EUROPEAN MEDICINES AGENCY (EMA) CONSULTATION

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).

In July 2017, the UKCRC Registered CTU Network submitted the following comments on the draft guideline on behalf of its members.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

11th 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
UKCRC Registered Clinical Trials Unit Network

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 guidance does not recognise the role of a clinical trials unit (CTU). Whilst the same principles exist regarding the clear, documented agreement of delegated duties including TMF management where a CTU is a different organisation to the Sponsor given that it is accepted within this guidance in cases where the Investigator is employed by the Sponsor the delegation of TMF management can be completely delegated to the Investigator can it be assumed this can also be applied where the CTU is part of the Sponsor Institution? It would be helpful to provide some examples of documents which would only ever be held by the Sponsor (line 132).	
	The previous consultation '*Risk proportionate approaches in clinical trials. Recommendations of the expert group on clinical trials for the implementation of Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use*' gave some, limited, information and examples regarding risk proportionality in relation to the TMF in low intervention trials. There should be more focus on the risk proportionate adaptations to the TMF which are permitted in particular for low intervention trials, through clear references to the associated Guideline and giving additional examples. Such examples may extend the risk adaptations previously described as	

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	permissible for low intervention trials. For example we would consider for 'low intervention trials' or those where no on-site monitoring visits are indicated based on risk assessment that to "make a documented assessment of the storage conditions at the investigator site for storage of the ISF" (line 292) is excessive.	
	It would be helpful to provide a clear distinction between an eTMF document management system and a systematic approach to storage of electronic copies or original documents on a secure network thereby allowing different working examples to be presented which do not assume that the only options to provision of a secure, access controlled audit trail are a paper TMF or a full document management system.	
	There are several references to ICH GCP within the guideline along the lines of 'sponsors must take appropriate account of ICH GCP E6' – there should be care taken to avoid appearing to mandate the use of ICH GCP E6 for all trials in its entirety, which was not the intention of its inclusion in the Regulation. We suggest the references are removed or clearly qualified to avoid misinterpretation / over interpretation particularly in the case of risk adaptation in low intervention trials. The use of terms ICH-GCP and GCP should be standardised throughout; preferably as 'GCP'.	

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)*
		Comment: The use of Investigator throughout the document is interchangeably used in reference to single and multi-site studies. Proposed change (if any): We suggest terminology in line with the Regulation is applied to avoid any confusion.	
Lines 87 - 88		Comment: "allows that the integrity of the trial data and the compliance of the trial with GCP can be evaluated" A TMF also importantly serves as a record of a completed trial. Proposed change (if any): "allows evaluation of the integrity of the trial data and the compliance of the trial with GCP"	
Line 94 (&226)		Comment: The requirement "at all times" means that the TMF should be updated, and completed in a timely manner. Where another party is responsible for producing TMF content (e.g. a central laboratory) what frequency is acceptable for these documents to be transferred into the TMF? Line 230 says the timelines should be defined but doesn't give expected timelines of what sort of interval would be considered appropriate or things to consider when setting acceptable timelines.	

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		Proposed change (if any):	
Line 142		Comment: A reference to Section 4.2.2 would be helpful to direct the reader. Proposed change (if any):	
Lines 292/293		Comment: Sponsors must make a documented assessment of storage conditions and investigators must provide this information. What constitutes 'documented assessment' on behalf of the Sponsor? Presumably risk proportionality can be applied in the case of low intervention trials and other trials e.g. where the Sponsor has previously worked with the organisation? Proposed change (if any):	
Lines 127 – 151		Comment: "the documentation in the investigator TMF will contain some source documents, for example, subject screening and identity logs and consent forms which should remain under the sole control of the investigator due to data privacy regulations". It is permissible, given appropriate consent, for copies of consent forms to be held centrally by the Sponsor for the purpose of central monitoring. The control of the original document would remain with the Investigator. Proposed change (if any):	

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Lines 130-131		Comment: "The entire TMF for the trial, both of the sponsor and of the investigator(s)/should be established at the beginning of the trial." – it would be helpful to define what is meant by 'the entire TMF' since the entire contents will not be available at the beginning of the trial. Proposed change (if any): Perhaps "format of the TMF" and/or "responsibilities for managing the TMF" could be used instead?	
Lines 146 – 151		Comment: "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". To clarify – presumably this relates to remote access to source data such as medical records and would not include data entered remotely at the trial site onto a trial specific database? Proposed change (if any):	
Line 173		Comment: "Essential documents should be complete, legible, accurate, unambiguous and signed and dated as appropriate". Further guidance regarding when it is considered appropriate for documents to be signed would be helpful. Proposed change (if any):	

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Line 180/181		Comment: The suggestion that the content of the TMF cannot be reduced once the trial has been initiated is unnecessarily restrictive and would not permit alterations e.g. following the amendment of a trial which legitimately alters the documents generated to evidence the trial. Proposed change (if any):	
Line 189		Comment: "Any documentation which has been created during the trial, for example from complying with formal quality system procedures and that helps reconstruct and evaluate the trial conduct should be filed in the TMF, irrespective of whether it is explicitly listed in these guidelines or not." This statement is too vague and could lead to significant over-interpretation. Proposed change (if any):	
Line 194		Comment: Examples of documents that are essential. Proposed change (if any): Examples of documents that would be essential, if relevant to the trial.	
Line 215		Comment: "The standards for electronic archiving in section 5.2.2 should be complied with". There is no section 5.2.2, we think this is now 5.1.	

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		Proposed change (if any):	
Line 223		Comment: "If using a central repository to store emails then ongoing review should take place to ensure all information in email is available." The practical resource implications of requiring an 'ongoing review' of emails is huge and in many cases could be disproportionate to the risks of the trial. A pragmatic approach to focussing on important areas such as authorisations and SUSARs would be a better use of resources. Proposed change (if any):	
Lines 225 – 234		Comment: These lines advocate actions which add little value and which do not take into account the reality of an individual truly being in a position to sign off the completeness of the TMF at the end of a trial. For example where there has been a change to Investigator during the trial how would this be practically managed when signing off the completeness of records generated before they were responsible for the trial. Proposed change (if any):	
Lines 242 – 264		Comment: These lines suggest that in the case of co-sponsorship each co-sponsor must agree to the content of the TMF held by the other organisation. If one organisation has responsibility for the TMF it seems rather officious to expect	

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		the other organisation to have to agree the file structure, formats for electronic data and systems for managing correspondence. Proposed change (if any):	
Line 261		Comment: This line seems incongruous without context. Proposed change (if any): "procedures, *in relation to TMF maintenance*, in case of an involved party closing down…"	
266		Comment: Section is referring to archiving, therefore the reference to 'prior to' on this line is confusing. Proposed change (if any): Suggested change from: "The entire TMF should be managed securely prior to and during formal archive to prevent…" To: "The entire TMF should be managed securely ~~prior to and~~ during **and after** formal archiv**ing** to prevent…"	
266-271		Comment: The title of this section 4.2 is "Security and control of TMF" – however Article 58, which is given as the reference for the section, relates only to archiving. We would suggest that the level of traceability for document addition/removal may not generally be feasible for an active trial where a TMF is in daily use.	

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		Proposed change (if any): We suggest the section title name should be changed to reflect that it relates to during archiving and once archived.	
Lines 296/297		Comment: Existing wording is confusing. Proposed change (if any): we suggest the words "there is" are removed from line 296.	
Line 346		Comment: Approval from whom? Proposed change (if any):	
Line 393		Comment: Existing wording is confusing. We suggest the risk assessment and decision taken when destroying paper copies of 'lower risk' documents should be documented. Proposed change (if any): Suggest remove the words, "*to destroy*".	
Line 469		Comment: It would be recommended that an insurance policy or some form of indemnification is agreed when working with a commercial archive as part of sub-contracting TMF storage.	

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		Proposed change (if any):	
Lines 482 – 484		Comment: As per Article 58 of the Regulation; should 'end of trial' be interpreted as the End of Trial Notification or End of Trial Report date for the purpose of determining the archive period? Are there are any specific expectations regarding how promptly trial documentation should be archived after the 'End of Trial'? Proposed change (if any):	

Please add more rows if needed.