11.07.2017

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:

KKS-Netzwerk e. V. – Netzwerk der Koordinierungszentren für Klinische Studien, Deutsche Hochschulmedizin e. V. und TMF Technologie- und Methodenplattform für die vernetzte medizinische Forschung e. V., Germany

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)*

We thank the European Medicine Agency for the possibility to comment on the Guideline. In our view, the Guideline is well written and clearly structured. In most parts, the proposed actions are realistic and feasible. Legibility of the documents is in part facilitated if read in conjunction with the consultation document “Recommendations of the expert group on clinical trials for the implementation of 13 Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use and the consultation document “Risk proportionate approaches in clinical trials”.

While most proposals are realistic and feasible, we would strongly recommend changes for some others. One should keep in mind that the guideline is applicable to all clinical trials under regulation EU 536/2014. The guideline asks for quite a few more documents to be part of the TMF as today, e. g. “timeline for submission and filing of documents to the TMF” or “written confirmation of sponsor and investigator that the TMF is complete”. Now, it seems to us, that the guideline often refers to processes and documents already established as “standards” in commercial clinical trials without a regulatory basis. It should be taken account of the fact that in clinical trials of academic sponsors the paper-based version of the TMF is and will be the standard for the next years. For academic sponsors the efforts required for the establishment and use of an eTMF will be in most cases too high. The requirements should therefore be adapted accordingly.

Furthermore in our view it does not make sense when in chapter 3.2. central documents which are part of the quality management system (e. g. SOPs, training records and training plans, system validation documentation, …) are defined as part of the TMF of a trial. Those documents are relevant for more than one clinical trial and as they are part of the Quality management system they need to be available centrally. In our view not all documents essential for the clinical trial infrastructure need to be part of the TMF itself. It should be sufficient that those documents are kept, stored for a sufficient time period, and are easily

accessible as is current practise. It would create a lot of additional administrative burden if it were necessary to make copies of all those documents and file them in the trial master file. This would exceed chapter 8 of ICH E6 and we do not think that this is meant in R2 (chapter 8.1 line 23/24).

At the same time, the requirements are more arbitrary and the guideline does in many parts leave things quite open. While some flexibility in the handling of the TMF is generally positive, we would find it helpful if in particular for low interventional clinical trials minimal contents of a TMF could be defined (3.3.1). In general, we would have appreciated examples/checklists that are more practical.

The Guideline also largely takes account of the concept of risk analysis and risk management. In parts it represents a helpful supplement to the chapter concerning the TMF in the Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice (E6(R2).

We very much welcome that documentation regarding the cooperation with external sponsors and / or several institutions is taken into account and the solutions suggested in the Guideline are generally feasible. In addition, we would find a proposal for the documentation of sponsor oversight helpful in cases where the paper-TMF is maintained by a CRO and there is no eTMF. In this case quite often there are discussions on which documents need to be given to and maintained by the sponsor to be able to document oversight over the trial.

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)*
153-155		3.2 TMF Structure “The sponsor and the investigator should identify and make a record of the location(s) of all of the potential documentation that is considered to form the TMF, even if several locations, departments, country organisations and systems are involved, so that it is effectively organised.” Comment: Instead of a record of locations there should be a process description of how the responsibility is split (effective organisation!) together with a list of the parties/responsible persons involved.	
155-167		3.2 TMF Structure “Some documents may be pertinent to more than one clinical trial; Provision should be made for all these documents to be identified and retained as part of the TMF even if stored separate from the main TMF itself….The documentation should be filed in each appropriate section of the TMF in date sequential order… “ Comment: This chapter is not written in a very clear way so that we are not sure what the requirements are. Documents such as SOPs, training records and validation documents of used systems should not itself be part of the TMF as proposed. They are part of the QM system and of course need to be kept, stored and accessible. Rather than documenting their location it should be documented who is responsible for maintenance and archiving of these documents as the location may change over time.	

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		If they were part of the TMF, one would have to make copies for each clinical trial. Proposed change: The documents should be referenced in the TMF, clearly defining version, date and document owner. E.g. a list of the SOPs and/or validation plans of electronic systems etc. which were used during the trial (instead of the SOPs/documents themselves) should be part of the TMF. If deemed necessary, an acknowledgement of the document owner regarding responsibility for archiving and continuous access could be filed.	
201-207		3.3.2 Superseded Documents Comment: We would deduce from what is written that previous versions of documents may be destroyed if all changes have been listed Is this correct? If yes, we would recommend that this is explicitly stated. The requirement of filing superseded documents is unspecific and there is no basis for this in ICH E6 chapter 8. In contrast, the chapter stated that trial specific documents should be filed as signed (finalized) or approved versions. To file superseded documents in the ISF is overreached and not constructive. The investigator is neither responsible for nor able to explain the development of a trial specific document because this is a sponsor task. Proposed change (if any):	

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229-234		3.3.4 Contemporariness of TMF “In trials that have more complex TMF arrangements with multiple parties involved, the timelines for submission and filing of documents to the TMF in procedural documents or TMF plans should be defined. A final close-out of a trial can only be done when the investigator and the sponsor have reviewed investigator/institution and sponsor TMFs respectively, and confirmed that all necessary documents are filed.” Comment: New documents are required here, e. g. a confirmation of sponsor and investigator that all necessary documents are filed. Will those be reliable statements? If there isn’t a procedure in place during the trial which ensures timely and complete filing of documents neither the sponsor nor the investigator will be able to guarantee completeness of the TMF at the end, even if final checks will be done. To ask for or to plan exact timelines for submission and filing of documents also will not add to compliance. Furthermore, those timelines would need to be valid for hundreds of different documents with different contents and requirements. It should be sufficient if documents are filed in a timely manner and a final review would be made before archiving. Proposed change (if any): It should be sufficient to state that documents need to be filed in a timely manner. The sentence “In trials that have more complex TMF arrangements…” should be deleted, because it is unspecific.	

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251		4.1.1. Contract research organisation and other sub-contractors "...lists of applicable procedures to be followed and training requirements;" Comment: The list of training requirement is, in our view, unnecessary as it is covered by ICH-GCP (5.5.1). It is a prerequisite for any CRO/study personnel to comply with ICH-GCP and the warranty is/should be part of the contract. Proposed change (if any): Delete	
292-294		4.2.1 Storage areas "It is essential that sponsors also make a documented assessment of the storage conditions at the investigator site for storage of the investigator TMF and that the investigator provides this information. The sponsor should be notified if the agreed arrangements are changed." Comment: From our point of view, it would be sufficient for the clinical monitor to check safekeeping of the relevant documents on behalf of the sponsor at initiation and close out visit. Is this meant here? Proposed change (if any):	
438-440		6.2 Archiving of the investigator TMFs "The sponsor should obtain the investigator's/institution's agreement to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed".	

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		Comment: The investigator should be able to automatically destroy the documents after the legally defined storage period of 25 years unless the sponsor has notified the investigator at least 6 months before the end of this period not to do so. Proposed change: Add a sentence to take account of this.	
467-469		6.3 Long term storage of the TMF “Therefore, they should undertake an assessment of the suitability of the facility prior to use and continue assessment once the organisation has been contracted.” Comment: A vendor audit and the assurance of the vendor regarding continued assessment of suitability by the vendor should be sufficient. It should not be necessary to repeat the audit several times. Proposed change (if any):	
511-514		6.4 Retention times of TMF “It is important that where an organisation has centralised records that may be relevant to a number of trials (for example staff training records or maintenance and calibration records for equipment used in the trial at a Phase 1 unit/hospital clinical research unit), that these are also considered in the arrangements for archiving and retention of specific trial records.”	

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		Comment: See comment to 3.2 above. Proposed change (if any):	
519-520		6.4 Retention times of TMF “The sponsor should notify investigators in writing when their trial records can be destroyed.” Comment: The investigator should be able to automatically destroy the documents after the legally defined storage period of 25 years unless the sponsor has notified the investigator at least 6 months before the end of this period to not do so. Proposed change: Add a sentence to take account of this.	

Please add more rows if needed.