International Journal of Science and Research (IJSR)
ISSN: 2319-7064
SJIF (2022): 7.942

# A Conceptual Workflow for Functional Quality Control Sign-Off in Clinical Trial Master Files

**Jyoti (Jo) Agarwal[1], Satyakam Singh, PhD[2]**

**Abstract:** ***The trial master file (TMF) is the organized collection of essential records used to assess trial conduct and the reliability of trial results. Functional quality control (FQC) reviews can identify missing, incomplete, or inconsistent records, yet review documentation and sign-off may be distributed across separate forms and system workflows. This paper presents a conceptual workflow and de-identified form mock-up for recording functional review completion through an electronic-signature platform and filing the resulting record in an electronic TMF (eTMF). A document-based design approach was used: a sponsor-provided FQC form was examined at the field level, public guidance on TMF management and electronic records was reviewed, and requirements were translated into a workflow and proposed form structure. The design captures review scope, dates, method, findings, reviewer attestations, signature meaning and timestamp, and final eTMF filing and approval references. No implementation, participant data, or measured effectiveness results are reported. A prospective evaluation is proposed using cycle time, on-time completion, signature completeness, rework, and user feedback. The mock-up is a conceptual design and requires sponsor quality, records-management, privacy, and system-validation review before operational use.***

**Keywords:** trial master file; functional quality control; electronic signature; eTMF; process design

## 1. Introduction

Clinical trials generate essential records that document important decisions, activities, and oversight. These records must remain identifiable, version controlled where appropriate, complete, readable, retrievable, and available for review. Current Good Clinical Practice guidance describes the TMF as a repository for records that support trial management and assessment of trial conduct and results [1]. The European Medicines Agency likewise describes expectations for the structure, content, management, and archiving of paper and electronic TMFs [2].

Functional quality control (FQC) is one operational method for assessing whether records associated with a functional area are present and meet defined quality expectations. A review record can document the functional area, reviewer, review period, scope, method, identified issues, requested corrections, missing records, and approval history. These details can support follow-up and provide evidence that review activities occurred.

A sponsor-provided FQC form used as a design input for this paper captures several of these elements and directs users to an eTMF approval workflow. Its instructions and revision history indicate that approval is expected to be recorded in the eTMF rather than through signature lines on the form. The accompanying draft proposal described adding functional reviewer sign-offs through a document-signing system, but did not specify how those sign-offs relate to final eTMF approval. This paper addresses that design gap by proposing a sign-off layer that is separately traceable and retains the eTMF as the filing and final approval record unless a sponsor-controlled procedure explicitly authorizes a different arrangement.

The objective is to define a practical, auditable workflow and a de-identified mock-up that organizations can evaluate before implementation. The proposal does not assert that electronic signatures alone ensure compliance or that the workflow has improved completion time.

## 2. Literature Survey

ICH E6(R3) states that essential records should be identifiable and version controlled when appropriate, should include authors, reviewers, and approvers as appropriate, and should be dated and signed when necessary. It also emphasizes timely filing, continued readability and availability, and traceable alteration [1]. These principles support a review record that ties the review scope, reviewer, decision, and resulting actions to a retrievable record.

The EMA TMF guideline addresses the structure, content, management, and archiving of paper and electronic TMFs and stresses the importance of maintaining an inspection-ready file [2]. A risk-based approach to TMF quality assessment has also been described in the literature; Hecht et al. proposed evaluating missing-document impact in relation to patient rights, safety, and trial-data integrity rather than treating all gaps as equivalent [3]. Together, these sources support documenting both review coverage and the significance and resolution of findings.

Electronic signature use requires controls appropriate to the applicable records and regulatory context. FDA guidance published in October 2024 provides recommendations for electronic systems, records, and signatures in clinical investigations [4]. In the United States, 21 CFR Part 11 includes requirements for controls over electronic records and for signature manifestations and record linking when applicable [5]. The proposed mock-up therefore treats a signature as a system-captured event associated with signer identity, date and time, signature meaning, and the specific review record. It does not make a claim that any particular signing product is compliant or validated.

## 3. Problem Definition

The process problem addressed is not the absence of FQC review fields. The source form already includes review context, functional area, reviewer name, start and completion dates, TMF level, review method, findings, document

changes, missing documents, and an eTMF approval instruction. The design opportunity is to make functional completion attestations and downstream record filing easier to trace within one review cycle, while avoiding ambiguity about the relationship between a signing platform and the eTMF approval workflow.

The original proposal also refers to a 45-day review window. The reviewed public guidance does not establish a universal 45-day FQC deadline. Any such interval must therefore be treated as a sponsor-defined operating target and verified against the applicable approved plan or procedure before inclusion in a live workflow. In the mock-up, the due date is configurable and linked to the governing plan or procedure.

The design question is: how can a functional review record capture each assigned reviewer's attestation and related findings, provide a traceable handoff to the eTMF, and preserve applicable final approval controls?

## 4. Methodology and Approach

This work used a conceptual process-design method. First, the sponsor-provided form was reviewed for field categories and workflow instructions. Second, relevant public guidance and literature on TMF management, essential records, risk-based quality review, and electronic signatures were reviewed. Third, the requirements were synthesized into a process sequence and an illustrative, de-identified form mock-up. No trial records, participant data, interviews, workflow logs, or operational metrics were collected or analyzed.

### 4.1 Design requirements

| Requirement | Design response |
|---|---|
| Define the review cycle and scope | Capture protocol or product identifier, TMF level, functional area, cycle dates, due date, review method, and referenced plan/procedure. |
| Record review work and findings | Capture whether records were reviewed, issue and missing-document details, requested actions, owners, due dates, status, and resolution evidence. |
| Attribute each functional sign-off | Capture signer identity through the signing platform, signature meaning, record version, and date/time for each functional reviewer. |
| Preserve record traceability | Link the signed record to a unique review-cycle identifier and the final eTMF record or workflow reference. |
| Retain governance controls | Keep final eTMF filing and approval steps unless the sponsor's quality system formally changes them. |
| Avoid unsupported compliance claims | Require quality, records-management, privacy, and system-validation assessment before use; do not label a platform compliant based solely on this design. |

### 4.2 Proposed workflow

| Step | Owner | Activity and control |
|---|---|---|
| 1. Initiate | Study lead / clinical project manager | Create a unique FQC cycle record; confirm scope, applicable function(s), review method, responsible reviewers, and procedure-defined due date. |
| 2. Distribute | Study lead / clinical project manager | Provide the controlled review package and current report version to assigned functional reviewers through the approved signing workflow. |
| 3. Review | Functional reviewer | Perform the planned review; document findings, missing records, requested changes, and follow-up actions in the review record or linked tracker. |
| 4. Attest | Functional reviewer | Submit an electronic attestation for the defined review scope. The system should preserve signer identity, signature meaning, date/time, and linkage to the signed record. |
| 5. Reconcile | Study lead / clinical project manager | Check that required functions have responded, resolve or assign outstanding actions, and preserve the final record version and completion status. |
| 6. File and approve | Authorized TMF record owner / approvers | File the signed review record and supporting tracker in the eTMF; complete the applicable eTMF approval workflow and retain its history reference. |

### 4.3 Proposed mock-up structure

Appendix A presents a de-identified conceptual mock-up. It expands the source form's existing review-context and findings fields with a per-function sign-off grid and explicit filing/approval traceability. It is not a controlled form, does not reproduce the sponsor's branding or identifiers, and should not be used operationally without formal review and approval.

## 5. Results and Discussion

### 5.1 Design outputs

The design produced two outputs: a six-step workflow and a form structure that connects review scope, work performed, findings, functional sign-off, and final eTMF handling. The central design choice is to distinguish a functional reviewer's attestation from the eTMF's final approval. This distinction reflects the source form's instruction to route the review record through an eTMF approval workflow while adding the proposed functional sign-off layer.

The proposed record is intended to reduce ambiguity about who reviewed which functional area, when the review was performed, what the reviewer attested to, and where the final approved record can be retrieved. The mock-up also separates open actions from missing records so that findings can be assigned and tracked without implying that a signature itself resolves a quality issue.

### 5.2 Electronic-record safeguards

A signing workflow should be assessed against applicable regulatory and organizational requirements before use. In the United States, 21 CFR Part 11 addresses, among other

controls, the manifestation of an electronic signature and its linkage to the electronic record [5]. FDA's 2024 guidance discusses electronic systems, records, and signatures in clinical investigations and recommends a risk-based approach [4]. The implementation assessment should therefore verify system intended use, validation status, identity and access controls, audit trail, record version control, signature meaning, retention, export, and transfer into the eTMF. A vendor or product label is not a substitute for this assessment.

The final record should remain readable and retrievable in the eTMF, with its signature evidence and approval history available as part of the retained record or through a stable, documented link. If the signing platform and eTMF are separate systems, the transfer and reconciliation controls should establish that the filed version is the version signed and approved.

### 5.3 Evaluation plan

Because this paper presents a conceptual design, no effect estimate is available. A prospective pilot should compare the proposed process with a documented baseline using comparable review cycles and should be approved through the sponsor's governance and quality processes. Measures should be defined before the pilot, with the same start and end events used in both periods.

| Measure | Operational definition | Interpretation |
|---|---|---|
| Review cycle time | Elapsed calendar days from initiation to completion of all required functional attestations. | Descriptive efficiency measure; stratify by number of functions and review scope. |
| On-time completion | Number of review cycles completed by the procedure-defined due date divided by all eligible cycles. | Measures adherence to the applicable local target, not a universal regulatory deadline. |
| Sign-off completeness | Required functional sign-offs present and linked to the correct review-cycle record. | Measures completeness and traceability of attestations. |
| Action closure time | Elapsed time from finding assignment to documented resolution or accepted disposition. | Measures follow-up performance; report by risk category where available. |
| Rework/ reconciliation events | Count of returned, corrected, or refiled review records due to missing fields, mismatched versions, or incomplete approvals. | Identifies avoidable process defects. |
| User experience | Structured feedback from reviewers and record owners on usability, clarity, and workload. | Exploratory measure; summarize response rate and themes. |

The pilot should report denominators, inclusion criteria, study and function mix, missing observations, and any concurrent process changes. If a before-and-after comparison is used, results should be described as observational unless the design supports stronger causal inference. Compliance conclusions should be limited to evidence reviewed by the responsible quality and regulatory functions.

## 6. Limitations

This paper is a conceptual design based on one de-identified form pattern and public guidance. It does not represent a validated workflow, formal usability study, regulatory interpretation for a specific sponsor, or evaluation of a named electronic-signature platform. No baseline or post-implementation data were available, so efficiency and compliance benefits remain hypotheses. The appropriate record owner, approval sequence, retention model, and signature meaning may vary by sponsor, study, jurisdiction, and system architecture.

The 45-day interval mentioned in the source draft was not treated as a generally applicable regulatory requirement. It should only be used if confirmed in a current sponsor-controlled plan or procedure. The mock-up omits proprietary identifiers and branding; permission to publish or adapt any organization-controlled source material should be obtained separately.

## 7. Conclusion

A traceable FQC sign-off workflow can be designed by linking the review scope, functional reviewer attestations, findings, corrective actions, and final eTMF filing. The proposed workflow preserves the distinction between functional completion and final eTMF approval and makes system and governance controls explicit. The accompanying mock-up is a starting point for sponsor review, not a released operational form. Its benefits should be established through a controlled pilot using predefined process measures; no effectiveness claim is made in this paper.

## 8. Future Scope

Future work should include sponsor quality and records-management review, role-based usability testing, assessment of electronic-signature and eTMF integration controls, and a prospective pilot across representative functions and study types. A subsequent evaluation could compare cycle time, on-time completion, sign-off completeness, action closure, and rework against baseline performance. The resulting workflow and form should then be revised through the sponsor's change-control and validation processes, with publication of results only after authorization and appropriate de-identification.

### Declarations

**Ethics statement:** No human participants, identifiable participant information, or clinical-trial datasets were involved in this conceptual design.

**Data availability:** No dataset was generated or analyzed for this paper.

**Publication authorization:** The proposed form mock-up is de-identified. Authorization to publish any organization-controlled process description or source material should be confirmed before submission.

## References

[1] International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Guideline for Good Clinical Practice E6(R3): Step 4 final consolidated guideline. Geneva: ICH

[2] European Medicines Agency. Guideline on the content, management and archiving of the clinical trial master file (paper and/or electronic). EMA/INS/GCP/856758/2018. London: EMA; 2018. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-content-management-and-archiving-clinical-trial-master-file-paper-andor-electronic_en.pdf

[3] Hecht A, Busch-Heidger B, Gertzen H, Pfister H, Ruhfus B, Sanden PH, et al. Quality expectations and tolerance limits of trial master files (TMF): developing a risk-based approach for quality assessments of TMFs. Ger Med Sci. 2015;13: Doc23. doi:10.3205/000227.

[4] US Food and Drug Administration. Electronic systems, electronic records, and electronic signatures in clinical investigations: questions and answers. Guidance for Industry. Silver Spring (MD): FDA; 2024 Oct. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/electronic-systems-electronic-records-and-electronic-signatures-clinical-investigations-questions

[5] Electronic Code of Federal Regulations. Title 21, Code of Federal Regulations, Part 11: Electronic Records; Electronic Signatures. Available from: https://www.ecfr.gov/current/title-21/chapter-I/subchapter-A/part-11

### Appendix A. Illustrative Functional Quality Control Review Record

Conceptual mock-up for manuscript discussion only. This is not a controlled document or an approved operational form. Complete the fields and workflow labels only after sponsor quality, records-management, privacy, and system-validation review.

| Review record field | Proposed entry / selection |
|---|---|
| Review-cycle ID | [System-generated unique identifier] |
| Protocol / product identifier | [Coded protocol or product identifier] |
| TMF level and location | ☐ Product ☐ Trial ☐ Country ☐ Site \| Location / repository: [specify] |
| Functional area(s) | [Select each assigned function] |
| Review cycle and scope | Cycle: [number/name] \| Documents / date range / report version: [specify] |
| Governing plan or procedure | [Title, version, and section that define scope and due date] |
| Review timing | Start date: [YYYY-MM-DD] \| Due date: [YYYY-MM-DD] \| Completion date: [YYYY-MM-DD] |
| Review method | ☐ Full review ☐ Approved risk-based sampling \| Sampling plan reference: [if applicable] |
| New records in scope? | ☐ Yes ☐ No \| Source / report reference: [specify] |
| Issues identified? | ☐ Yes ☐ No \| If yes, complete the findings/action log below. |

**A1. Findings and missing-record action log**

| Type | Record / artifact identifier | Finding or requested action | Owner and due date | Status / resolution evidence |
|---|---|---|---|---|
| ☐ Quality issue ☐ Missing record | [ID / title] | [Describe objectively] | [Role / YYYY-MM-DD] | [Open / closed; evidence reference] |
| ☐ Quality issue ☐ Missing record | [ID / title] | [Describe objectively] | [Role / YYYY-MM-DD] | [Open / closed; evidence reference] |
| ☐ Quality issue ☐ Missing record | [ID / title] | [Describe objectively] | [Role / YYYY-MM-DD] | [Open / closed; evidence reference] |

**A2. Functional reviewer attestations**

Suggested attestation meaning: "I completed the functional quality review for the scope and review period identified in this record. Findings and required follow-up actions are documented or linked above. This attestation does not by itself close open actions or replace required final eTMF approval."

| Functional area | Reviewer name / role | Attestation status | Electronic signature evidence | Date and time |
|---|---|---|---|---|
| [Function 1] | [Name / role] | ☐ Complete ☐ Not applicable | [Signing platform record ID / link] | [System-captured] |
| [Function 2] | [Name / role] | ☐ Complete ☐ Not applicable | [Signing platform record ID / link] | [System-captured] |
| [Function 3] | [Name / role] | ☐ Complete ☐ Not applicable | [Signing platform record ID / link] | [System-captured] |

**A3. Reconciliation and eTMF filing**

| Control point | Record / status |
|---|---|
| Required functions reconciled by | [Name / role; date] |
| Open actions transferred to tracker | ☐ Yes ☐ No \| Tracker ID / link: [specify] |
| Signed record version | [Version / checksum or controlled version identifier] |
| eTMF filing reference | [Repository / artifact / record ID and filing date] |
| Final eTMF approval workflow | [Workflow ID / status / completion date; retain approval history] |
| Exceptions or comments | [Explain any missing signature, scope change, overdue item, or approved deviation] |

**Design note.** The signature manifestation, audit trail, record linkage, retention, and transfer controls must be confirmed for the selected system and applicable jurisdiction. The due date is governed by the applicable sponsor procedure; this mock-up does not prescribe a universal review interval.