White Paper

SIGNATURE REQUIREMENTS FOR THE eTMF:

A Regulatory and Technological Assessment

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OVERVIEW

Sponsors and CROs want to ensure that the processes and workflows they use in their electronic Trial Master Files (TMF) comply with all regulatory requirements, resulting in a robust system that will produce complete documentation able to withstand an agency audit.

While working with our clients, we at IQVIA often participate in discussions around which documents in an electronic Trial Master File (eTMF) really require signatures. To provide a solid basis for decision-making, we've researched both the regulatory basis for signatures and the technology implications around how to collect signatures.

Research shows that relatively few documents have signature requirements based on regulations. Often, signatures are obtained because of an organizational policy, written or unwritten, not based on regulations. The UK Medicines and Healthcare Products Regulatory Agency (MHRA) reinforces this distinction in its 2012 Good Clinical Practices Guide:

> "Signatures on documents are recommended only where it adds value; many documents require wet-ink signatures as a result of internal written procedures, without clarity on what the signature is actually for. Some documents should be expected to be signed as part of GCP requirements (for example, the clinical trial protocol)."

Often, obtaining signatures is a holdover from the paper world where signatures were the only way to prove that an individual had an opportunity to review a document before it was finalized. Since modern electronic document management systems provide this information in logs and audit trails, the record exists without the need for signatures.

Knowing the actual regulatory requirements will assist organizations in making sound decisions about which signatures add value, and eliminating signatures they deem unnecessary.

SIGNATURES REQUIRED BY GOOD CLINICAL PRACTICES

Of course, the requirements around signatures aren't actually related to the electronic system – as the FDA has made clear in documents such as "Part 11, Electronic Records; Electronic Signatures — Scope and Application", which states that 21 CFR Part 11 applies to:

> "Electronic signatures that are intended to be the equivalent of handwritten signatures, initials, and other general signings required by predicate rules. Part 11 signatures include electronic signatures that are used, for example, to document the fact that certain events or actions occurred in accordance with the predicate rule (e.g. approved, reviewed, and verified)."

Signature requirements for TMF documents are established in several predicate rules related to Good Clinical Practice (GCP), and are the same for paper and electronic documents.

- The International Conference on Harmonisation (ICH) documents GCP in "Guideline for Good Clinical Practice E6 (R1)".
- The US Food and Drug Administration (FDA) considers ICH GCP only a recommendation, and does not codify GCP in a single set of regulations. Instead, regulations are scattered through the Code of Federal Regulations (CFR) as documented on the FDA's web page "FDA Regulations Relating to Good Clinical Practice and Clinical Trials".

The following table provides an analysis of requirements for signature appearing in predicate rules. A very conservative position was used; that is, any reference to approvals, initials, authorizations, etc. was interpreted as a potential signature requirement.

For each citation related to a signature, the associated artifact name from the Trial Master (TMF) Reference Model 2.0 is identified to assist in determining how to implement the requirement. Finally, notes provide details on how a signature is likely to be obtained and whether signature within an eTMF would be feasible. If a signature is more likely to be obtained in a Regulatory Electronic Document Management System (EDMS), Clinical Trials Management System (CTMS), or Electronic Data Capture (EDC) system, the specifics are noted.

A broad set of clinical requirements is examined. Some documents are needed only for submissions related to clinical trials and are not actually required in the TMF. These documents are noted in the table as not being part of the TMF.

Table 1 GCP Signature Requirements Analysis

Citation	Extract of Rule	TMF Reference Model Artifact Name	Notes	Likely Signature Category
50.23(d)(1) ICH 8.3.3	IRB must review and approve use of investigational drug without informed consent when informed consent is not feasible.	**"IRB/IEC Approval"**	An IRB would not normally have access to any form of eSignature.	Handwritten/ scanned
56.115(a)(1), 812.62, 812.64, ICH 8.2.7, ICH 8.3.3	DATED, DOCUMENTED APPROVAL/ FAVOURABLE OPINION OF INSTITUTIONAL REVIEW BOARD (IRB) / INDEPENDENT ETHICS COMMITTEE (IEC) OF THE FOLLOWING: • protocol amendment(s) • revision(s) of: • informed consent form • any other written information to be provided to the subject • advertisement for subject recruitment (if used) • any other documents given approval/ favourable opinion • continuing review of trial (where required)	**"IRB/IEC Approval"**	An IRB would not normally have access to any form of eSignature.	Handwritten/ scanned
50.27(a), 50.27(b)(1), ICH 1.28, ICH 4.8.8, ICH 8.3.12	SIGNED INFORMED CONSENT FORMS	**Signed informed consents are not part of the TMF Reference Model.**	External tools exist for eSignature of informed consents, but subject would not sign in eTMF. An IRB would not normally have access to any form of eSignature.	Handwritten/ scanned or exported from an eInformed Consent system
50.27(b)(2)	Short form written consent document to be signed by witness and subject or representative.	**"Informed Consent Form"**	(Alternative to standard Informed Consent) External tools exist for eSignature but subject would not sign in eTMF.	Handwritten/ scanned or eInformed Consent
50.27(b)(2)	Written summary of elements of consent to be signed by witness and person obtaining consent and IRB to approve written summary.	**"IRB/IEC Approval"**	An IRB would not normally have access to any form of eSignature.	Handwritten/ scanned
56.102(m), 56.108(a)(4), 56.108(c), 56.109(a), ICH 8.3.3	IRB reviews and approves the clinical investigation and changes.	**"IRB/IEC Approval"**	An IRB would not normally have access to any form of eSignature.	Handwritten/ scanned

Table 1 GCP Signature Requirements Analysis

Citation	Extract of Rule	TMF Reference Model Artifact Name	Notes	Likely Signature Category
312.120(c)(3)	For foreign studies (outside US), research is approved by an independent review committee.	**Not included in TMF reference model**	Not part of the TMF	eSignature or Handwritten/ scanned signature, probably in regulatory EDMS
54.4(a)(1)	Financial Disclosure Form FDA 3454 shall be dated and signed by the chief financial officer or other responsible corporate representative.	**"Financial Disclosure Form"**	FDA form 3454 does not allow for eSignature.	Handwritten/ scanned, probably in regulatory EDMS
312.53(c)(1)	Investigator Statement (Form FDA-1572) to be signed by investigator.	**"Form FDA 1572"**	FDA form that has Adobe self-sign mechanism	Signature within FDA form or Handwritten/ scanned signature
312.23(a)(1)(ix), 314.50(a)(5), 314.94(a)(1)	IND cover sheet, NDA and Abbreviated NDA application forms require signature of sponsor. Countersignature of US-based representative also required if sponsor has no US base.	**Not included in TMF reference model**	Not part of the TMF	eSignature within FDA form or Handwritten/ scanned signature, probably in regulatory EDMS
314.72(a)(2)	If ownership of NDA changes, new owner signs an application form.	**Not included in TMF reference model**	Not part of the TMF	eSignature within FDA form or Handwritten/ scanned signature, probably in regulatory EDMS
314.23(b), 314.50(g)(1)	Written statement signed by the original submitter is required to authorize references to information submitted previously by a person other than the applicant.	**Not included in TMF reference model**	Not part of the TMF	eSignature or Handwritten/ scanned signature, probably in regulatory EDMS
312.30(a), 312.30(b)(2)(i)	Protocol amendments are approved by IRB.	**"IRB/IEC Approval" artifact**	An IRB would not normally have access to any form of eSignature.	Handwritten/ scanned
312.59 ICH 4.6.3	Sponsor may authorize alternative disposition of unused supplies.	**Does not appear to have any *authorization* for destruction, only records/ certificates. Possibly Trial Master File Plan.**		eSignature or Handwritten/ scanned signature in eTMF
312.60(c) ICH 5.14.3	Person who ships drug may authorize in writing alternative disposition of unused supplies.	**Does not appear to have any *authorization* for destruction, only records/ certificates. Possibly Trial Master File Plan.**		eSignature or Handwritten/ scanned signature in eTMF

Table 1 GCP Signature Requirements Analysis

Citation	Extract of Rule	TMF Reference Model Artifact Name	Notes	Likely Signature Category
314.50(g)(3)	For foreign studies (outside US), research is approved by an independent review committee.	**Not included in TMF reference model**	Not part of the TMF	eSignature or Handwritten/ scanned signature, probably in regulatory EDMS
314.53(c)(2)(i), 314.53(c)(4)	Statement signed by applicant or patent owner that a given patent applies to the NDA.	**Not included in TMF reference model**	Not part of the TMF	eSignature or Handwritten/ scanned signature, probably in regulatory EDMS
314.200(d)(3) iv	Statement signed by person responsible for such submission that includes all required studies and information.	**Not included in TMF reference model**	Not part of the TMF	eSignature or Handwritten/ scanned signature, probably in regulatory EDMS
314.200(e)(2) iv	Statement signed by person responsible for such submission that all records have been searched and the submission is true and accurate.	**Not included in TMF reference model**	Not part of the TMF	eSignature or Handwritten/ scanned signature, probably in regulatory EDMS
314.420(b)	NDA, abbreviated NDA application, amendment, or supplement may incorporate by reference all or part of any drug master file if the holder authorizes the incorporation in writing.	**Not included in TMF reference model**	Not part of the TMF	eSignature or Handwritten/ scanned signature, probably in regulatory EDMS
(not an agency requirement)	To document that IB was sent and received.	**"Acceptance of Investigator Brochure" (05.02.01)**		eSignature or Handwritten/ scanned signature in eTMF
ICH 8.2.2	To document investigator and sponsor agreement to the protocol.	**"Protocol Amendment Signature Page" (05.02.02)**		eSignature or Handwritten/ scanned signature in eTMF
ICH 8.2.2	To document investigator and sponsor agreement to the protocol amendment.	**"Protocol Amendment Signature Page" (05.02.03)**		eSignature or Handwritten/ scanned signature in eTMF
ICH 4.1.5, ICH 8.3.24 But does not dictate signature	To document delegation by the Principal Investigator of trial specific tasks to site personnel conducting the trial.	**"Site Signature Sheet" (05.02.19)** **Aka "Delegation of Authority, Site Responsibility Log"**		eSignature or Handwritten/ scanned signature in eTMF

Table 1 GCP Signature Requirements Analysis

Citation	Extract of Rule	TMF Reference Model Artifact Name	Notes	Likely Signature Category
Not an agency requirement	Various plans, procedures, etc. that do not require signature per GCP but may be signed per the sponsor's practice	**Various**		eSignature or Handwritten/ scanned signature in eTMF
ICH 8.3.24	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	**Presumably "Site Signature Sheet" (05.02.19) although definition does not match**		Handwritten/ scanned as the purpose is to document signatures
ICH 7.5	Signature page for Investigator's Brochure (optional)	**"Investigator Brochure" (02.01.01)**		eSignature or Handwritten/ scanned signature in eTMF; might be signed in regulatory EDMS
ICH 1.17, 8.2.6, 812.43(c)	Contracts A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract. **SIGNED AGREEMENT BETWEEN INVOLVED PARTIES, e.g.:** • investigator/institution and sponsor • investigator/institution and CRO • sponsor and CRO • investigator/institution and authority(ies) (where required)	**"Site Contact Details" (05.01.01)** **"Clinical Study Agreement, Investigator Financial Agreement, Investigator Contract" (05.02.12)** **"Contractual Agreement" (09.02.03)**	Does not specify which signatures are required Highly unlikely to be signed in the eTMF	Handwritten/ scanned or possibly eSignature in a contract management system.
ICH 8.2.2	SIGNED PROTOCOL AND AMENDMENTS, IF ANY, AND SAMPLE CASE REPORT FORM (CRF)	**"Protocol" (02.01.02)** **"Protocol Amendment" (02.01.04)** **"Sample Case Report Form" (02.01.07)**	Note: Does not specify which signatures are required – or that any signatures are required for sample CRF	eSignature or Handwritten/ scanned signature, probably in regulatory EDMS or CTMS
ICH 8.3.14	SIGNED, DATED AND COMPLETED CASE REPORT FORMS (CRF)	**CRFs are not part of the TMF Reference model**	Changes to CRFs would not be created in the eTMF; final copies might possibly be stored in the eTMF	eSignature or Handwritten/ scanned signature within an Electronic Data Capture (EDC) system.

HOW ARE SIGNATURES OBTAINED?

Although the documents requiring signature by GCP are not numerous, signatures are needed from a diverse set of collaborators and sources.

- Clinical scientists, statisticians, data managers and clinical executives sign investigator brochures, protocols and reports, usually in a regulatory EDMS
- Various site personnel sign CRFs (sometimes within an EDC system) and signature logs
- Investigators and sub-investigators sign FDA 1572s and investigators acknowledge receipt of protocol amendments and Investigator Brochure updates
- Subjects sign informed consent agreements, on paper or in an eInformed Consent system
- IRB/IEC members sign a number of approval forms and acknowledgements in accordance with their documented operating procedures
- Personnel from the sponsor, CRF, investigator/institution, labs, etc. sign contracts, on paper or within a contract management system
- The chief financial officer or other responsible corporate representative signs the Financial Disclosure Form FDA 3454

Many of these collaborators will not have access to the eTMF. As a result, their signatures must be applied externally.

- For documents originating in other electronic systems, the signature mechanisms available in those systems will be used and normally a copy of the signed document made available in the eTMF. For example, a protocol might be authored, reviewed and signed in a regulatory EDMS and a final PDF copy uploaded to an eTMF.
- For documents completed on paper, signatures are generally handwritten and the signed document scanned to PDF format and released or imported into the eTMF as needed. Some documents may never be scanned – for example, signed informed consent forms are not required as part of the sponsor's files and need not be imported to an eTMF.
- For documents created electronically on a file system, signatures may be obtained electronically if a mechanism is available to the signer. For example, an FDA 1572 Statement of Investigator form can be filled out within Adobe and signed using an available digital certificate outside of any document management system. However, it is still more common that these documents are printed, signed and scanned.

It's also worthwhile to consider the impact of how the documents are signed. The signature mechanism that is used may impact the willingness of sponsors or regulatory authorities to trust that the signatures are valid.

Table 2 - How Documents are Signed

Type of Signature	Definition	Acceptability	Portability
Handwritten	Signature executed using a pen, including signatures captured on a capture pad using a stylus unless biometric characteristics are captured in order to qualify as an electronic signature.	**Handwritten signatures are accepted by all health authorities.**	Handwritten signatures can be verified only by comparison with signature logs or records such as those required by GCP. It is not possible to verify the integrity of a document signed with a handwritten signature except by comparing it to a paper original or a certified copy (a copy of original information that has been verified, as indicated by dated signature, as an exact copy having all of the same attributes and information as the original).
Electronic – Non Digital	Computer data compilation of any symbol or series of symbols executed, adopted, or authorized by an individual to be the legally binding equivalent of the individual's handwritten signature.	**Electronic signatures are accepted by the FDA as long as the regulations defined in 21 CFR Part 11 are met. Other authorities have not generally established a position.**	The validity of signatures and integrity of the document can be verified inside the system where the signature was applied, but not outside of the system.
Electronic - Digital	Electronic signature based upon cryptographic methods of originator authentication, computed by using a set of rules and a set of parameters such that the identity of the signer and the integrity of the data can be verified.	**Digital signatures are accepted by the FDA as long as the regulations defined in 21 CFR Part 11 are met. Other authorities have issues specific rules on the acceptability of digital signatures.**	The validity of signatures and integrity of the document can be verified. Verification of the identity of the signer requires access to a trusted third party who can validate the signer.

THE SIGNATURE BURDEN

Moving away from handwritten signatures is a goal of many electronic document management systems. However, it's particularly challenging in an eTMF system.

- Many documents originate in other electronic systems and are received as final. As a result, the signature mechanism chosen for these documents has already been decided before they enter the eTMF.
- A typical TMF still consists of a good deal of scanned content signed on paper.
- A significant number of signers do not have access to the eTMF to participate in workflow and electronic signature. Furthermore, even if these signers could be granted access, the resulting burden on a company's IT staff would be significant in order to support a steady stream of incoming and outgoing investigators, partners and IRB/IEC members.

Moving Towards a Digital Future

Substantial obstacles exist in moving away from paper to a eTMF where all documents originate electronically and are signed digitally. As a result, many sponsors and CROs continue to rely heavily on scanned content for TMFs. This imposes the burden of maintaining paper documents, which remain the official records for a trial unless an extensive process is put in place for certifying copies in order to allow the destruction of paper originals. Resulting costs and delays include those associated with couriering documents for signature, archiving paper documents, and ensuring they are retrievable for their required retention periods and especially in case of an audit.

While a total shift to electronic documents and signatures may not be realistic at this time, incremental steps can reduce the burden. Possibilities include reducing signatures to those required by authorities, providing additional collaborators with access to the eTMF or implementing a system that allows signatures outside the eTMF.

Although eTMF access can be expanded to investigators and other site staff, IRBs and IECs, and other third parties, the impact must be carefully considered. Some software systems rely on a per-user licensing model that may result in significant initial and ongoing costs, or may require components or access mechanisms that third party users may not have. In addition, managing accounts and confirming digital identities for constantly changing third party users can become a sizable IT burden unless a more lightweight approach to account provisioning that still ensures validity of users can be implemented. On the positive side, providing eTMF access results in a number of benefits around processes and notifications beyond obtaining signatures.

Likewise, implementing an external system for applying digital signatures sounds attractive but has its own set of issues. 21 CFR Part 11 requirements must be maintained, which eliminates a number of commercial solutions from being used off the shelf. The establishment and maintenance of digital identities is a major consideration.

SUMMARY

A significant number of signers do not have access to the eTMF to participate in workflow and electronic signature. Furthermore, even if these signers could be granted access, the resulting burden on a company's IT staff would be significant in order to support a steady stream of incoming and outgoing investigators, partners and IRB/IEC members.

- A discussion of signatures needed and how they will be gathered
- An evaluation of whether copies will be certified to allow the elimination of paper
- An assessment of which collaborators will access the system directly
- An assessment of how the system will withstand an audit by a health authority accessing it directly or through inspection of records

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