White Paper

IQVIA eTMF: RESPONSE TO EMA REFLECTION PAPER ON GOOD CLINICAL PRACTICE COMPLIANCE:

TMF Related Elements

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INTRODUCTION

Recently, the European Medicines Agency (EMA) issued a draft "Reflection paper on GCP compliance in relation to trial master files (paper and/or electronic) for management, audit and inspection of clinical trials".

This paper is the first published framework for eTMF for an entire region. EMA states that the paper is provided in response to the numerous questions they have been receiving regarding TMF / eTMF, as well as in response to inspection findings.

EMA states that the aim of the paper is to "set out the requirements for the TMF as covered in directives and guidance and to give recommendations to assist organizations in maintaining a TMF that facilitates trial management, GCP compliance and inspection. The paper also addresses archiving of the TMF, clarifying retention times and gives some recommendations regarding destruction of paper documentation."

IQVIA has studied the paper to ensure that we comply with the key points. We also used the paper 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.

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The following table details key points of the reflection paper and the IQVIA eTMF's response to these points.

Section	Key Point	IQVIA Response
4. Organisation and control of Trial Master Files		
4.1. Sponsor and Investigator Files	In organising the TMFs, it is essential to segregate some documents that are generated or held by the sponsor from those of the investigator and vice versa (Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 8.2, 8.3 and 8.4, Recommendations on the content of the trial master file and archiving Sections 3.1, 3.2 and 3.3), as some documentation held by the investigator should not be provided to the sponsor, for example those documents that would result in breach of subject confidentiality…	Document types to be managed in the IQVIA eTMF are designated in advance in a Master Document List. This list would not include those investigator documents that should not be provided to the sponsor, and as a result there would be no way to file them in eTMF.
4.2. Contract Research Organisation (CRO)	The sponsor is still responsible for the trial and will need to maintain oversight (Directive 2005/28/EC Article 7 and Recommendations on the content of the trial master file and archiving Section 6), so access to the TMF (e.g. remote access to eTMF) may be necessary or the sponsor may decide that the CRO needs to provide documents to the sponsor.	The IQVIA eTMF allows remote access requiring only a browser from anywhere with internet connectivity. VPN access is not required. We have a proven track record of reliable access around the world including countries such as India and China. Our security model, when used in a sponsor system, allows CROs to be designated for specific trials and limits CRO access to relevant trials. Conversely, in CRO systems, access may be provided to sponsors but visibility is completely limited to their own trials (i.e., the trials of other sponsors are not visible in any way including searching and dropdown lists). The study bulk export feature provides an authorized user with the ability to export study documents and metadata for an ongoing or completed trial, on demand. Export is to a security FTP area.
	In conducting these allocated duties and functions, the CRO will be generating documentation that will need to reside in the TMF (Directive 2005/28/EC Article 16). In addition, the CRO may have been delegated the duty of managing the sponsor's TMF.	The IQVIA eTMF is designed to allow collaboration between sponsors and CROs, whether the system owner is the sponsor or the CRO. For a sponsor's eTMF, CROs can be provided with direct access and their personnel allocated the appropriate roles in TMF management, ranging from reader through contributor, QC associate, or study manager. Access will be restricted to appropriate trials. Conversely, for CRO-owned systems, sponsors can have access to their own trials and can be placed in any appropriate roles. They are not limited to read-only participation.

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	The contract or other document or procedure is recommended to outline the arrangement for the TMF in some detail. This is recommended to address: • which party holds the official TMF (or which parts of the TMF each party holds when this is divided); • the process for filing documentation in the TMF; • the access arrangements for both parties; • the structure and indexing of the TMF; • where an eTMF is being used, the details of the system; • lists of applicable procedures to be followed and training requirements; • documents that both parties must retain; • arrangements for managing correspondence; • how the TMF would be made available if either party was inspected; • arrangements for when the trial is completed (the CRO may archive the TMF [or parts thereof] on behalf of the sponsor); • arrangements for oversight of the quality control/quality assurance of the TMF by the sponsor and how this would be documented (e.g. audit reports, QC8 reports).	As described in the previous topic, the IQVIA eTMF is designed to allow sponsors and CROs to collaborate on trials. For CRO systems, each trial can be tailored to account for the specific requirements of the sponsor for that trial, including the exclusion of documents that the CRO will not be responsible for if the sponsor is not providing them for inclusion. Sponsor access ensures that the sponsor can provide oversight of the quality control/quality assurance of the TMF throughout the course of the trial, not just at the end.
4.3. TMF structure	In large organisations, the TMF could include documents from across a variety of different departments and systems other than clinical for example, Data Management, Statistics, Pharmacovigilance, Clinical Trial Supplies, Pharmacy, Legal, Regulatory Affairs etc., as well as those provided or held by CROs.	Documents from other eClinical systems can be bulk uploaded through the use of web services if desired. Otherwise, placeholders for these documents can annotated to indicate the document is being held in another system.
	Sometimes documents may need to be located in a separate location to the main TMF records, for example those that contain information that could unblind the study team.	There is no need to exclude documents that contain information that could unblind the study team from the eTMF. These documents are simply marked as unblinded and access to the content in them limited to named individuals per trial. In the meantime, all users with access to the trial are able to see the document's status and metadata.

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	Some documents may be pertinent to more than one clinical trial. For example, product development level documents such as the Investigator Brochure or documents that are stored in a centralised system, for example central training records, SOPs and delegation logs. Provision must be made for these to be identified and retained as part of the TMF for the required retention period…	Documents that are pertinent to more than one trial can be established at two levels in the IQVIA eTMF: • enterprise documents used across products or programs – for example, certain computerized system validation documents • program level documents applicable across trials – for example, safety documents or the investigator brochure These documents are then linked into relevant studies. As a result, even if the study records no longer need to be retained under retention rules, the centralized document will remain and will still apply to trials where the end of the retention period has not been reached.
	There should be a suitable indexing system in place for the TMF to ensure that the documentation is appropriately sorted and filed, which facilitates audit, inspection and trial management (Recommendations on the content of the trial master file and archiving Section 2). This is recommended to be implemented across the sponsor organisation so that the TMF has the same structure irrespective of the location of the trial and the organisation.	The IQVIA eTMF uses a Master Document List based on the TMF reference model for indexing and filing documents. Although each trial will use only a trial-specific subset of the documents in the master list, each specific document type will have uniform naming, indexing and business rules across all trials.
	There could be some flexibility in the index to facilitate the TMF is fit for purpose for the actual study (for example, removal of sections that are clearly not applicable)	Using IQVIA's unique Study, Country and Site wizards, the study owner answers questions about the study. This results in the automatic removal of sections that are not applicable. For example, if no interim analysis is planned, the set of documents associated with interim analysis will not be expected or that study. if conditions change later, the list of expected documents can be adjusted.
	The documentation is recommended to be filed in each section of the TMF in date sequential order as this facilitates provision of a clear audit trail. The index could be provided to inspectors and auditors to assist in locating documents in the TMF.	Document date is captured for each document as it is indexed, and can then be used to display documents in date order.
4.4. TMF security and control	It is recommended that it is stored such that those who access the TMF in order to add or remove documentation are controlled whilst the trial is in progress. The risk of a lack of control would potentially be missing documentation at the end of the trial.	The IQVIA eTMF provides the ability to control access per trial, and also to assign users to roles that control whether they can contribute content, perform QC processes, manage studies, view reports and metrics, and more.

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5. Trial Master File contents		
5.1. Essential documents	The essential documents listed in regulatory guidance can be regarded as a subset of the potential documentation that could be regarded as essential for reconstruction of the conduct of the trial. Any document which has been created during the trial and that helps reconstruct and evaluate the trial conduct must be filed in the TMF, irrespective of whether it is explicitly listed in these guidelines…	The IQVIA eTMF's Master Document List is based on the TMF Reference Model, but is easily expanded to include any document deemed to be essential.
5.2. Superseded documents	Superseded versions of documents must be retained within the TMF (Directive 2005/28/EC Articles 16 and 17), for example the Investigator's Brochure or the protocol as these are necessary to reconstruct activities in the earlier part of the trial.	eTMF provides the ability to superseded documents. In addition, document version trees are constructed in document date order rather than in receipt date order. This prevents common problems where an earlier version of a document is received after a later version. In most EDMS, this would result in the later version being superseded, but in the IQVIA eTMF an earlier version received after a later version is automatically created as superseded, without impacting the later effective version.
5.3. Correspondence	Relevant correspondence that is necessary for reconstruction of key trial conduct activities and decisions or that contains other significant information must be retained.	The IQVIA eTMF includes standard correspondence documents and can be configured for original documents.
	Emails are recommended to be saved to ensure that the associated metadata is retained, for example as .pst files rather than pdf documents or being printed and signed.	Most of IQVIA's clients are not comfortable in importing .PST files, although this is possible. However, eTMF can import .msg files and retains those files, rendering the message and attachments to PDF for ease in viewing.
	Correspondence (paper and emails) are recommended to be effectively organised and filed in chronological order in an appropriate section in the file.	Correspondence is normally filed under section (TMF Reference Model zone is used out of the box). As with all other files, correspondence can be viewed sorted by date order.
5.4. Documents from following quality system procedures	Any quality record produced from following a quality system procedure must be retained in the TMF to demonstrate compliance (Directive 2005/28/EC Articles 2[4], 16 and 17). Examples include evidence of QC checks, documentation on Regulatory Green Light, Database Lock Forms etc.	All of these records can be stored in eTMF.

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5.5. Contemporariness of TMF	The TMF should to be up to date, with documents placed in the TMF in a timely manner with the aim to maintain the TMF "inspection ready" (Directive 2005/28/EC Article 16 and Recommendations on the content of the trial master file and archiving Section 3).	The IQVIA eTMF was designed to provide insight into the ongoing status of a trial to facilitate inspection readiness. The expected documents for the trial are defined in advance and tied to study and site milestones. As a result, insight is available in real time concerning which documents are coming due and overdue. Icons draw a user's attention to coming due and overdue documents, and study owners receive periodic emails alerting them to coming due and overdue documents. They can also execute a report on demand to summarize coming due and overdue documents. eTMF also tracks the amount of time needed to finalize documents after receipt, so that timeliness can be assessed and improved for a single trial, a program, a country, a partner, or many other conditions or combinations of conditions.
6. Provision of Trial Master Files for inspection		
	Sponsors and investigators are recommended to have considered how to make the TMF readily available to the inspectors, this includes making arrangements to review the TMF at a CRO site (where the TMF maintenance has been delegated by the sponsor). … Access to eTMFs (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).	Auditors can be provided with accounts and set up with access to a specific trial only in a manner of minutes.
	The inspectors must have direct access to the entire TMF (Directive 2005/28/EC Article 16 and Recommendations on the content of the trial master file and archiving Section 2), which means reviewing the TMF as used by the staff conducting the trial. A copy or artificial construction of it is unlikely to be accepted for trials currently in the live phase and puts an additional QC requirement on the sponsor. A copy may be acceptable for archived TMFs (see below). Direct access includes all the systems that comprise the TMF as defined by the sponsor. GCP inspectors may not wish to be supervised during the review of the TMF.	The IQVIA eTMF allows the auditor direct access to the same eTMF that is used by staff conducting the trial. We have a proven track record of successful direct use by auditors. Our easy to use interface means inspectors can use the system with little or no training.

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	Remote access to eTMF without the inspector visiting the site may assist in planning inspections and could, in future, potentially form part of the inspection dependent upon national legislation and inspection practices.	Auditors can be provided with accounts and set up with access to a specific trial only in a manner of minutes.
7. Electronic Trial Master Files		
7.1. eTMF content	Version control should be applied to electronic documents in the system and if the document is printed to paper the same version control should be apparent on the printed version.	Version control is automatically applied to eTMF documents. Where applicable, version information is generally contained within the document.
7.2. Controls and security, training and validation of eTMF	The eTMF system should enable appropriate security to be in place (Recommendations on the content of the trial master file and archiving Sections 5 and 6), which is recommended to include, as a minimum: • user accounts could be created and deleted within a formal approval process and in a timely manner; • secure passwords for users; • a system in place locking/protecting individual documents or the entire eTMF (e.g. at time of archiving) to prevent changes to documents; • regular back up Additionally, the eTMF would ideally have the following attributes: • where there is approval of documents via a workflow system, there should be use of digital signatures; • role based permissions for activities being undertaken; • audit trail in place to identify date/time/user details for creation, uploading, approval and changes to a document	User account creation and deletion processes are under the control of our clients. Passwords are secure and encrypted. Documents are automatically locked upon finalization and cannot be modified or deleted, although newer versions can be created. An entire study can be locked, which will prevent the creation of new content or versioning of existing content. We are not supporting digital signature at this time due to the complexity and expense of managing digital certificates for signers, many of whom are outside of the sponsor's or CRO's organization. Audit trials track date/time and user information for all events related to creation, uploading, approval and changes to a document.
	The eTMF should be validated to demonstrate that the functionality is fit for purpose, with formal procedures in place to manage this process and for change control... The documentation for this process must be retained.	IQVIA performs IQ, OQ and PQ on our cloud platform and makes all changes under strict, documented change control. Our clients generally perform an additional User Acceptance Test.
7.3. eTMF at the investigator site	N/A	

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7.4. Scanning or transfers to other media	The use of eTMFs and electronic archiving generally require the scanning of some paper records to generate electronic copies of the documents. The QC of the scanning, as part of the validation or subsequent sample QC activities could assess, for each document reviewed, one or more of the following: • accuracy of the metadata attributed to the document (it is recommended that the sponsor has defined the required metadata in a formal procedure); • quality of the image (readability, reproduction of colour, the quality of wet ink signature or annotations and handwriting in general etc.); • whether it was the correct document (as expected); • that the document had the correct number of pages; • the eTMF audit trail associated with the document; • chain of records transfer documentation; • approval process (where applicable); • scanned images should be at appropriate resolution so that when viewed at actual size on the screen (as per the original) the image is clear and legible	IQVIA's QC process is specifically targeted towards performing these types of checks. If issues are found, they are logged against specific defect codes that provide insight into what kinds of issues are occurring and allow corrective actions to be taken.
	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 (Recommendations on the content of the trial master file and archiving Section 5). A certified copy can replace the original paper record.	The IQVIA eTMF provides the tools to allow certification of copies in conjunction with valid training and procedures. Some of our clients are choosing to use these tools and processes to destroy all paper except those documents containing wet ink signatures.
	All transfers should be certified for accuracy and completeness by someone with appropriate authority (e.g. trial manager) as part of the quality assurance system (Recommendations on the content of the trial master file and archiving Section 5). This does not necessarily mean that the individual reviews every document, but that they have adequately approved the validated system that is being used. If 100% checks are not performed proper justification is recommended to be provided, including validation files proving that the process provides reliable and unaltered copies.	eTMF requires 100% QC of documents with the possible exception of those documents imported directly from another validated system. In addition, study owners can do spot checks on TMF content.

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7.5. eTMF vendors	It should be ensured that the transferred documentation can not be modified or deleted.	Content and metadata of final documents cannot be edited.
7.5. eTMF vendors	N/A	
7.6. GCP Inspection of eTMF	It is acknowledged that inspectors may need to familiarise themselves with an eTMF. Any training should be an option for the inspector to choose and is anticipated to be very brief (taking no more than an hour).	The IQVIA eTMF has been successfully used by regulators in auditing large trials, with little or no training.
	GCP Inspectors will require direct access to the eTMF system as used by the organisation (Directive 2005/28/EC Article 16 and Recommendations on the content of the trial master file and archiving Sections 2 and 3). The access is recommended to be a read only access without any restriction to any part of the TMF.	The IQVIA eTMF allows an auditor direct access to a designated trial or trials in eTMF without restriction.
	The system is recommended to have an efficient speed of access and ideally not require the use of a nomenclature document or require time spent opening non self-evident named files to determine their content.	eTMF's auto-naming feature provides clarity in the contents of each document and distinguishes multiple documents of each type. We also provide thumbnail previews to further minimize the need to open documents to determine content.
	The system and equipment would ideally be akin to flipping the pages of a book and it would be useful if there is a system tool available to print or mark documents for subsequent retrieval and examination as well as the ability to compare documents side by side.	Auditors can page through individual PDFs or through document sets they select by adding documents to a clipboard. eTMF also provides the ability for users to mark documents as favorites and to create private study or document-specific notes which can then be collected and printed. Documents can be viewed side by side in Acrobat.
	Finally, if documents from the eTMF are required to be copied and retained by the inspector, the organisation is recommended to be able to facilitate this. A search tool in the eTMF is also recommended.	eTMF provides a robust search tool and the ability to export or print documents.
8. Retention and destruction of Trial Master File contents		
8.1. Retention times	Various	Documents are retained in eTMF until a decision is made by a sponsor or CRO to purge them.
8.2. Named individual responsible for archiving TMF	In respect of the sponsor TMF, the sponsor must appoint a named individual within the organisation to be responsible for archiving the documents which are, or have been, contained in the eTMF, and access to these documents shall be restricted to those appointed individuals and auditors or inspectors.	The IQVIA eTMF provides a study archiving feature that includes collection 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.

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8.3. Pre-archive checks	Prior to the storage of the TMF, it should be checked to ensure it is complete and that all necessary documentation has been filed appropriately (Recommendations on the content of the trial master file and archiving Section 3).	An extensive series of checks is run prior to lock and archive. This includes checks for missing documents, incomplete drafts, documents in workflows, and more.
8.4. Storage areas/ conditions	Various	The IQVIA eTMF is hosted by AWS, a top-rated service provider. **Security.** IT assets are safeguarded against man-made and natural disasters. Data center locations are designed to withstand extreme weather events and prevent unauthorized access to IQVIA's data center. AWS offers a wide range of Managed Security Services that help IQVIA to prevent potential data compromises, network breaches and unauthorized system access. • On-premise security guards • Security systems on the building exterior: cameras, false entrances, vehicle blockades, customized parking lot designs, bulletproof glass/walls and unmarked buildings • Biometric systems, including palm scanners • Numerous security cameras with digital recorders • Portals and person-traps that authenticate only one person at a time **Power.** Utilize power management, power monitoring, advanced fire suppression, and HVAC (Heating, Ventilation & Air Conditioning) systems. AWS data centers are designed to prevent "single points of failure" that can reduce availability of your infrastructure and impact the quality of end-users' experiences. **Network Connectivity.** High-availability network and carrier connections provide strong global reach. Locations in North America, the United Kingdom and Asia-Pacific regions, address specialized business continuity and disaster recovery objectives. AWS geographical diversity may be leveraged to provide robust failover and redundancy capabilities.

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8.5. Subcontracting archiving	The storage of the TMF may be transferred to a sub-contractor (e.g. a commercial archive) but the ultimate responsibility for the quality, integrity, confidentiality and retrieval of the documents resides with the sponsor and investigator for their part 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.	Our eTMF cloud application hosting environment is provided by AWS, a top ranked infrastructure provider in terms of reliability and ability to execute. AWS provides: • A scalable, load balanced pool of application servers providing outstanding performance and automatic failover. • Redundant hardware with automatic, near immediate failover. • Firewall through which all traffic and encryption as it enters and exits the site. • Safeguarding of IT assets against man-made and natural disasters. • High-availability network and carrier connections for strong global reach. • Power management, power monitoring, advanced fire suppression, and HVAC (Heating, Ventilation & Air Conditioning) systems.
8.6. Archiving of investigator TMF by the sponsor	N/A	N/A
8.7. Electronic archiving	The use of electronic systems for such activities as data management, statistical analysis, reporting, trial management systems means that electronic documentation and data are likely to need to be retained. The data may be on a server or on transportable media, e.g. media drives/pens drives, Compact Discs, tapes etc. The following is recommended to be considered with respect to electronically archived data: • it could be subject to back up (with the back up media stored in a separate location); • storing the data in differing formats on different types of media (or even on the same media from different manufacturers.); • access to archived data should be suitably restricted; • the electronic documents or data that been archived must be protected from unauthorised changes to maintain authenticity (Recommendations on the content of the trial master file and archiving Section 5); • future access to records and data should be maintained (processes to overcome media, software and hardware becoming obsolete) (Recommendations on the content of the trial master file and archiving Section 5); • periodic test retrieval or restores to confirm that ongoing availability of the data is being maintained; • where data is required to be migrated to new media or a new format, then the transfer/migration of data to a new media/format should be validated (Directive 2005/28/EC Article 5, Recommendations on the content of the trial master file and archiving Section 5 and Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 5.5.3) (no loss, changes or corruption to the data or meta data and that authenticity is maintained).	The IQVIA eTMF ensures long-term access to and safeguarding of archived data. The safety and integrity of customer data is paramount in the high availability architecture of the IQVIA eTMF. Every system component is provided in redundant pairs such that if one unit should fail the other immediately and automatically takes up operation. Data replication is heavily leveraged resulting in multiple backup copies of content as soon as it enters the system. We maintain a Recovery Time Objective and Recovery Point Objective of 24 hours. Periodic testing of backup and recovery is included as a standard part of our contracts. Once a trial is archived, access to the trial is restricted to a small number of individuals as designated by the organization.

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Section	Key Point	IQVIA Response
8.8. Destruction of original paper	N/A	This is a sponsor/CRO responsibility.
9. Problems found with Trial Master Files from GCP inspections		
	Organisation was unable to provide a full TMF (paper and electronic) for inspection purposes on request of the GCP inspectors, in some cases resulting in additional inspection days required. This is often as a result of the contents being restricted to the contents of Note for Guidance on Good Clinical Practice CPMP/ICH/135/95 Section 8 documents. The organisation should be aware of the locations within the organisation (and that includes all the global locations) of all the documentation that comprises the TMF and situations arise where there is complete lack of clarity on what constituted the TMF for the trial. This includes issues with the location of documents that are common across several clinical trials (for example, the investigator's brochure).	Documents that are common across trials are added once and then linked into placeholders created in advance for relevant trials.
	Failure to fully document and perform effective QC checks on documents uploaded into eTMF – the result being that the inspectors had no confidence that the eTMF was accurate. Discrepancies were seen, as were missing pages, incorrect documents, poor quality scans	eTMF includes 100% QC checks in a process designed to prevent these types of issues.
	Incorrect documents located in the TMF and eTMF – for example from other trials.	eTMF includes 100% QC checks in a process designed to prevent these types of issues.
	There was poor, often repetitive, sometimes incorrect labelling of files, resulting in excessive time wasted opening and closing pdf documents in the eTMF when attempting to locate documents.	eTMF includes 100% QC checks in a process designed to prevent these types of issues.

REFERENCES

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