EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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:

Name of organisation or individual
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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).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	EUCROF welcomes the opportunity to provide comments on the Guideline on 'GCP compliance in relation to trial master file (paper and/or electronic) for content, management, archiving, audit and inspection of clinical trials'. This guideline is very helpful. Our general comments refer mainly to terminology. We suggest to streamline terminology with both, the Regulation 536/2014 and ICH-GCP as both documents are taken as basis for this guideline. 1. In Article 57, the Regulation refers to "clinical trial master file". While it is seen cumbersome to always use "clinical TMF" instead of "TMF", it would be appropriate to make a note in the introduction that "TMF" is equivalent to "clinical TMF". 2. ICH-GCP consequently uses investigator/ institution. This guideline is switching between investigator, healthcare institution, institution, site. Especially for early phase units, the term "healthcare institution" is not appropriate. We suggest to use "investigator/ institution" throughout the document, as does ICH-GCP.	

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	3. Where the word "sub-contractor" is used in this guideline, ICH-GCP uses "contractor" and reserves "sub-contractor" for a situation when contractors further outsource to "sub-contractors". We suggest to align with ICH-GCP.	
	In line with the above said, we also suggest to either add the definition of "certified copy" also in this Guideline or make a clear reference to the ICH-GCP definition, in particular as there are other definitions as well (for example from the FDA).	

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)*
81-83		"This guideline aims to collate and explain the requirements for the TMF as covered in the Regulation and ICH-GCP E6 to assist organisations in maintaining a TMF that facilitates trial management, GCP compliance and inspection." Comment: "To assist organisations" is not covering all possibilities of addressees, as also individuals could be addressed. Proposed change (if any): "This guideline aims to collate and explain the requirements for the TMF as covered in the Regulation and ICH-GCP E6 to assist sponsors and investigators/ institutions in maintaining a TMF that facilitates trial management, GCP compliance and inspection."	
86-88		"A TMF is the collection of essential documents that facilitates the conduct and management of the clinical trial and allows that the integrity of the trial data and the compliance of the trial with GCP can be evaluated." Comment: The above sentence should also mention the Regulation and align wording with Article 57 of the Regulation. Proposed change (if any):	

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		A TMF contains the essential documents that facilitate the conduct and management of the clinical trial and allows that the integrity of the trial data and the compliance of the trial with GCP and the Regulation can be evaluated.	
99-100		"The same requirements for access to the TMF should be in place for the monitors, auditors and ethics committees." Comment: Direct access to the TMF also includes direct access to personal data in case of the investigator/ institution TMF. Legal provisions must be in place for direct access to personal data. For Ethics Committees, direct access to personal data is not stipulated in the local law in all Member States (e.g., Germany). Proposed change (if any): "The same requirements for access to the TMF should be in place for the monitors, auditors and also for ethics committees, as applicable according to the national law of the Member States."	
116-118		"Consideration should be given to ensuring that the TMF is a set of documentation and/or computer systems that together confirm the validity of the trial conduct and the integrity of data collected without the need for additional explanation from the associated sponsor or site staff."	

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		Comment: We think that the above wording is not optimal, for example, the TMF does not consist of a set of computer systems but of a set of electronic records that must be accessible with the support of a computer system. Proposed change (if any): "Consideration should be given to ensuring that the TMF is a set of paper and/or electronic records that must be accessible and that together confirm the validity of the trial conduct and the integrity of data collected without the need for additional explanation from the associated sponsor or site staff."	
135-138		"Where the investigator is employed by an institution which is the trial sponsor, the sponsor may delegate the task for maintaining the sponsor TMF to the investigator. In this circumstance, it is possible to combine the sponsor and investigator TMF for that site, which avoids the duplication of documentation." Comment: EUCROF finds the above sentences too risky. The investigator might have access to sponsor documents which should not be in the hands of an investigator, e.g., unblinded safety information. We would prefer to keep the sponsor and the investigator TMF separate, also for the purpose of archiving. Archiving of the institution might go different routes than archiving of investigators. The combined TMF should only be	

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		possible for the situation of a sponsor-investigator, i.e. the sponsor and the investigator are the same person. Proposed change (if any): See comments above	
135-138		Comment: Especially for early phase CROs (combination of CRO and site) it would be helpful to clarify that the investigator TMF (ISF) and sponsor TMF can't be combined where the sponsor has delegated TMF tasks to the CRO as the ISF must stand alone at the site in order to be able to recreate the trial.	
142-143		"The investigator TMF may be electronic, with the system either provided by the sponsor, a vendor or by the health care institution." Comment: For early phase CROs it would be more appropriate to add "investigator" as an option as it is not really a healthcare institution. Also, we suggest to be in line with the ICH-GCP wording (see general comments). Proposed change (if any): The investigator TMF may be electronic, with the system either provided by the sponsor, a vendor or by the investigator/ institution.	
214-215		"The standards for electronic archiving in section 5.2.2 should be complied with."	

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		Comment: There is no section 5.2.2 in the document. Proposed change (if any): "The standards for electronic archiving in section 4.2.2 should be complied with."	
216-218		"Correspondence (paper and/or electronic records) are recommended to be effectively organised and filed in chronological order in an appropriate section in the TMF, i.e. not all in one section, but placed in the section relevant to what the correspondence concerns." Comment: The above recommendation is well applicable to paper TMFs, however for electronic TMFs, the recommendation might add a lot of burden. Emails are usually sent (cc-ed) to a trial-specific inbox, and would have to be sorted by section afterwards. However, search functions (using key-words) and sort functions (e.g., by date or by subject line) are available and facilitate orientation for external reviewers in an eTMF Correspondence Section. Unambiguous subject headings should be used, of course. In addition, in many cases, correspondence covers more than one section and therefore the above recommendation can lead to a lot of duplication. In any case, we propose the TMF index makes it very clear in what way correspondence is organized. Proposed change (if any): Correspondence (paper and/or	

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		electronic records) are recommended to be effectively organised and filed in chronological order in an appropriate section in the TMF, i.e. not all in one section, but placed in the section relevant to what the correspondence concerns. Exceptions might be feasible when the correspondence covers multiple sections or the TMF being an eTMF. For electronic correspondence, this should be easily searchable e.g., by use of clear subject headings.	
226-229		"As Article 57 states that the "TMF shall at all times contain the essential documents relating to that clinical trial"; it is important, therefore, to keep the TMF up to date, with documents placed in the TMF in a timely manner as this greatly assists the successful management of a trial by the investigator and sponsor (or party to whom the sponsor has delegated its duties)." Comment: It would be very useful to learn more about the expectations regarding "in a timely manner"	
235-237		**4. Organisation, security and control of TMF** ***4.1. Organisation of TMF*** **4.1.1. Contract research organisation and other sub-contractors** Comment: As there is no section 4.1.2, the above structure is	

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		not logical – the third level (4.1.1) could be skipped. Proposed change (if any): See comments above	
246-261		Comment: The list of bullet points should be supplemented by an additional bullet regarding the archiving of and access to centralised systems (such as central training records, SOPs, delegation logs, validation of computer systems) that are not trial specific. Proposed change (if any): • arrangements regarding the archiving of and access to centralised systems (such as central training records, SOPs, delegation logs, validation of computer systems) that are not trial specific.	
251		" • lists of applicable procedures to be followed and training requirements; " Comment: It is not clear to us whether the complete list of SOPs is meant or only SOPs (procedures) pertaining to the handling of the TMF. Please clarify. We think the SOPs referenced here should be limited to TMF procedures. Proposed change (if any): • lists of applicable procedures to be followed <u>for maintaining the TMF</u> and any training requirements;	

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252		" • documents that both parties should retain;" Comment: To give an example would be helpful Proposed change (if any): " • documents that both parties should retain (e.g. contracts);"	
267-268		"Those who access the TMF in order to add or remove documentation should be controlled at all times (see 7.1)." Comment: We think what is probably meant is, that the access should be controlled at all times and not the people. You cannot control the people at all times. Also, while it is possible to control access to a certain extent, the investigator files need to be readily accessible for the investigator's team during a trial. In addition, reference should be "6.1" instead of "7.1" Proposed change (if any): "During a trial, it should be clear who is responsible for filing in the TMF and who has access to the TMF. Access to the TMF should be restricted as far as practicable. Following completion of a trial, the access of those who add or remove documents should be controlled at all times (see 6.1)."	

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336-337		"Digitised documents in the e-TMF should be a certified copy of the original." Comment: It would be very helpful to receive a few examples as to how the certification should be documented. Mention of an "electronic tick" provided by an eTMF system or, less sophisticated, maintaining a paper certification log with dated signatures/initials. However, that log will have to be archived as a paper document – at least the last dated signature pertaining to the scanning of the certification log. When large amounts of documents are being scanned, QC of the scanning procedure might be performed using a sampling method. It is not addressed in the guideline whether such a method is acceptable. As this document is a guideline, more practical guidance regarding such an important topic like certification would be very helpful and welcome. Proposed change (if any): See comments above	
347, 348, 352		„ • transportation of the records to the location of digitisation; • preparation and digitisation of the records;	

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		• destruction of the records;" Comment: As this is about digitisation of paper records, it would be clearer to use "paper records" instead of "records" only. Proposed change (if any): " • transportation of the paper records to the location of digitisation; • preparation and digitisation of the paper records; • destruction of the paper records;"	
392-394		"Destruction of such paper original documents by the sponsor or investigator would be of particular higher risk to destroy than the following examples:" Comment: The above sentence is a little confusing and difficult to read: "Destruction … is of higher risk to destroy …" Proposed change (if any): "Destruction of such paper original documents by the sponsor or investigator would be of particular high risk. The following examples describe a situation of lower risk: • …	

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		• … “	
405		“The TMF should be archived appropriately to allow for supervision after the trial has ended.” Comment: We think that “access” and/or “reconstruction of the clinical trial” is meant instead of “supervision” Proposed change (if any): “The TMF should be archived appropriately to allow for access and reconstruction of the clinical trial after the trial has ended.”	
237, 379, 427, 432, 465, 473		Comment: In those lines, the word “sub-contractor” is used in the context of a sponsor outsourcing to a CRO. In ICH-GCP 5.5.2 (ADDENDUM), the word “sub-contractor” is used for a situation when a CRO sub-contracts to another service provider. EUCROF suggests to use the word “contractor” or “contracted CRO” for “first line outsourcing” and save the word “sub-contractor” for outsourcing by the contracted CRO. If it is decided to stick to the word “sub-contractor”, it should be spelled always in the same way (with hyphen or without hyphen, but not mixed). Proposed change (if any): See comments above	

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429-431		Comment: The point is made regarding CRO's process for documentation handed over to sponsor to be included in contract. We suggest to add this to list in section 4.1.1 and cross reference which makes it easier to see all items to be considered in a contract in one place. Proposed change (if any): The CRO may wish to retain certified copies of the documentation from following its own internal procedures after the originals are handed over to the sponsor for archiving and the contract between the sponsor and CRO should address this (refer to section 4.1.1).	
506		"…the data can be retrieved in the future (see section 6). Comment: wrong reference. Proposed change (if any): the data can be retrieved in the future (see section 5).	
515-516		The point is made regarding retention requirements to be included in contract. As this is already included in the list in section 4.1.1 (line 260) we propose to add a cross-reference which makes it easier to see all items to be included in contract in one place.	

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		Proposed change (if any): The above-mentioned retention requirements for the documentation and medical records held by the investigator should be formalised, for example in the contract between the sponsor, the investigator and the institution (refer to section 4.1.1).	
534		"(refer to section 4.1)." Comment: Wrong reference Proposed change (if any): "(refer to section 3.1)."	
544-549 550 - 558		"Prior to the inspection, the inspector will usually discuss with the sponsor and investigator(s) the logistics of making the TMF available to the inspectors. A paper TMF (or e-TMF stored on media archived elsewhere) or certified copies relevant to the inspection site should be available for the inspection upon reasonable notice, whereas, access to e-TMFs (live and archived on servers) would be expected by inspectors to be essentially immediate (time only required to set up inspector access to the trials requested by the inspectors)." "With reference to Article 57 of the Regulation, direct access to the TMF is expected. The inspectors should have read only access, without any restriction (e.g. to final documents), to the entire TMF for inspection during preparation and conduct	

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		of the trial, which means that they can review the same TMF as used by the staff conducting the trial. Direct access includes all the systems that comprise the TMF as defined by the sponsor, however, due to the technical nature of some of these systems, for example those containing data rather than documents, these may require the direct access to be assisted by a representative of the sponsor familiar with the system. Organisations should be aware that GCP inspectors may have rights to seize original trial documentation if circumstances arise that require it. 557 GCP inspectors can always request copies or print outs and can retain some or all of these. Comment: The first paragraph makes reference to access to the TMF to inspectors, either paper or eTMF (line 545). In next paragraph, it however specifies reading access (line 551) therefore implying reference to an eTMF. It stresses the need for access without restriction up to "final documents". It is not clear what is meant by "final documents": does it mean original with – for example - wet ink signature where applicable (suggested by line 557) or would certified copies qualify as "final documents" in the context of an eTMF?	
559		"…inspectors' expectation is that an e-TMF should adequately replicate the paper based system …" Comment: EUCROF thinks that the word "adequately" should	

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		be skipped as the question has to be raised what "adequately" means in the given context. The e-TMF should simply be a replication of the paper-based system. Proposed change (if any): "…inspectors' expectation is that an e-TMF should replicate the paper based system …"	

Please add more rows if needed.