White Paper

IQVIA eTMF: RESPONSE TO MHRA GOOD CLINICAL PRACTICES GUIDE:

TMF Related Elements

KATHIE CLARK, Senior Director - Offering Management, Orchestrated Content Management

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INTRODUCTION

In 2012, the UK Medicines and Healthcare products Regulatory Agency (MHRA) published their Good Clinical Practices Guide.

The Guide was published based on feedback from stakeholders, who felt that there was a lack of comprehensive and authoritative guidance on how the clinical trial regulations, and in particular GCP principles, should be implemented in practice.

This compliance position paper focuses on Chapter 10 of the guide, "Trial master file and archiving", which covers the legislative requirements and gives recommendations on how effective TMF management can be implemented. The move to electronic records is also discussed in this chapter.

IQVIA has studied the guide to ensure that we comply with the key points. We also used the guide to enhance our product roadmap to include important requests from the regulators. The remainder of this paper provides insight into the key eTMF-related points of the paper and how IQVIA eTMF complies with or supports those requirements.

Much of this chapter was later incorporated into the European Medicines Agency (EMA) draft "Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials". As IQVIA has issued a position paper on compliance with the Reflection Paper ("IQVIA eTMF: Response to EMA Reflection Paper on GCP Compliance"), this paper only addresses elements unique to the MHRA GCP Guide.

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The following table details key points of the guide and the IQVIA eTMF's response to these points. Points already covered in "IQVIA eTMF: Response to EMA Reflection Paper on GCP Compliance" are not reiterated.

Section	Key Point	IQVIA Response
10.2.2 Sponsor trial master file levels	Typically documentation is organized in the sponsor file at three levels… Global/trial-level files, Country-level files, Site- level files.	The IQVIA eTMF manages documents at the study, country and site levels. Documentation also exists at the enterprise level (across programs) and program/ product level. This documentation is consciously linked into specific studies as it does not automatically apply to all studies.
10.2.3 Identification of the location of trial master file documentation	The sponsor organization should identify where all of the potential documentation that should be filed in the TMF is located, as the TMF must at all times retain the essential documents relating to the trial. The documentation does not all necessarily need to be in the same location, but it must be clear where it is held from TMF procedures or indexes as it must be readily available both during the trial and during the archiving retention period following the trial.	The IQVIA eTMF provides an ability to "fulfill without content" when documents are located in another electronic system. Using this approach, a study manager can indicate the whereabouts of a document. When an expected document is tracked in this manner, it no longer shows as overdue or missing in reports and metrics. A client may also choose to use IQVIA Web Services to replicate content into eTMF. When this replication is performed, the source repository and unique ID in that repository are captured.
10.2.4 Indexing	It is recommended that the documentation is filed in date sequential order (usually with the most recent on top) to enable a clear audit trail of, for example, communications with sites, research ethics committees (REC) and competent authorities.	Document date is captured as standard metadata for all eTMF documents, and can be used to sort documents in any view. If document versions are uploaded out of order (for example, if a document dated 1-June-2013 is uploaded, and later another version of the same document dated 1-Feb- 2013 is uploaded), the version tree is constructed such that the later dated version is considered current, not the last uploaded version.
10.2.5 Written procedures for controlling the trial master file	The use of a formal procedure and a standard indexing system (rather than creating 'trial-specific' indices repeatedly) in organizations sponsoring several trials is recommended as it tends to facilitate compliance.	The IQVIA eTMF builds the expected contents (index) of each TMF based on the TMF Master List of Documents, tailored for each trial through use of the Study Wizard. As a result, document types are always categorized and managed in a uniform manner across trials, even though each trial only requires a subset of document from the Master List. IQVIA also provides template SOPs for study creation, maintenance and monitoring that our clients can adapt to their own specific procedures.

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10.2.6 Vendor involvement in the trial master file	If the documentation is returned to the vendor from the sponsor for inspection, or indeed if the vendor's documentation is inspected at the sponsor site, it is recommended that the vendor is able to demonstrate that the documentation is the same as that which was sent to the sponsor. The lack of this ability could be a problem if the documentation revealed an offence had been committed, in particular on the part of the vendor, as the vendor would not know whether the documentation had been changed in some way. A recommended solution to this, in line with due diligence, would be for the vendor to maintain its own copy of key documentation, which could be on paper or electronic media (subject to appropriate QC and archive controls). This arrangement would need to be part of the contract or TMF plan to ensure sponsor agreement to the vendor retaining a copy of the TMF documents.	Authorized IQVIA eTMF business users can export the TMF for exchange between a sponsor and CRO on demand.
10.3.1 Essential documents	Where the risk-adapted approaches to trial management are being followed some documents listed in the guidance may not be in the TMF - for example, IMP temperature storage records, IMP accountability, laboratory reference ranges - and the rationale for this would be in the trial risk assessment.	The decision as to whether to include documents on a risk-adapted basis can be controlled through wizard questions that determine what documents are needed for a trial.
10.3.3 Document duplication	It is recommended that duplication of documents within the TMF is avoided, where possible, as this can hinder the effective use of the TMF.	The IQVIA eTMF provides several features aimed at reducing duplicates: • A single document can be multi-indexed to fulfill a number of expected documents. For example, a single document can be used for both an IRB Charter and IRB Member list without duplication. • A single document can be used across a subset of sites. For example, an advertisement applying to several, but not all, sites can be multi-indexed to only the appropriate sites without duplication. • Enterprise and program level documents are added to eTMF only once, and then linked into relevant studies. • Study level documents automatically apply to all countries and sites within the study. Country level documents automatically apply to all sites within the country for the given study.

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10.3.4 Impact of the risk- adapted approach on trial master file content	The risk-adapted approach to clinical trial approvals and trial management was implemented on 1 April 2011. Trials that have been categorized as Type C, involving unlicensed medicines, would be expected to have few, if any, modifications to the documentation contained in section 8 of ICH GCP and Chapter 3 of the TMF guidance document. Trials categorized as either Type A or B are, however, highly likely to have such modifications. This would be in relation to the sponsor's risk assessment of the trial, with a focus on those activities that are important to meeting the objectives of the trial. This assessment would be reflected in the documentation generated and retained for the trial. This approach would easily result in differential documentation requirements.	The decision as to whether to include documents on a risk-adapted basis can be controlled through wizard questions that determine what documents are needed for a trial.
10.4 Control of the trial master file	The arrangements for who should access the TMF in order to add or remove documentation are important points to consider and must be controlled.	Individuals who can upload, QC, or delete documents can be controlled on a study-by-study basis. CROs are limited to accessing studies in which they are participating. All users have access to functionality based on the role or roles in which they have been placed.
10.4 Control of the trial master file	It should be remembered that MHRA GCP inspections can be unannounced or performed at short notice and even routine inspections may not contain a notification of the trials to be inspected until shortly before the inspection, thus the TMF must be maintained in an 'inspection-ready state'. This particularly applies to TMFs after the trial has completed, as these TMFs must be 'complete and legible'.	The IQVIA eTMF focuses on providing the visual cues, reports and notifications that allow a study to be maintained in an inspection-ready status at any time. In addition, before a trial can be locked and archived, a series of quality and completeness checks must be passed.
10.5.3 Controls, security, training and validation	Records that exist only in a digital format are often only printed onto paper at the time of an inspection as they are normally accessed in their digital form. This can result in loss of any version control applied in the computer system (for example, a dated filename). An example of this could be the 'edit checks' specification used by data management. Such documents, when uploaded into the eTMF, may also have the same potential issue, which reinforces the requirement that all documents should have clear version control that is maintained on transition from one type of media, or from one system, to another.	Since the document date is captured for each eTMF document, the version history is always evident, and never depends on the dates or order in which document versions were uploaded or released into eTMF.

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10.5.3 Controls, security, training and validation	Unlike a paper TMF, documents loaded into the eTMF will need the addition of metadata to enable the document to be identified within the system. Metadata are data which are associated with the document (but not the document itself), typically would be identifying codes for the trial, site, protocol and product. The type of metadata is recommended to be formally defined to ensure consistency across all documents.	Each document type has standard metadata defined as part of the TMF Master Document List. Although individual document types needed in a trial may vary, a specific document type will always be standardized across trials.
10.5.4 Scanning or transfers to other media	When original paper TMF documents are transferred to an electronic format (or other media) the system of transfer should be validated in order to ensure that the transfer of documents is without loss and to ensure that certifiable copies are made (such that there should be a demonstrable 1:1 mapping between the content of the original TMF and the eTMF, which essentially means a QC check of the original TMF against the eTMF).	Standard QC checks based on client-defined criteria are built into the IQVIA eTMF.
10.6.2 Inspection of the electronic trial master files	MHRA GCP inspectors will require direct access to the eTMF system (not a copy), without reliance on an eTMF 'super-user', so the system should ideally facilitate a read-only inspector or auditor view access.	The IQVIA eTMF includes a read-only inspector view as a standard feature. This feature has been used in a number of real-life audits by regulatory authorities.
10.7.4 Review of trial master file prior to archiving	Before the TMF is archived, it is recommended that it is checked to ensure that it is complete and that all necessary documentation has been filed. This would often be done by the trial monitor (particularly at the close-out visit at the investigator site) but may also be undertaken by other appropriate individuals. It is recommended that this check is documented and that, for organizations which sponsor numerous trials, a written procedure is produced to cover this process. A documented check usually involves completing a checklist of the expected documentation, although it should be remembered that this needs to be comprehensive so as to record all of the documentation that has been filed to allow reconstruction of the trial conduct.	The IQVIA eTMF provides study lock and archive features that execute an extensive series of checks prior to lock and archive. This includes checks for missing documents, incomplete drafts, documents in workflows, and more. We also provide our clients with a template Study Lock and Archive SOP for them to adapt to their own processes. Archiving requires identification of a named study archivist. Archiving a study also removes access for most roles and changes the access level of remaining roles to read only.

REFERENCES

1. https://www.ema.europa.eu/en/documents/scientific-guideline/reflection-paper-good-clinical-practice-compliance-relation-trial-master-files-paper/electronic-management-audit-inspection-clinical-trials_en.pdf

CONTACT US

iqvia.com/contactus

LOCATION

460 Norristown Road, Suite 200

Blue Bell, PA 19422

USA

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IQVIA™