in the relevant document).” However, a risk-proportionate approach is not confined to low-intervention clinical trials and, in any trial, there may be justification for reducing some documentation requirements based on risk proportionate considerations. Consequently, ACRO recommends revising this sentence as proposed below. Proposed change (if any): Revise the sentence to read “Article 57 of the Regulation states that the trial master file essential documents content shall take into account “all characteristics of the clinical trial, including in particular whether the clinical	

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)*
		trial is a low-intervention clinical trial" therefore some documentation specified in the ICH-GCP E6 guideline may not be necessary due to the implementation of a risk proportionate approach (approach and examples can be seen in the relevant document). The justification for reducing documentation requirements on this basis should be documented in the TMF."	
202 - 207		Comment: It is not clear what is being recommended in this paragraph. If the meaning is that it is acceptable for the investigator not to hold all versions of sponsor-created documents as long as the changes are clearly documented in a change log/version history, the guideline should simply state this. The requirement for documents created by the site should also be clarified – would all versions of site-created documents need to be retained in the site TMF or would a change log/version history suffice? Proposed change: Expand the paragraph to express recommendations clearly.	
209 - 224		Comment: Again, it is not clear what is being stated in this paragraph. The statement in lines 217-218 implies that emails should be retained in the relevant folder of the TMF whereas the statement in lines 223 – 224 implies that a central email repository may be used.	

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)*
		Proposed change (if any): Rewrite the paragraph to express recommendations clearly.	
336 - 337		Comment: The statement “Digitised documents in the e-TMF should be a certified copy of the original” is unclear as it is not obvious up to this point in the guideline what constitutes a certified digitised copy. This information is given later in Section 5.1 and ACRO recommends including a reference to that section here. Additionally, the statement introduces a requirement that is not always possible for a Sponsor or CRO organisation to fulfil as the point at which digitisation is conducted may be beyond the control of the organisation that holds the eTMF, and the use of the word “should” suggests that there are circumstances where the inclusion of uncertified digitised copies may be acceptable. Proposed change (if any): Add a reference to Section 5.1. and include a description of circumstances wherein the inclusion of uncertified copies of original documents may be justified, such as under circumstances where the holder of the TMF was not responsible for the digitisation, and does not hold a copy of the paper original.	
332 - 357		Comment: The draft guideline states “Validation should comprise the following process steps” and then lists the steps as a series of bullets. However, these bullets describe a process for documenting the digitisation procedure rather than	

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)*
		for validating the process (for instance, there is no mention that the equipment used to digitize the paper is required to be calibrated / validated). Additionally, the current wording is not clear as to whether a certified copy (with date and signature) can replace the “validation” process or is an output of the “validation” process. The section should be expanded and reworded to define the validation process clearly, and to explain how a certified copy should be derived. Proposed change (if any): Expand and reword the section to define the validation process clearly, and to explain how a certified copy should be derived.	
389 - 400		Comment: To assist sponsors, ACRO recommends adding a statement to this section, as proposed below. Proposed change (if any): Add a statement to this section to the effect that signatures on documents are recommended only where they add value, and that it has been noted on inspection that many documents require wet-ink signatures as a result of internal procedures, without clarity on what the signature is actually for.	
429 - 431		Comment: The draft guideline notes that “The CRO may wish to retain certified copies of the documentation from following its own internal procedures after the originals were handed over to the sponsor for archiving and the contract between 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)*
		sponsor and CRO should address this." In fact, a CRO may wish to retain copies of documentation for various different business purposes, not all of which would require that certified copies are retained. ACRO therefore proposes that the sentence is rephrased as below. Proposed change (if any): Rephrase the sentence to read "Should a CRO wish to retain certified copies, after the originals were handed over to the sponsor for archiving, in order to retain evidence of compliance with the CRO's procedures, the contract between the sponsor and CRO should address this."	
477 - 478		Comment: The draft guideline states "For guidance on these provisions see the guideline on transitory period for the application of Regulation (EU) No 536/2014." However, ACRO understands that a guideline on the transitory period is no longer planned and that this will be addressed within a proposed Q&A document on Regulation (EU) No. 536/2014. ACRO therefore recommends that this is clarified in the final guideline and the Q&A document is included in the reference list in Section 8. Proposed change (if any): Provide an accurate reference to where guidance on the transitory period will be available and include this document in the reference list in Section 8.	

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)*
550 - 553		Comment: The phrase “The inspectors should have read only access, without any restriction (e.g. to final documents), to the entire TMF” is confusing. ACRO recommends that the guidance should indicate specifically that only final documents are required in the TMF and that it is not necessary to retain draft versions for inspection purposes (see also comment on lines 169 – 200 above). Proposed change (if any): Revise the phrase to read “The inspectors should have read only access, without any restriction, to the entire TMF”, and include a statement in section 3.3.1 of the guideline that only final documents are required in the TMF and that it is not necessary to retain draft versions for inspection purposes.	
		ACRO thanks the Agency for the opportunity to comment on this Guideline on GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials (EMA/15975/2016). Please contact ACRO (knoonan@acrohealth.org) if we can provide additional details or answer any questions at all.	

Please add more rows if needed.