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Sponsor Standard Operating Procedure

Title: **TRIAL MASTER FILE / TRIAL SITE FILE: SET-UP AND MAINTENANCE**

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Document history:	**Modification to previous version:**
1. Version 1.0 11th November 2008 2. Version 1.5 3rd January 2012	1. Update to sections 2 and 4 to reflect the need for all relevant documentation to be retained in the TMF. 2. Additions to appendix A, notably trial development evidence and documentation relating to database build and testing

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1. PURPOSE and SCOPE

PURPOSE:
To describe the procedure for setting-up, contents of and maintenance of the Trial Master File (TMF) and Trial Site File (TSF) for clinical trials.

SCOPE:
Applicable to all clinical trials that are subject to jurisdiction of the UK Policy Framework for Health and Social Care Research, 2017 and/or the Medicines for Human Use (Clinical Trials) Regulations, SI 2004, 1031. This SOP is applicable to such clinical trials sponsored by the University of Nottingham (UoN) only.

2. NOTES

2.1 The Trial Master File and Trial Site File are hard copy paper files constructed to contain both the 'essential documents' of the trial as described in ICH/GCP section 8 and all documents and evidence that permits the reconstruction of the trial and all of its decision making..
Documents that need to be stored in the TMF are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, Sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

2.2 It is the responsibility of the Chief Investigator to set-up and for the maintenance of a Trial Master File. The day-to day maintenance may be delegated to a suitably trained person and authorised so on the Site Responsibility (Delegation) Log, RF2 TA008.

2.3 The TMF should be established as soon as possible after the UoN has agreed to sponsor a study and maintained from this time until the trial is formally closed and archived as per SOP QA005, Archiving.

2.4 A separate TSF must be set-up in each participating site. The local Principal Investigator is responsible for the maintenance of a Trial Site File. The day-to day maintenance may be delegated to a suitably trained person and authorised so on the Site Responsibility (Delegation) Log, RF2 TA008

2.5 The TSF should be established as soon as the site has all approvals and prior to recruitment of participants at that site. The TSF should be maintained from this time until the trial is formally closed and archived as per SOP QA005, Archiving.

2.6 TMF and TSF contain original and confidential documentation and must be secured accordingly i.e. locked storage with restricted access according to local rules.

2.7 All files shall be made available for internal and external audit purposes as requested by authorised individuals and shall be made available for inspection by the MHRA

3. CROSS REFERENCES

3.1 International Conference on Harmonisation Guideline for Good Clinical Practice, section 8.
3.2 Site Responsibility (Delegation) Log RF2 TA008
3.3 Archiving SOP QA005
3.4 TMF and TSF layout Appendix A

4. PROCEDURE

TMF/TSF Set Up

4.1 Obtain and prepare a set of files (A4 lever arch files or similar and A4 dividers) each labelled with:
4.1.1 The trial title and any acronyms to be used
4.1.2 The Sponsor's protocol number and any other relevant references
4.1.3 The site name and address
4.1.4 The REC reference, and where applicable, the MHRA reference.

4.2 Insert labelled dividers to divide the files to allow storage of the documents into suitable sections. Section 8 of the ICH GCP guidelines layout is given in Appendix A. Each file should contain a table of contents.

Note: The TMF/TSF may consist of more than one volume and each should be labelled appropriately with indications of the sections contained therein.

TMF/TSF Maintenance

4.3 Collate trial documentation and file under the relevant section according to the stage of the trial. Where originals are to be sent to the Chief Investigator for the TMF retain a copy in the TSF.

4.3.1 The essential documentation to be retained is specified in section 8 of the ICH GCP Guidelines, in addition **all** documents needed to reconstruct and evaluate the conduct of the trial must be included. The essential documents are covered in Appendix A, additional sections and documents should be added as needed.

Note: Appendix A is not an exhaustive list. It is the responsibility of the Chief Investigator to ensure that all documents and evidence that permits the reconstruction of the trial is stored in the TMF. Seek advice from the Sponsor as required

4.4 All documents must be dated and appropriately authorised by signature where required.

4.5 File all documentation in chronological order within their sections, keeping **all** copies of documents even when updating. When amending documents initial and date any changes, crossing out original text – do not cover with liquid paper or obscure, all text must be legible for audit purposes.

4.6 4.6.1 If a document is missing or unobtainable or a section is inappropriate for a particular trial then add a "file note" dated and signed to this effect and offering an explanation or alternative documentation where possible.

4.6.2 Some sub-sections may become bulky so a separate file may be created. Ensure that this is appropriately labelled and referenced in the main file of its whereabouts.

Archiving of the TMF

4.7 The TMF and TSF are considered "controlled documents". At the end of the trial the TMF/TSF must be archived in accordance with SOP (QA005), Archiving.

5. FLOW CHART

Not applicable

Appendix A

TMF and TSF layout

Section A: Pre-trial opening

A.1 Trial Development Documentation
Minutes of initial meeting with the Sponsor and confirmation of Sponsor support, evidence of investigator selection, evidence of site selection, evidence of vendor selection and RF1 TD002, risk assessment, peer review reports, funding application and all contracts with the funder and vendors.

A.2 Study Protocol and associated documents (final versions)
Protocol, information sheet, consent form and investigator brochure/IMP-D (where applicable) final versions. Protocol to be fully signed
Case Report Forms and any other data collection documents, final versions.

A.3 Approval and Agreements
National ethical, Health Research Authority and competent authority (where applicable) approval
EudraCT email (where applicable)
Local Site Specific Assessment (where applicable)
Local NHS Trust R&D or host organisation approval and confirmation of capability and capacity
Sponsor / Chief Investigator agreement - TMF only
Sponsor / participating site non-commercial agreement

A4 Staff Participation
Site Responsibility (Delegation) Log, TA008
Curriculum Vitae and Training Records
Attendance at Investigator Training, RF1 TA008
SOP Compliance Form RF3 TA008
Evidence of site initiation
Regulatory green light email from the Sponsor

A.5 Medical Testing and Pharmacy (where applicable)
Accreditation / certification of supporting Laboratories and pharmacies
'Normal ranges' issued by local laboratories
Investigational product handling (where applicable) – local procedures where not in the study protocol
Investigational product control (where applicable) – local procedures where not in the study protocol
Investigational medicinal product records – certificate of analyses, shipping records, labelling to be used
QP certification

A.6 Randomization and Blinding
Randomization, blinding and un-blinding procedures where not in the study protocol

A.7 Database Build
Database specification documentation, user acceptance testing, validation documentation, security and access arrangements, and disaster recovery plan

Section B: Ongoing Trial

B.1 Study Protocol Amendments and Approvals
Log of study documentation amendments, RF1 TA013

Current versions of trial documentation: protocol to be fully signed
Previous versions of trial documents when superseded, clearly marked as such
Sponsor confirmation of amendment categorisation
Ethics committee, Health Research Authority and competent authority approvals of amendments

B.2 Staff Participation

Updated RF1TA008 to include new trial staff
Updated CVs and training records
Updated Attendance at Investigator Training, RF1 TA008

B.3 Informed consent

Signed consent forms of all trial participants
Participant Screening and Enrolment Log, RF1 TA011

B.4 Medical Testing and Pharmacy

Updated accreditation / certification of supporting laboratories and pharmacies
Updated 'normal ranges' issued by local laboratories
Documented evidence of any changes and their implementation to Investigational product handling (where applicable) – local procedures where not in the study protocol
Documented evidence of any changes and their implementation to investigational product control (where applicable) – local procedures where not in the study protocol
Updated investigational medicinal product records – certificate of analyses, shipping records, amended labelling to be used 9if any)

B.5 Case Report Forms, Source Documents and Data Management

Completed CRFs (copy where originals are sent to a central collection repository) and amended CRFs
Source documents related to the trial
Ongoing database amendments, alterations and revision documentation and evidence
Data management plan, database lock plan and procedures
Monitoring plan

B.6 Serious Adverse Events and Serious GCP Breaches

SAE reporting forms, RF1 TA014.
eSUSAR / CIOMs form (IMP trials only)
SAE reporting forms to the ethics committee
Annual safety reports and Development Safety Update Reports (DSUR) to ethics committee and regulatory authority (where applicable)
Evidence of notification of actions to be taken and their implementation following a SUSAR (where applicable).
GCP breach report, correspondence with the MHRA and REC and subsequent corrective action documentations and evidence

B.7 Biological Materials (if relevant to the study)

List and location of retained samples and Tumour Banking
Transfer agreements to other institutions

B.8 Audit and Reporting

Annual progress report(s) to host institution, the ethics committee and competent authority (where applicable)
Monitoring reports
Sponsor audit reports and corrective action forms
Data Monitoring Committee reports (as applicable)
Trial Steering Committee reports (as applicable)
Statistical analyses reports

Funder reports

B.9 Vendor Management

Correspondence with and evidence of vendor performance oversight.
Contracts for new vendors and correspondence with and evidence of performance management and oversight

B.10 Miscellaneous

Correspondence letters, relevant emails etc

Section C: Trial Completion

C.1 Closure

Notification of study closure to the ethics committee
Notification of study closure to the competent authority (where applicable): CESP emails
Notification of study closure to the host organisation
Notification of study closure to the Sponsor
Treatment allocation and decoding documentation
Documentation of IMP return and/or destruction and pharmacy records

C.2 Audit and Publication

Final study report to REC and funder
Evidence of upload of trial results to EudraCT
Final close-out audit report (as applicable)
Publication

C.3 IMP Management

IMP and placebo accountability logs
Evidence of destruction of surplus stocks