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 documents relating to a study will be filed in such a manner as to allow reporting, interpretation and verification of the conduct of the study. Essential documents also demonstrate compliance with the standards of good clinical practice. This requirement is outlined in ICH GCP:

> "Trial master files should be established at the beginning of the trial, both at the investigator/institution site and at the sponsor's office" – ICH GCP (E6)

1.3 For each trial there will be a Trial Master File (TMF) and an Investigator Site File (ISF). Where the TMF has been delegated to a third party, there will also be a Sponsor File.

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 documentation in the TMF or Sponsor File e.g. Admin, Research Governance (UoE and NHSL) 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. 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.

4 RESPONSIBILITIES

4.1 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 documents as the study progresses.

4.2 The ACCORD Clinical Trials Monitor is responsible for reviewing the TMFs/ISFs and Sponsor File. 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) and QA) are responsible for filing essential study documents in the TMF or Sponsor File.

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

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 site.

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

5.1.3 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.

5.1.4 This SOP and the ACCORD Essential Document 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.

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

5.1.6 The ISF will be held in a secure location 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 documents provided by the Clinical Research Facilitator in accordance with SOP FA001 (Facilitating a Regulated or Complex Research project).

5.2.3 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.

5.2.4 This SOP and the ACCORD templates (referred to in 5.1.4) will be used unless other arrangements are formally agreed and documented by the ACCORD Senior Clinical Trials Monitor, or designee.

5.2.5 All relevant documents will be filed in the TMF in accordance with the Document checklist.

5.2.6 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 documents by showing which files contain which documents i.e. identifying where essential documents are located throughout the study, in order to reconstruct the trial, if required.

5.2.7 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 both parties.

5.2.8 The TMF will be held in a secure location 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 The Senior Clinical Trials Monitor, or designee, will establish a Sponsor File at the ACCORD office 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 The Sponsor File will be held in ACCORD 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.

5.4 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 documents as the study progresses, in accordance with the relevant Essential Documents Checklist (CR001-T01 CTIMP), CR001-T02 Non-CTIMP or CR001-T03 Medical Device).

5.4.2 All filing will be done in a timely manner, to assist in the successful management of the study.

5.4.3 It is acceptable to retain evidence that essential documents have been implemented, and in order to reduce duplication, the actual documents can be filed to the TMF or Sponsor File.

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

5.4.5 ISFs, TMFs and Sponsor Files will be reviewed by the Clinical Trial Monitoring team, or designee in accordance with the monitoring plan.

5.4.6 The Essential Document 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.

5.4.7 Superseded versions of essential documents will be retained in the ISF, TMF and/or Sponsor File.

5.5 Preparing an ISF for Archiving

5.5.1 After an investigator site 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 documents are in the appropriate files, including details of the pharmacy file, ensuring file notes are in place where necessary.

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

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

5.6 Preparing a TMF and Sponsor File for Archiving

5.6.1 After receipt of the "end of study declaration" or after the study has reached the defined end point, whichever is the later date, the TMF and Sponsor File (if applicable) will be archived.

5.6.2 The ACCORD Monitor, or designee, will ensure the filing is completed and review the TMF/Sponsor File to ensure that all essential documents are in the appropriate files, including details of the product specification file (PSF) if the study has involvement from the Investigators Supply Group (ISG), ensuring file notes are in place where necessary.

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

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

5.6.5 If the "end of study declaration" and/or the end of study report has not yet been received, the ACCORD Clinical Trials Monitor will clearly note this on the file and will advise the R&D Administration Manager, or designee, of such.

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

6 REFERENCES AND RELATED DOCUMENTS

- CR001-T01 Essential document checklist – CTIMP
- CR001-T02 Essential document checklist – non-CTIMP
- CR001-T03 Essential document 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 Essential Study Documentation
- ICH-GCP E6 (R2) 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.)

8 APPROVALS

Sign	Date
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