Establishing and Maintaining Investigator Site Files, Trial Master Files and Sponsor Files

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1 Introduction

1.1 The Academic & Clinical Central Office for Research & Development (ACCORD) is a joint office comprising clinical research management staff from NHS Lothian (NHSL) and the University of Edinburgh (UoE).

1.2 Essential records are the documents and data (and relevant metadata), in any format, associated with a clinical trial that facilitate the ongoing management of the trial and collectively allow the evaluation of the methods used, the factors affecting a trial and the actions taken during the trial conduct to determine the reliability of the trial results produced and the verification that the trial was conducted in accordance with GCP and applicable regulatory requirements

1.3 The nature and extent of those records generated and maintained are dependent on the trial design, its conduct, application or risk proportionate approaches and the importance and relevance of that record to the trial.

1.4 Essential records will be maintained in repositories held by the sponsor and by the investigator/institution. These repositories are referred to as a Trial Master File (TMF) or Investigator Site File (ISF). Such files will be established at the beginning of the trial, both at the investigator/institution and at the sponsor's office.

1.5 A TMF will be produced for all studies subject to Combined Risk Assessment (GS002) and sponsored by UoE and/or NHSL. Where the TMF has been delegated to a third party, there will also be a Sponsor File.

1.6 All study locations will have an ISF containing essential records specific to location-level conduct.

1.7 Where the TMF, and/or ISF is maintained in an electronic format, the electronic systems must provide controlled access, audit trails, version control, and secure storage that prevents unauthorised alteration or loss of data. The Sponsor will formally review and approve any electronic system for combined risk assessed studies (GS002) used for TMF / ISF management prior to implementation, including systems operated by third-party vendors, in accordance with POL007.

2 Purpose

2.1 To outline the procedures for establishing, maintaining and archiving an Investigator Site File (ISF), a Trial Master File (TMF) or a Sponsor File;

3 Scope

3.1 The SOP applies to the ACCORD staff responsible for establishing and maintaining a TMF or Sponsor File. This includes the Clinical Trials Monitoring team and those responsible for filing essential study records in the TMF or Sponsor File e.g. Admin, Research Governance (UoE and NHSL), Pharmacovigilance (PV) and Quality Assurance (QA).

3.2 It also applies to any other individual(s) given the responsibility for setting up and maintaining a TMF or ISF for an NHSL/UoE co-sponsored or singly sponsored CTIMP, CIMD or non-CTIMP. This can include clinical researchers working on behalf of the Sponsor(s) (UoE and/or NHSL), for example the Chief Investigator (CI) or an ACCORD collaborative unit, unless it has been agreed that other procedures will be followed.

3.3 For activities that are transferred or delegated to service providers by the sponsor or investigator/institution, respectively, arrangements should be made for the access and management of the essential records throughout the trial and for their retention following completion of the trial.

4 Responsibilities

4.1 For studies subject to a combined risk assessment, the ACCORD Senior Clinical Trials Monitor, or designee, is responsible for ensuring the TMF (and where applicable the Sponsor File) is established prior to the start of a study and updating the file with relevant and applicable records as the study progresses.

4.2 The ACCORD Clinical Trials Monitor is responsible for reviewing the TMFs/ISFs and Sponsor File in accordance with the source data verification plan. The ACCORD Monitor, or designee, will ensure the file is bound in a suitable manner for archiving

and that the contents are secure.

4.3 ACCORD staff (e.g. Admin., Research Governance (UoE and NHSL), PV and QA) are responsible for filing essential study records in the TMF or Sponsor File.

4.4 For all studies, the Principal Investigator (PI) is responsible for ensuring an ISF is established prior to the start of a study at their location and updating the file with relevant and applicable records as the study progresses. The PI is also responsible for archiving the ISF at the end of the study.

4.5 Service providers are responsible for the management of their essential records which form part of the TMF. These will be retained as required following completion of the trial.

5 Procedure

5.1 Procedure for Establishing an Investigator Site File (ISF)

5.1.1 The PI, or designee, will establish an ISF prior to the start of a study at their location. Where a study location elects to maintain the ISF electronically, the system must be appropriately validated following ACCORD Policy POL007 (Computer System Validation & Data Integrity) to ensure the integrity, reliability, and security of all essential records.

5.1.2 Where a site uses a location-owned eISF platform (e.g., Florence), the Sponsor will document its use at site feasibility (GS013) and confirm that the system is appropriately governed by the institution and capable of generating accurate, complete, and retrievable essential records. Any risks or gaps identified will be escalated to the QA Manager by the Sponsor Reviewer for proportionate mitigation.

5.1.3 Where a validated eISF system is not available and an alternative electronic storage solution is proposed (e.g., shared drive, network folder, SharePoint site), the institution or service provider must complete a documented risk assessment before any essential study records are stored electronically.

5.1.4 The risk assessment must: identify which records may be held electronically and which must remain in controlled paper form, assess risks and limitations of the proposed system (e.g., access control, audit trails, version control, backup, security, data integrity), describe mitigation measures to ensure compliance with ICH-GCP,

applicable regulations and Sponsor requirements, and confirm how ongoing oversight and monitoring of the system will be maintained.

5.1.5 Low-risk study records are defined as non-essential records that do not impact subject safety, data integrity, or regulatory compliance and are readily replaceable (e.g., CVs, GCP certificates, superseded documents, administrative correspondence, draft documents, and other non-critical records). These may be stored temporarily on an institutional network drive, shared drive, or SharePoint location. These locations must be institutionally managed and routinely backed up. Where a document does not meet the low-risk definition, a proportionate risk assessment must be documented. All documents must be migrated to a validated electronic system or paper file at the point of archiving following ACCORD SOP GS005. Consideration of access to these records in case of audit and inspection will be taken into account.

5.1.6 For studies subject to a Combined Risk Assessment (GS002), the QA Manager, or designee, must review and approve the risk assessment prior to Sponsor Authorisation to Open (SATO) and confirm that the proposed mitigations are adequate.

5.1.7 For studies not subject to GS002, the Sponsor will not review or approve these risk assessments. The Investigator and their institution are responsible for ensuring that the storage solution is suitable, that risks are assessed and mitigated, and that documentation is maintained.

5.1.8 All risk assessments and mitigation plans must be retained within the ISF.

5.1.9 The task of establishing and/or maintaining an ISF may be delegated to another suitable individual in the local study team.

5.1.10 In some instances, an ISF may be set up by the ACCORD Senior Clinical Trials Monitor, or designee, and provided to the PI prior to the start of the study.

5.1.11 For studies subject to a Combined Risk Assessment (GS002), the ACCORD Essential Records Checklist templates (CR001-T01 CTIMP, CR001-T02 Non-CTIMP or CR001-T03 Medical Device) will be used unless other arrangements are formally agreed and documented by the ACCORD Senior Clinical Trials Monitor, or designee.

5.1.12 The PI, or designee, will populate the appropriate checklist, which will be used as an index, and to track all records by showing which files contain which records i.e. identifying where essential records are located throughout the study, in order to reconstruct the trial, if required.

5.1.13 The ISF will be held securely with access restricted to the local study team, ACCORD Clinical Trials Monitors and designated representatives of the Sponsor(s) e.g. ACCORD Auditors. Access will also be granted to regulatory inspectors upon request.

5.2 Procedure for Establishing a Trial Master File (TMF)

5.2.1 A TMF will be produced for all studies subject to Combined Risk Assessment (GS002) and sponsored by UoE and/or NHSL

5.2.2 The ACCORD Senior Clinical Trials Monitor, or designee, will establish a TMF prior to the start of a study, which will include all essential records provided by the Clinical Research Facilitator in accordance with SOP FA001 (Facilitating a Regulated or Complex Research project).

5.2.3 Where a TMF is maintained electronically, the system must be appropriately validated following ACCORD Policy POL007 (Computer System Validation and Data Integrity). For studies subject to a combined risk assessment (GS002), the proposed eTMF will be subject to CSV review by the QA Manager following SOP QA010 to ensure the integrity, reliability, and security of all essential records.

5.2.4 Where a validated eTMF system is not available and an alternative electronic storage solution is proposed (e.g., shared drive, network folder, SharePoint site), the institution or service provider must complete a documented risk assessment following sections 5.1.3 and 5.1.4 before any study records are stored electronically.

5.2.5 For studies subject to a combined risk assessment, Sponsor QA will formally review and approve the electronic system risk assessment prior to first Sponsor Authorisation to Open (SATO) (CM001) in addition to performing a CSV review (QA010).

5.2.6 Other members of the ACCORD Clinical Trials Monitoring team, or a third party, as described in the scope, may be formally delegated to carry out the practical aspects of setting up a TMF.

5.2.7 This SOP and the ACCORD templates (referred to in 5.1.11) will be used unless other arrangements are formally agreed and documented by the ACCORD Senior Clinical Trials Monitor, or designee.

5.2.8 All relevant records will be filed in the TMF in accordance with the Essential Records checklist.

5.2.9 The person responsible for establishing and maintaining the TMF will populate the appropriate checklist, which will be used as an index, and to track all records by showing which files contain which records i.e. identifying where essential records are located throughout the study, in order to reconstruct the trial, if required.

5.2.10 In some cases, the ACCORD Senior Clinical Trials Monitor, or designee, can delegate the responsibility of storage and maintenance of the TMF to a third party. When a TMF is delegated, CR001-F01 (Delegation of TMF) will be completed and signed by the third party accepting the delegation.

5.2.11 The TMF will be held securely with access restricted to the ACCORD Clinical Trials Monitoring team/third party holders of the TMF and designated representatives of the Sponsor(s) e.g. ACCORD Auditors. Access will also be granted to auditors and monitors appointed by the Sponsor(s) and regulatory inspectors.

5.3 Procedure for Establishing a Sponsor File

5.3.1 For studies subject to Combined Risk Assessment (GS002), the Senior Clinical Trials Monitor, or designee, will establish a paper Sponsor File when the maintenance of the TMF is delegated to the Investigator or a third party. The Delegation of TMF form (CR001-F01) will be filed in the Sponsor File.

5.3.2 For studies subjected to Combined Risk Assessment, all relevant records will be filed in the paper Sponsor File in accordance with the Essential Records Checklist. This template records where essential records are located throughout the study. The paper Sponsor File will contain records specific to the Sponsor and Sponsor processes. The Sponsor File will be held securely with access restricted to the ACCORD

Clinical Trials Monitoring team and ACCORD members. Maintenance of the Sponsor File is the responsibility of the Clinical Trials Monitoring team.

5.3.3 For non-CTIMP studies, relevant Sponsor records will be filed in the appropriate study specific Sponsorship Review folder on the ACCORD SharePoint site.

5.4 Maintaining an ISF, TMF and Sponsor File

5.4.1 The responsible person, or designee, will update the ISF, TMF or Sponsor File with relevant and applicable records as the study progresses, in accordance with the relevant Essential Records Checklist (CR001-T01 CTIMP, CR001-T02 Non-CTIMP or CR001-T03 Medical Device).

5.4.2 The sponsor and investigator/institution will ensure that the essential records are collected and filed in a timely manner to assist with the successful management of the study. The sponsor and investigator/institution will retain the essential records in a way that ensures that they remain complete, readable and readily available and are directly accessible upon request by regulatory authorities, monitors and auditors. Alteration to the essential records will be traceable.

5.4.3 It is acceptable to retain evidence that essential records have been implemented, and in order to reduce duplication, the actual records can be filed to the TMF or Sponsor File. The original records will generally be retained by the responsible party who generated them.

5.4.4 Any essential correspondence that is relevant to the running of the trial and would be needed to reconstruct the trial will be filed to the ISF and/or the TMF/Sponsor File.

5.4.5 When a copy is used to permanently replace the original essential record, the copy will fulfil the requirements for certified copies. The copy will be verified (i.e. by dated signature or by generation through a validated process) to have the same information as the original, including relevant metadata, where applicable.

5.4.6 ISFs, TMFs and Sponsor Files will be reviewed by the Clinical Trial Monitoring team, or designee in accordance with the Source Data Verification (SDV) plan.

5.4.7 The Essential Records Checklist (CR001-T01 CTIMP, CR001-T02 Non-CTIMP or CR001-T03 Medical Device) will be used to guide the reviewer in checking the file for

completeness and the review section of the document checklist will record details of the review.

5.4.8 Superseded versions of essential records will be retained in the ISF, TMF and/or Sponsor File as appropriate.

5.5 Preparing an ISF for Archiving

5.5.1 The PI, or designee, will ensure that the ISF is archived in a suitable fashion. The file must be archived in accordance with the protocol and SOP CR009 (Study Closure and Archiving).

5.5.2 For studies subject to a combined risk assessment, after an investigator location has been "closed" by the ACCORD Monitoring Team, or designee, in accordance with SOP CR009 (Study Closure and Archiving), the ISF will be archived. The ACCORD Monitor, designee, or third party will ensure the filing is completed and review the ISF to ensure that all essential records are in the appropriate files, including details of the pharmacy file, ensuring file notes are in place where necessary.

5.5.3 The Monitor, or designee, will ensure the file is bound in suitable manner for archiving (if paper) and that the contents are secure and in compliance with local archiving requirements.

5.6 Preparing a TMF and Sponsor File for Archiving

5.6.1 Archiving will be conducted in accordance with the requirements of the protocol, SOP CR009 (Study Closure and Archiving) and SOP GS005 (Archiving Research Essential Records).

5.6.0 The Sponsor and/or CI, or designees, will make arrangements to archive the TMF and Sponsor File (if applicable) at the end of the study, referring to SOP GS005 (Archiving Research Essential Records), where applicable.

5.6.1 For studies subject to monitoring, the ACCORD Monitor, or designee, will ensure the filing is completed and review the TMF/Sponsor File to ensure that all essential records are in the appropriate files, including details of the product specification file

(PSF) if the study has involvement from the Healthcare Technology Accelerator Facility (HTAF), ensuring file notes are in place where necessary.

5.6.2 The ACCORD Clinical Trials Monitor, or designee, will ensure the files are bound in a suitable manner for archiving (if paper) and that the contents are secure and in compliance with local archiving requirements.

5.6.3 The ACCORD Clinical Trials Monitors or designee will notify the R&D Administration Manager, or designee, that the study is ready to be archived.

6 References and Related Documents

- CR001-T01 Essential Records checklist – CTIMP
- CR001-T02 Essential Records checklist – non-CTIMP
- CR001-T03 Essential Records checklist – medical device
- CR001-F01 Delegation of TMF form
- SOP CR009 Study Closure and Archiving
- SOP FA001 Facilitating a Regulated or Complex Research Project
- SOP GS002 Combined Risk Assessment
- SOP GS005 Archiving Research Essential Study Records
- SOP QA010 Use of Computerised Systems in Research
- POL007 Computer System Validation and Data Integrity
- ICH-GCP E6 (R3) Guidelines
- EMEA, "Note for Guidance on Good Clinical Practice" (E6) R1, CPMP/ICH/135/95.
- The Medicines for Human Use (clinical trials) Regulations 2004 as amended.
- http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/02/WC500138893.pdf

7 Document History

Version Number	Effective Date	Reason for Change
1.0	22 MAR 2011	Addition of administrator roles including TMF review and SPC review. Addition of CIMD TMF checklist.
2.0	20 FEB 2014	Addition of ISF and Sponsor File management procedures.

3.0	09 SEPT 2016	Title change. Addition of Responsibilities section. Amalgamation of file review tracker (CR001-T04), now obsolete, with the relevant essential document checklist. Change of The University of Edinburgh Clinical Research Administrator to Research Governance Manager. Removal of CR001-W01 Summary of Product Characteristics Update, now obsolete. Reference to Product Specification File added to section 5.6. Administrative changes made throughout SOP.
4.0	31 OCT 2018	Scheduled review. Minor administrative changes.
5.0	09 DEC 2020	Change to section 5.6 replacing Business Research Manager with R&D Administration Manager. Administrative updates to Document checklists (CR001-T01, T02 and T03 updates to section 2.4 amendments, 2.6 end of trial, 7 Monitoring, 8 Labs, 9 Data management and 10.1 DMC. CR001-T01 and T03 in addition to changes listed above update to section 3.1 Sponsorship. CR001-T01 in addition to changes listed above update to section 8 Pharmacy.)
6.0	01 AUG 2023	Update to sections 3.1 and 4.3 to include the Pharmacovigilance (PV) team in the scope of the SOP. Update to section 5.4.5 to clarify that file review frequency is documented in the Source Data Verification plan. Updates to document checklists CR001-T01, CR001-T02 and CR001-T03; including addition of the combined review process for T01 in section 2. For all checklists, further guidance provided regarding how to use the checklist and "comments" field added. For all checklists, updates to section 2 (approvals), section 5 (safety), section 6 (research team), section 7.3 (monitoring reports), section 8.1 (IMP/medical device), section 8.2/8.3 (labs) and section 9 (data management).
7.0	05 JUN 2026	Updated to align with the amended Clinical Trial Regulations and ICH GCP E6 (R3).

		SOP updated throughout to document process to follow regarding use of eTMF and/or eISF. Update to section 4 to add responsibilities for service providers. Updates to section 5.3 to further expand the definition of the Sponsor File. Addition of section 5.4.5 regarding requirements for certified copies. ISG updated to HTAF in section 5.6.1. Updates to records checklists (including change to excel format) CR001-T01, CR001-T02 and CR001-T03: terminology updated to align with the amended Regs and Sponsor processes, addition of delegation of TMF form in section 1, removal of APR in section 2, addition of suspected serious breach in section 5, minor clarifications throughout.

8 Approvals

Sign	Date
Alice Graves Alice Graves (21-May-2026 14:00:04 GMT+1) AUTHOR: Alice Graves, Senior Clinical Trials Monitor, NHSL, ACCORD	21-May-2026
Elizabeth Craig Elizabeth Craig (21-May-2026 14:15:27 GMT+1) APPROVED: Elizabeth Craig, Senior Clinical Trials Monitor, NHSL, ACCORD	21-May-2026
L. Mackenzie AUTHORISED: Lorn Mackenzie, QA Manager, NHSL, ACCORD	21-May-2026

CR001 Establishing and Maintaining ISFs TMFs and Sponsor Files v7.0

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