UKCRC Registered Clinical Trials Units

UKCRC Registered CTU Network – Guidance on the use of document management systems to provide eTMF capability

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Guidance on the use of document management systems to provide eTMF capability

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1. Abbreviations

CTU – Clinical Trials Unit

EMA – European Medicines Agency

eTMF – Electronic Trial Master File

GCP – Good Clinical Practice

GDPR – General Data Protection Regulation

IMP – Investigational Medicinal Product

IQ – Installation Qualification

MHRA – Medicines and Healthcare products Regulatory Agency

OQ – Operational Qualification

PQ – Performance Qualification

QC – Quality Control

SOP – Standard Operating Procedure

TMF – Trial Master File

2. Introduction

2.1. Background

A Trial Master File (TMF) is the collection of essential documents used to manage and allow reconstruction of a clinical trial. Essential documents are those which enable the evaluation of both the conduct of the trial and the quality of its data, and which demonstrate that the trial has been conducted in accordance with applicable regulatory and good practice requirements.

It is a regulatory requirement[1] for Clinical Trials of Investigational Medicinal Products (CTIMPs) that Sponsors maintain a TMF during a trial and retain it for at least five years after the end of the trial. The TMF must be complete and legible; any amendments made to it must be traceable. It must be accessible and readily available to auditors and inspectors.

For other clinical studies (i.e. non-CTIMPs), maintenance of a TMF is required in order to comply with the principles of Good Clinical Practice (GCP)[2] and the UK Policy Framework for Health and Social Care Research[3], namely that research must be managed in a way which ensures integrity and quality and that information collected must be recorded, handled and stored in such a way to allow accurate reporting, interpretation and verification.

The regulations do not specifically refer to electronic TMF (eTMF) systems, however guidance in this area exists from the Medicines and Healthcare products Regulatory Agency (MHRA)[4] and European Medicines Agency (EMA)[5]. MHRA blogs and talks discussing the transition to an eTMF have highlighted the positives of electronic working (e.g. sustainability) but have also emphasised the potential challenges, e.g. issues with inspector access, implementation of systems that are hard to navigate and the requirement for increased time to determine which documents are essential at inspection.

eTMF solutions are usually either in-house bespoke systems or off the shelf commercially available systems. Both present challenges for academic Clinical Trials Units (CTUs) in terms of either costs to purchase or resource to build/maintain. The COVID-19 pandemic with a shift to remote working has accelerated the need to identify pragmatic, cost-effective and efficient practical potential solutions to transition to an eTMF whilst maintaining regulatory compliance.

There are two options to consider:

[1] The Medicines for Human Use (Clinical Trials) Regulations 2004 (as amended) – see SI 2004/1031, Regulation 31A.
[2] ICH GCP E6 (R2) – see Principles 10 and 13.
[3] UK Policy Framework for Health and Social Care Research, v3.3, 017/11/2017 – see Principles 5 and 14.
[4] The Medicines and Healthcare products Regulatory Agency (MHRA) guide to Good Clinical Practice (GCP) chapter 10.5
[5] Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic) EMA/INS/GCP/856758/2018

1) An eTMF software solution: generally software that is developed for the sole use of providing an eTMF
2) A document management system, developed for broader use, but with sufficient functionality to host a user specified eTMF structure.

Validated document management software (option 2) can provide improved security and real-time access to trial documentation beyond that offered by a paper-based TMF. However, document management software functionality is highly dependent on the features an organisation subscribes to and ultimately implements. The MHRA have indicated that document management systems may fail to meet the regulatory functionality expectations for an eTMF solution (see section 2). It may be possible to provide risk proportionate solutions to address any gaps in the functionality of the document management system, but this should be assessed and planned prior to the purchase or implementation of such system. Any system choice should be supported by an appropriate evaluation against a user requirements specification and validation exercise.

2.2. Project Aims and Scope

This project aims to review the published guidance, highlighting key requirements and identifying pragmatic and practical implementation suggestions within an academic CTU. This can then be adapted and used as a starting point to create either:

- a specification to develop bespoke software solutions, or
- a vendor and risk assessment tool to assess the suitability of existing software and their implementation at a CTU.

This document is intended to provide a guide for CTUs to start from, but it should be noted that the MHRA are not able to endorse a solution which is not validated specifically for the intended purpose. It is therefore stressed that this is not an exhaustive list of implementation suggestions.

Whilst the TMF is the whole collection of essential documents used to manage and allow reconstruction of a clinical trial, some parts of a TMF are usually already electronic (e.g. databases, email accounts); and some parts are held by different host institutions (e.g. trial sites, central laboratories, pharmaceutical partners). The focus of this project was to provide guidance for assessment and implementation of an electronic solution for what had traditionally been printed and stored in paper format at CTUs. However, it should be noted that it is critical that the full TMF and all its different sections and locations be properly mapped - e.g. TMF of CTU, third-party vendor TMF (e.g. central labs, IMP manufacturer,

clinical database etc.), Investigator Site File. To ensure a robust and complete eTMF, adoption of the Trial Master File Reference Model[6] should be considered and adapted as required.

Updating SOPs previously reliant on paper-based systems will be required. Regular internal audits to ensure compliance with the TMF reference model and CTU SOPs will be required. During the conduct of the trial, it may not be appropriate to hold all documents within the TMF unless access can be restricted. An option would be to hold such documents elsewhere and then ensure these are moved appropriately at the archival stage (e.g. randomisation specification and schedules, closed reports). Where this is the case, the eTMF should signpost to the location of the documents.

3. Interpretation & Implementation of Requirements for selecting and implementing eTMF solutions

REQUIREMENT	REFERENCE TO SOURCE	IMPLEMENTATION
1. Selection Process		

1.1	Selection	• Check Institutional procurement requirements can be met
		• Determine user requirements and evaluate the proposed solutions against them
		• Undertake a risk assessment against criteria set by CTU including
		  ○ A check that the proposed solution has the longevity required to support operations and regulatory requirements
		  ○ Availability of escrow
		  ○ Ability to export eTMF following end of contract to another software or system provider
		  ○ Location of any external servers e.g. UK, EU, etc
		• Documentation that supports the selection of the eTMF system based upon user requirements. This may be via internal CTU SOPs

2. Security, Access & Edit Controls		

2.1 System security	b
	c (section 10.5.3 and 10.5.4)
	GDPR Article 5 (integrity & confidentiality principle) & Article 32
		• Access to system via individual log-on (username & password)
		• System firewall / encryption protection etc. [to prevent unauthorised access e.g. hackers]
		• System maintains pseudonymisation (for participant clinical data)
		• IT Policy/SOP on system accounts & security, to include:
		  ○ Process for adding/removing users and changes to user roles (including timeframes)
		  ○ Requirement for formal authorisation of new users.
		• CTU process (e.g. SOP/Policy/etc.) on management of personal log-on details (prohibited sharing of details)

2.2 System integrity & back-up	b
	c (section 10.5.3 and 10.5.4)
	f
	GDPR Article 5 (integrity & confidentiality principle) & Article 32
		• System back-up procedures in place [e.g. to be able to reconstruct system if virus, etc. or accidental deletion]
		• CTU process on system back-up procedures and disaster management, to include:
		  ○ management of software updates;
		  ○ regular back-up processes;
		  ○ scheduled disaster checks.

2.3 Role-based permissions	b
	c (section 10.5.3)
	d (section 4.1)
		• System functionality includes general access-levels (read only / edit / manage permissions)
		• System structure allows different access-levels to be applied across different trials (e.g. one staff member with different roles on multiple trials)
		• System structure allows different access-levels to be applied within a single trial (e.g. to handle blinded information)
		• Documentation in place to evidence:
		  ○ user details: names, usernames, job roles;
		  ○ access details: appropriate access-levels given, date access given, access approval (approver name/date) and access removed date.
		• CTU process detailing description of access-level roles and process for adding/removing users (incl. approval and timelines).

2.4 Auditor / Inspector access	a c (section 10.6.2) f	• System can be made available to external (non CTU) users – e.g. Sponsor, auditors, inspectors, etc who may have different needs/requirements. • System can be made available in short notice (e.g. to accommodate triggered inspections). • System can be made accessible remotely (e.g. to accommodate office-based inspections). • System functionality allows access level of “read-only” (see role-based permissions above for more detail). • Brief training materials in place to cover inspector/auditor read-only access and use of the system (to facilitate independent use of the system by auditor/inspector).

2.5 Version control • **in-system** • **within documents**	b c (section 10.5.3)	• System functionality includes structuring of files/folders to allow clear demarcation of areas for "current", "superseded/withdrawn" and "draft" documents. • Process in place for document metadata to identify "current", "superseded/withdrawn" and "draft" documents (see metadata section below for more details). • CTU process on version control to include: o Versioning details in document itself (e.g. header/footer); o eTMF to be structured with clear areas within eTMF for "current", "superseded/withdrawn" and "draft" documents.
2.6 Audit trail	b c (section 10.5.3) f	• System functionality includes audit trail to record at a minimum date/time/user details for: o Log-in/log-out o User access permissions including the ability to demonstrate control over unblinded areas o Document creation/upload; o Document changes. o Document deletion (recorded in audit trail) and recovery capability • System functionality allows audit trail retrieval at different levels – document, folder, trial and audit trail access. *If system being used to document approval of documents -* • System functionality to record approval (e.g. e-signature) by individual users (user and date).
3. Structure & Naming		
3.1 Structure	Ref b c (section 10.5.3)	• A defined and version-controlled structure should be used. A TMF index is expected and should be reflected in the efolder structure. The TMF reference model has been adopted by many commercial and non-commercial CTUs • System functionality allows and ensures structuring and naming of folders and sub-folders. • CTU process to ensure consistency across the CTU covering: o mapping of full TMF (e.g. database, eTMF, randomisation system, Investigator Site File, vendor sections of TMF, etc.) A plan should be put in place to ensure that all parts of the

		TMF are locatable and could be obtained for inspection/audit, even once the trial has been archived. Template eTMF folder structure to be used; ○ naming conventions for eTMF folders and files across the CTU prescribed within the eTMF or via SOPs. ○ Ensuring files are commonly named e.g. approval letters, helps with tracking of completeness of TMF and general navigability between trials ○ Workflows to ensure files are accurately named, filed to the correct location, electronic documents are validated, and that they are not duplicated
3.2 Metadata	b c (section 10.5.3)	• System functionality allows naming of documents. ○ This should include prevention and detection of poor naming/inconsistent naming etc to prevent against an unusable eTMF • CTU process to ensure consistency across the CTU covering: ○ naming conventions for TMF documents both across the CTU and within a single trial (e.g. convention for trial site name); ○ versioning format for documents ensuring it is clear what is draft and what is an effective/superseded version.
4. Usability		
4.1 Interface and searching		• A user friendly and intuitive interface • Search functions • Ability to sort and filter documents within folders, bookmarking and ability to select favourites, • Approval functions built in for CTU and external staff • Ability to assign tasks with deadlines for reviews and approvals • Ability to monitor TMF completeness.

5. Quality Control		

5.1 System Validation
(Initial and Change control)
	b
	c (section 10.5.3)
		• Documentation of validation, testing through to report and release/deployment is required. Documentation should be reconstructable regardless of the method of validation used.
		• Evidence of Operational Qualification (OQ) obtained, either:
		  ○ performed by CTU,
		  ○ OR from third-party software provider with the addition of validation of local configurations.
		• Evidence of Installation Qualification (IQ) obtained, either performed by:
		  ○ performed by CTU Information Systems teams,
		  OR
		  ○ central IT services.
		• Evidence of Performance Qualification (PQ) obtained, either:
		  ○ produced by CTU when agreeing to use the system as eTMF,
		  OR
		  ○ from third-party software provider if software specifically designed for eTMF use, with the addition of validation of local configurations.
		• CTU process on eTMF validation covering:
		  ○ Process for initial validation/configuration of system for CTU use as its eTMF;
		  ○ Processes for handling any subsequent changes to the system with appropriate validation;
		  ○ Documentation requirements to demonstrate validation / configuration and change control.

5.2 Certified copies
(paper to electronic / between electronic systems)
	c (section 10.5.4 & 10.7.9)	*N.B. This section is only applicable where electronic copies of paper documents are required to be created or where documents/full eTMFs are transferred between different electronic systems.*
		• CTU process requiring validation of the transfer process, covering:
		  ○ Acceptable modifications (e.g. resolution) to documents;
		  ○ QC checks required to ensure transfer maintains accuracy and completeness;
		  ○ Sign-off of transfer by staff member with appropriate authority;
		  ○ Documentation requirements to evidence the validation undertaken.

6. Archiving		
6.1 Access restrictions ***(named person responsible for archive)***	c (section 10.7.9) f	• System functionality allows removal of access from pre-archive users and restricts to post-archive users (i.e. named person(s) responsible for archiving). OR • Dual systems (LIVE/ARCHIVED) maintained with ability to transfer whole trial eTMF at point of archive and ARCHIVE system access restricted to named person(s) responsible for archiving.
6.2 Maintenance of Authenticity ***(prevent unauthorised changes)***	b c (section 10.5.3 & 10.7.9) f	• System functionality prevents changes after point of archive for both: o individual documents (change to, deletion & addition of, documents), and o overarching eTMF structure (i.e. folder structure). OR • System functionality allows identification of changes made, with back-up version available for "pre-changes".
6.3 Integrity ***(complete and legible)***	c (section 10.7.9)	• System allows long-term retention of documents (& audit trails) in accessible format. • More than one copy of archived eTMF held via either: o system being backed-up with back-up on separate server, OR o second copy of the trial's whole eTMF in separate system/server. • System can accommodate regular checks to be performed during archive period (e.g. testing that media still accessible and docs/info intact; checking of access restrictions; etc.). • CTU process to ensure archived media's continual and long-term access, covering: o scheduled checks to be performed to ensure media still accessible and documents/information intact; o consideration of transfer from one type of software/hardware to another if software/hardware becomes obsolete (see "certified copies" section above).

7. Training		

7.1 Staff training in system use	c (section 10.5.3)
	b
		• User training material available for system.
		• CTU process on user training covering:
		  ○ training requirements for user roles (content/frequency/timing)
		  ○ documentation requirements for evidence of training undertaken.

8. Third-party systems *N.B. this section is relevant where eTMF management is delegated to a third-party*		

8.1 Vendor assessment	c (section 10.5.4)	• Pre-qualification checks are undertaken (i.e. vendor selection).
		• Contract in place between sponsor and vendor.
		• Length of contract/license is adequate to accommodate archive periods.
		If original TMF (e.g. paper) transferred to vendor (e.g. paper records for scanning) -
		• CTU process to guarantee chain of custody, covering:
		  ○ records of transfer maintained when TMF documents moved from sponsor to vendor.
		  ○ checks in place to ensure what was stored matched with the original

9. GDPR requirements *N.B. eTMFs will at a minimum hold research team Personal Data in the form of names, job titles and professional contact details. They may also contain participant clinical data (i.e. "Special Category") in the form of data query forms, database snapshots, line-listings in oversight committee reports, etc.*		
9.1 Security & Integrity	GDPR Article 32	*See above sections on security and integrity.*

9.2 Transparency Information	GDPR Articles 12-14	• CTU process to ensure Transparency Information disseminated to data subjects, to include:
		  ○ Template wording.
		  ○ Method and timing of dissemination.

9.3 Third-party Data Processors	GDPR Article 28	• System must have clarity of which organisations are involved in its management (and so have access to its contents, e.g. Microsoft staff). • CTU process to ensure GDPR compliance, in particular: ○ where third-party (non CTU) processors involved, data processing agreements must be put in place.
9.4 International dataflows	GDPR Articles 44-50	• System must have clarity of where data flows (e.g. location of users) and is stored (e.g. location of servers). • CTU process to ensure GDPR compliance, in particular: ○ where personal data flows or is stored outside of the UK, an appropriate legal pathway must be established for the transfer.

4. References and Further Reading

a) Francis G. Inspecting clinical trials- The trial master file. MHRA Inspectorate Blog published 30July 2015. – last accessed 12/03/2024 https://mhrainspectorate.blog.gov.uk/2015/07/30/inspecting-clinical-trials-the-trial-master-file/

b) MHRA Forum Q&As. Is it acceptable for the TMF to be electronic? last accessed 12/03/2024 https://forums.mhra.gov.uk/showthread.php?1665-MHRA-produced-FAQs-for-Trial-Master-Files-(TMF)-and-Archiving/page2

c) Medicines and Healthcare products Regulatory Agency. Good Clinical Practice Guide. pp. 344-351 (Section 10.5 Electronic TMF) and pp. 357-358 (Section 10.7.9 Electronic archiving)

d) EMA "Guideline on the content, management and archiving of the clinical TMF (paper and/or electronic) Dec 2018

e) The Medicines for Human Use (Clinical Trials) Amendment Regulations 2004 (SI 2004/1031) as amended by SI 2006/1928 (Regulation 31A) and Schedule 1 Part 2 (9)

f) Medicines & Healthcare products Regulatory Agency (MHRA) 'GXP' Data Integrity Guidance and Definitions

g) Commission Directive 2005/28/EC of 8 April 2005 laying down principles and detailed guidelines for good clinical practice as regards investigational medicinal products for human use, as well as the requirements for authorisation of the manufacturing or importation of such products.

h) Integrated Addendum to ICH E6(R1): Guideline for Good Clinical Practice E6(R2)

i) CDISC. The Trial Master File Reference Model. https://www.cdisc.org/standards/trial-master-file-reference-model (last accessed 21/03/2025)

j) Medicines & Healthcare products Regulatory Agency (MHRA) 'GXP' Data Integrity Guidance and Definitions https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/687246/MHRA_GxP_data_integrity_guide_March_edited_Final.pdf (last accessed 21/03/2025)

k) European Medicines Agency. Notice to sponsors on validation and qualification of computerised systems used in clinical trials (EMA/INS/GCP/467532/2019). 07 April 2020 https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/notice-sponsors-validation-qualification-computerised-systems-used-clinical-trials_en.pdf

l) European Medicines Agency. Guideline on computerised systems and electronic data in clinical trials. EMA/INS/GCP/112288/2023 (9 March 2023) https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-computerised-systems-and-electronic-data-clinical-trials_en.pdf (last accessed 12/03/2024).

Other national legislation should be considered for international trials e.g. FDA 21 CRF Part 11.