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# SOP 305 Creating and Maintaining the Trial Master File or Investigator Site File

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|---|---|
| **For Use in:** | Research |
| **By:** | All staff |
| **For:** | All staff involved in the conduct of research |
| **Division responsible for document:** | Research & Development |
| **Key words:** | Trial Master File, Investigator Site File |
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| **Job title of document author:** | Commercial Research Coordinator |
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| **Assessed and approved by:** | Julie Dawson: Research Services Manager NNUH<br><br>Sarah Ruthven: Research Manager UEA |
| **Date of approval:** | 17/05/2023 |
| **To be reviewed before:**<br>This document remains current after this date but will be under review | 17/05/2026 (3 years, unless legislation or process changes) |
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| **Version No:** | 2 |
| **Description of changes:** | New template: objectives, scope<br>5. reference to multi-centre studies<br>Reference to 'completed and signed' delegation log<br>9. New para. For NCTU |

This Standard Operating Procedure (SOP) is available on the Research & Development pages on the NNUH website

Copies printed from the website are only valid on the day of printing.

# SOP 305 Creating and Maintaining the Trial Master File or Investigators Site File

## 1. Contents



## 2. Definitions of Terms Used / Glossary

| | |
|---|---|
| ARSAC | Administration of Radioactive Submission Advisory Committee |
| CI | Chief Investigator |
| CRF | Case Report Form |
| CTSA | Clinical Study Site Agreement |
| CTIMP | Clinical Trial Investigational Medical Product |
| DSUR | Development Safety Update Report |
| GCP | Good Clinical Practice |
| GTAC | Gene Therapy Advisory Committee |
| HEFA | Human Fertilisation and Embryology Authority |
| HRA | Healthcare Regulatory Authority |
| HTA | Human Tissue Authority |
| IB | Investigator Brochure |
| ICF | Informed Consent Form |
| IMPD | Investigational Medical Product Dossier |
| IMP | Investigational Medical Product |
| IRMER | Ionising Radiation Health Research Authority |
| IRAS | Integrated Research Application System |
| ISF | Investigator Site File |
| MHRA | Medicines & Healthcare Products Regulatory Agency |
| NCTU | Norwich Clinical Trials Unit |
| N/RES | National/Research Ethics Service |
| PI | Principal Investigator |
| PIF | Patient Identifiable Data Folder |
| PIS | Patient Information Sheet |
| REC | Research Ethics Committee |
| R&D | Research and Development |
| SAE | Serious Adverse Event |
| SIS | Subject Information Sheet |
| SmPC | Summary of Product Characterisation |
| SOP | Standard Operating Procedure |

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|---|---|
| SSIF | Signed Site-Specific Form |
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TMF | Trial Master File |

## 3. Objectives

This SOP is intended as a practical guide to setting up a TMF and/or ISF and the essential documents these should contain. See appendices 001, 002, and 003 for suggested contents.

## 4. Scope

The aim of this Standard Operating Procedure (SOP) is to describe the process for creating and maintaining the Trial Master File (TMF) and/or Investigator Site File (ISF) for all health care research activities within the UEA and NNUH.

## 5. Introduction

The TMF contains all essential documents held by Chief Investigator (CI) or Principal Investigator (PI) conducting a trial or study; the essential study documents stored in the TMF individually and collectively permit the evaluation of the conduct of a trial and the quality of the data produced by the site(s). For multi-centre studies, copies of relevant essential documents should be kept at each site in an ISF.

The purpose of this SOP is to outline the procedure for creating and maintaining a TMF/ISF and to provide guidance on the content, management and archiving of the TMF/ISF.

## 6. Rules

Rules & Responsibilities

- The TMF/ISF should be set up at the beginning of the trial or study
- The TMF/ISF must be kept on paper (as opposed to in electronic format)
- The TMF/ISF should be maintained and kept up to date throughout the course of the trial or study
- The CI/PI is responsible for establishing and maintaining the TMF/ISF. This activity can be delegated to research team members - if activities are delegated, this should be recorded in the study Delegation Log (SOP 325 Study Start-up Activities for Clinical Research Trials) and stored in the TMF/ISF.
- The Sponsor is responsible for ensuring that the TMF/ISF is set up at the start of a study, and that these are available for audit and inspection.
- The CI/PI is responsible for advising the Sponsor of the location of the TMF/ISF.
- The TMF/ISF should be stored in a secure but accessible location, such as a lockable filing cabinet or lockable room with restricted access to protect confidentiality of the participants and data integrity

## 7. Procedure NNUH

- The TMF/ISF must be set up by the CI/PI/delegated study team member during the planning stage of the research and before confirmation of capacity capability is issued.
- The TMF/ISF contents should be established by the CI/PI (see Appendices)
- The file shall contain the completed and signed delegation log, described in SOP 325
- All essential documents must be version controlled (See SOP 800 Non-Study Specific Research Documentation Management)
- Documents such as the Trial Protocol must be dated and signed by the CI/PI when filed in the TMF/ISF
- All previous versions of documents must be retained and noted as superseded, initialled, and dated
- A file note (dated and signed) should be placed in the file giving explanation of any missing or unavailable documentation
- On completion of the study, the TMF/ISF should be archived (see SOP 900 Archiving, retrieval and destruction of research documents)

## 8. Procedure UEA (if applicable)

Procedure will be as defined in the local working practice documentation.

## 9. Procedure for Norwich Clinical Trials Unit (NCTU)

For trials delegated by the NNUH to NCTU, a template TMF is provided in the document ‘NCTU_O_TaT_19 TMF checklist’ and further guidance is given on the process of setting up the TMF in the document ‘NCTU_O_WI_1 Trial Master File Guidance’.

## 10. References and Related Documents

| **References** |
|---|
| ICH GCP E6 / SI 2004/1041 |
| |

| **SOP No.** | **SOP Title** |
|---|---|
| SOP 001 | Production, Review, Approval and Control of SOPs Related to Research Activities |
| SOP 325 | Study Start-up Activities for Clinical Research Trials |
| SOP 800 | Non-Study Specific Research Documentation Management |
| SOP 900 | Archiving, retrieval and destruction of research documents |

## 11. Approval

| | |
|---|---|
| **Author** | Ania Spurdens |
| **Role** | Commercial Research Coordinator |
| **Approved & Authorised NNUH** | Julie Dawson |
| **Role** | Research Services Manager |
| **Signature** | DocuSigned by: Julie Dawson 4CBAB366CF354A2... |
| **Date** | 17 May 2023 \| 3:00 BST |
| **Approved & Authorised UEA** | Sarah Ruthven |
| **Role** | Research Manager |
| **Signature** | DocuSigned by: Sarah Ruthven 6EB42B4E497249C... |
| **Date** | 18 May 2023 \| 6:21 BST |

## 12. Reason for new version and Training Implication

This SOP replaces the previous version number V1.6

| Changes made | What changes have been made to the contents of the document |
|---|---|
| Reason | • New layout<br>• Revision in procedure (5. reference to multi-centre studies<br>• Reference to 'completed and signed' delegation log)<br>• 9. New para. For NCTU |
| Training Implication | **Yes** |
| Actions required | List any actions that may be required i.e.<br>• Additional training may be required |

# Trial Master File Contents (CTIMPS)

## Insert study title/acronym

**Guidance:**
Delete text in *red italics.*
Amend highlighted text with study specific information.

| Section Number | Documentation | Comments |
|---|---|---|
| **1** | **Protocol and Key Documents** | |
| 1.0 | Signed current protocol | |
| 1.1 | Signed superseded protocols | *Ensure superseded versions are clearly marked and that details of any amendments are included in subsequent protocols* |
| 1.2 | Sample Case Report Forms (CRFs) | *Include clearly marked superseded versions* |
| 1.3 | Participant Documentation | *Include Participant Information Sheets (PIS), consent forms, treatment or diary cards, recruitment advertisements etc.* |
| 1.4 | GP Letter | *Include clearly marked superseded versions* |
| 1.5 | Patient Identification form and Patient recruitment /screening form | |
| 1.6 | Risk Assessments | |
| 1.7 | Trial Registrations | *Include all systems in which the trial has been registered e.g. clinicaltrials.gov, EudraCT, ISRCTN* |
| **2** | **Investigational Medicinal Product** | |
| 2.1 | Investigator Brochure (IB) and/or Summary of Product Characteristics (SmPC) | *Include any clearly marked superseded versions. Include any signed confidentiality documents from IMP suppliers.*<br><br>*File note if IB not required for the trial.* |
| 2.2 | Sample Labels | *Include a copy of the labels approved by the MHRA and superseded versions* |
| 2.3 | Summary of Drug Arrangements (SoDA) | *Include any additional detail to that which is contained in the protocol, special storage or dispensing arrangements. Include superseded versions* |
| 2.4 | Certificates of Analysis and QP Release | *Include certificate of analysis, QP release certificates for all the batches, product specifications* |

| | | |
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| | | *and QP release supporting documents* |
| 2.5 | Shipment Records | *Include any documentation supporting request and shipment (order requests, delivery and receipt confirmations)* |
| 2.6 | Temperature Excursion Records | *Include T excursion logs and any relevant correspondence* |
| 2.7 | IMP Accountability and Return Logs | *Site-specific accountability logs should be kept in the ISF section of the TMF. Include superseded versions* |
| 2.8 | Trial Prescription | *Site-specific trial prescriptions should be kept in the ISF section of the TMF. Include superseded versions* |
| 2.9 | Drug Destruction Documentation | *Include permissions/instructions from the sponsor and any destruction logs, certificates of destruction, trial specific instructions, or NHS Trust/other local procedures. Site specific drug destruction documentation should be kept in the ISF section of the TMF* |
| 2.10 | Unblinding Information and Records | *Include any unblinding cards, forms, and central procedures. File note site-specific un-blinding documents should be kept in the restricted-access un-blinded folders* |
| 2.11 | Communication with IMP Supplier/Manufacturer | *Include copies of relevant correspondence. Arrange for additional sub-sections (i.e. agreements, finances, manufacturing, packaging, to further structure the filing in this section technical documentation, quotations)* |
| **3** | **Finances** | |
| 3.1 | Initial Funding Application | *Include copies of notification of intent to fund, research application form, fund confirmation letter* |
| 3.2 | Correspondence with the Funder | *Include copies of relevant correspondence* |
| 3.3 | Funding and Expenditure Reports | *Include copies of progress report* |
| 3.4 | Financial Agreements | *Include copies of financial agreement with other parties e.g. funder agreement* |
| **4** | **Insurance and Sponsorship** | |
| 4.1 | Sponsor Insurance Certificate | *Include copies of current and superseded certificates throughout* |

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| | | *the duration of the study. File note for NHS sponsor* |
| 4.2 | Confirmation of Sponsorship | |
| 4.3 | Sponsor Documentation | *File note to detail the location of R&D/Sponsor documentation* |
| **5** | **Agreements** | |
| 5.1 | IMP Manufacturer/Supplier Agreement | |
| 5.2 | Collaboration Agreements | *Arrange for additional sub-sections to arrange if various collaboration agreements are in place.* |
| 5.3 | Site Agreements | |
| 5.4 | Other Agreements | |
| 5.5 | Material Transfer Agreement | |
| **6** | **Ethical and Regulatory Approvals** | |
| 6.1 | Original application | *Authorised IRAS form* |
| 6.2 | MHRA Approval Letter | |
| 6.3 | Research Ethics Committee Letter of Approval | *Favourable Opinion* |
| 6.4 | Health Research Authority Initial Assessment Letter | |
| 6.5 | Health Research Authority Letter of Approval | |
| 6.6 | Licensing and Other Approvals | *Include any other approvals (i.e. ARSAC, CAG)* |
| 6.7 | Annual Progress Reports to Ethics Committee | |
| 6.8 | End of Trial Notification and Report | *Include any acknowledgment and response* |
| 6.9 | Correspondence | *Include correspondence with ethics committee and regulatory authority throughout the approval process.* |
| **7** | **Other Approvals** | |
| 7.1 | R&D Approval | *Confirmation of Capacity and Capability* |
| **8** | **Amendments** | |
| 8.1 | Log of Amendments | |
| 8.2 | Version History Log | *Version history log contains versions and implementation dates of trial specific documentation modified to support amendment submissions* |
| 8.3 | Amendments | *Applications for any amendments to be filed. Ensure amendment tool, cover letters (where required), all documents submitted with dates and version numbers, and approvals are included* |
| **9** | **Data Management** | |
| 9.1 | Database User List | *(Database Delegation Log)*<br>*Location of database e.g. website address*<br>*Access instructions* |

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| | | *Log of who has access to which functions on the database. Permissions should be approved by the database programmer for new staff. Include database training certificates for users in the database delegation log* |
| 9.2 | CRF Design Records | *If applicable, include copies of all drafts of CRFs/documentation related to CRF design and approval process (please file the drafts and final CRF page where the questionnaires have been integrated in the database) no template necessary* |
| 9.3 | Database Specification Documentation | |
| 9.4 | Database Testing and Release Documentation<br><br>Internal User Testing<br><br>Defect List Template<br><br>System Acceptance<br><br>System Release Note | *Include copies of all database testing procedure including any findings and the final release documentation* |
| 9.5 | End User Testing | *Include the dummy data/completed CRFs used in the testing (in development)* |
| 9.6 | Data Management Plan | *Include draft and superseded versions* |
| 9.7 | Data Queries | *Include copies of data query documentation* |
| 9.8 | Data Transfer Records or Dataset Request | *Include copies of records of all data transfers (paper and electronic) including acknowledgment of receipt* |
| 9.9 | Randomisation | *Include all relevant randomisation documentation (i.e.randomisation emails, randomisation procedures for sites and correspondence)* |
| 9.10 | Recruitment | *Include copies of all recruitment documentation (i.e. accrual spreadsheet, upload of accrual data acknowledgment emails)* |
| 9.11 | Data Validation Plan | |
| 9.12 | Database Lock before Unblinding | |
| 9.13 | Database Lock before Archiving | *Locking of database after unblinding* |

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| 9.14 | Archiving of Datasets | *Include location of archived datasets* |
| **10** | **Methodology** | |
| 10.1 | Statistics | |
| 10.1.1 | Statistician Contact List | |
| 10.1.2 | Sample Size Calculations and Software | *Verification by an independent statistician and full details of any revisions made during the trial* |
| 10.1.3 | Methods of Group Allocation | *Randomisation / minimisation, details of implementation and a file note giving the electronic location of the explicit list of randomisation allocations if applicable.* |
| 10.1.4 | Statistical Analysis Plan | |
| 10.1.5 | List of Data Files created for Analysis | *(Statistical analysis data file specifications)*<br><br>*Include details of the data file structure and coding lists* |
| 10.1.6 | Data, Analysis and Output Files | *File note the location of the data, methodology and output files used to generate each analysis* |
| 10.1.7 | Statistical Analysis Programmes Summary | *A collection of all statistical programme 'header information' with any additional comments to aid interpretation should be included* |
| 10.1.8 | Interim Statistical Report(s) | *File note giving the location of the hard copy of statistical report(s)* |
| 10.1.9 | Data Monitoring Committee (DMC) | *Include blinded DMC reports. File note the location of un-blinded DCM reports* |
| 10.1.10 | Final Statistical Report | *Include copy of the final statistical report and any relevant draft version* |
| 10.1.11 | Close Down & Merging SMF with TMF | *Include documentation and correspondence relating to merging the Statistical Master File with the Trial Master File* |
| 10.2 | Health Economics | |
| 10.2.1 | Health Economics Questionnaires | |
| 10.2.2 | Health Economics Review and Correspondence | |
| 10.2.3 | Health Economics Analysis Plan | |
| 10.3 | Process Evaluation | |
| 10.3.1 | Process Evaluation Questionnaires | |
| 10.3.2 | Correspondence | |
| **11** | **Research Staff and Training** | |
| 11.1 | Signed and dated CVs and Good Clinical Practice Certificates | |

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| 11.2 | Delegation Log | |
| 11.3 | Training Logs | *Include copies of training relating to the trial protocol, safety management plan etc.* |
| **12** | **Trial Management** | |
| 12.1 | Trial Management Group (TMG) Terms of Reference (ToR) | *Include current and superseded versions* |
| 12.2 | TMG Meetings | *Include final versions of agendas, minutes, circulations and associated documents* |
| 12.3 | Trial Steering Committee (TSC) ToR | *Include current and superseded versions* |
| 12.4 | TSC Meetings | *Include final versions of agendas, minutes, circulations and associated documents* |
| 12.5 | Independent Data Monitoring Committee (DMC) ToR | *Include current and superseded versions* |
| 12.6 | DMC Meetings | *Include final versions of agendas, minutes, circulations and associated documents* |
| 12.7 | Launch Meetings and Publicity | *Include slides, training, attendees signature lists, minutes, newsletters and any other relevant communication* |
| 12.8 | Monitoring Plan | *Include drafts/superseded versions* |
| 12.9 | Monitoring | *Include monitoring findings, reports, actions follow-up and any relevant correspondence* |
| 12.10 | Monitoring log | *To be completed by monitor on each visit (delete if only centralised monitoring takes place)* |
| 12.11 | Audit | *Include internal, external and sponsor audit reports, actions follow-up and any relevant correspondence* |
| 12.12 | Protocol Deviations | *Include non-conformance reports and any supporting documentation* |
| **13** | **Laboratory** | |
| 13.1 | Laboratory Manuals | *Include drafts/superseded versions* |
| 13.2 | Sample Lab CRFs and Request Forms | |
| 13.3 | Normal Ranges | |
| 13.4 | Accreditation Certificates | |
| 13.5 | Delegation of Responsibility and Signature Log | *Include all copies of signed delegation logs for laboratory staff* |

| | | |
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| 13.6 | Lab Sample Storage | *Include detail of processes for deviations* |
| 13.7 | Sample log / Chain of Custody Logs | *Include transfer for both analysis and storage, as well as receipt and onward distribution* |
| 13.8 | Lab Supplies | *Include relevant documentation regarding lab supplies* |
| 13.9 | Correspondence | *Include all correspondence with the laboratory* |
| **14** | **Pharmacovigilance/Safety** | |
| 14.1 | Safety Management Plan | *Include drafts/superseded versions* |
| 14.2 | Serious Adverse Event (SAE) and Notifiable Adverse Event (NAE) Reports | *Include hard copies of all information received relating to the event* |
| 14.3 | Serious Adverse Event Reports | |
| 14.4 | Notifiable Adverse Event Reports | |
| 14.5 | SAE Logs and Checklists | |
| 14.6 | Notifications to Ethics and MHRA | *Include all correspondence* |
| 14.7 | Notifications to Principal Investigators | *Include all correspondence* |
| 14.8 | Development Safety Update Report (DSUR) | *Include all correspondence* |
| **15** | **Investigator Site Files** | For multisite studies only |
| 15.1 | Investigator Site File | |
| 15.2 | Pharmacy Site File | |
| **16** | **Miscellaneous** | |
| 16.1 | Correspondence | *Include any relevant correspondence that is not site specific (i.e. instructions sent out to all sites). It is advisable to break this section down into discussion areas. Ensure that all conversations are 'closed' (i.e. that all queries and questions have all been resolved and the discussion is auditable. If necessary, follow up until you have a resolution filing element of the discussion as they are sent or received until a resolution is reached (at which* |

| | | |
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| | | *point you may be able to remove some of the interim communication)* |
| 16.2 | File Note Log | |
| 16.3 | Superseded File Notes | |
| **17** | **Clinical Study Report and Publications** | |
| 17.1 | End of trial report | |
| 17.2 | Publications | |

# Trial Master File Contents (Medical Devices studies)

## Insert study title/acronym

**Guidance:**
Delete text in *red italics.*
Amend highlighted text with study specific information.

| Section Number | Documentation | Comments |
|---|---|---|
| **0** | **Pre-funding Documentation** | *Include any documentation and relevant correspondence supporting pre-funding discussions and agreements* |
| **1** | **Clinical Investigation Plan and Key Documents** | |
| 1.0 | Signed current clinical investigation plan | |
| 1.1 | Signed superseded clinical investigation plans | *Ensure superseded versions are clearly marked and that details of any amendments are included in subsequent clinical investigation plans* |
| 1.2 | Sample Case Report Forms (CRFs) | *Include clearly marked superseded versions* |
| 1.3 | Participant Documentation | *Include Participant Information Sheets (PIS), consent forms, diary cards, recruitment advertisements etc.* |
| 1.4 | GP Letter | *Include clearly marked superseded versions* |
| 1.5 | Risk Assessments | |
| 1.6 | Trial Registrations | *Include all systems in which the trial has been registered e.g. clinicaltrials.gov, EudraCT, ISRCTN* |
| **2** | **Medical Device** | |
| 2.1 | Investigator Brochure (IB) | *Include any clearly marked superseded versions. Include any signed confidentiality documents from device suppliers.*<br><br>*File note if IB not required for the trial.* |
| 2.2 | CE Marking | |
| 2.3 | Instructions for use of Device | |
| 2.4 | Device Labels | |
| 2.5 | Summary of all bench testing and pre-clinical testing conducted | |
| 2.6 | Summary of all clinical experience with the device to date | |

| | | |
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| **3** | **Finances** | |
| 3.1 | Initial Funding Application | *Include copies of notification of intent to fund, research application form, fund confirmation letter* |
| 3.2 | Correspondence with the Funder | *Include copies of relevant correspondence* |
| 3.3 | Funding and Expenditure Reports | *Include copies of progress report* |
| 3.4 | Financial Agreements | *Include copies of financial agreement with other parties e.g. funder agreement* |
| **4** | **Insurance and Sponsorship** | |
| 4.1 | Sponsor Insurance Certificate | *Include copies of current and superseded certificates throughout the duration of the study. File note for NHS sponsor* |
| 4.2 | Confirmation of Sponsorship | |
| 4.3 | Sponsor Documentation | *File note to detail the location of R&D/Sponsor documentation* |
| 4.4 | Risk Assessment | |
| **5** | **Agreements** | |
| 5.1 | Device Manufacturer/Supplier Agreement | |
| 5.2 | Collaboration Agreements | *Arrange for additional sub-sections to arrange if various collaboration agreements are in place.* |
| 5.3 | Site Agreements | |
| 5.4 | Other Agreements | |
| **6** | **Ethical and Regulatory Approvals** | |
| 6.1 | Original application | *Authorised IRAS form* |
| 6.2 | Notification to MHRA | |
| 6.3 | MHRA Approval Letter | |
| 6.4 | Research Ethics Committee Letter of Approval | *Favourable Opinion* |
| 6.5 | Health Research Authority Initial Assessment Letter | |
| 6.6 | Health Research Authority Letter of Approval | |
| 6.7 | Licensing and Other Approvals | *Include any other approvals (i.e. ARSAC, CAG)* |
| 6.8 | Annual Progress Reports to Ethics Committee | |
| 6.9 | End of Trial Notification and Report | *Include any acknowledgment and response, and any publications* |
| 6.10 | Correspondence | *Include correspondence with ethics committee and regulatory authority throughout the approval process.* |
| **7** | **Other Approvals** | |
| 7.1 | R&D Approval | *Confirmation of Capacity and Capability* |

| | | |
|---|---|---|
| **8** | **Amendments** | |
| 8.1 | Log of Amendments | |
| 8.2 | Version History Log | *Version history log contains versions and implementation dates of trial specific documentation modified to support amendment submissions* |
| 8.3 | Amendments | *Applications for any amendments to be filed. Ensure amendment tool, cover letters (where required), all documents submitted with dates and version numbers, and approvals are included* |
| **9** | **Data Management** | |
| 9.1 | Database User List | *(Database Delegation Log)*<br>*Location of database e.g. website address*<br>*Access instructions*<br>*Log of who has access to which functions on the database. Permissions should be approved by the database programmer for new staff. Include database training certificates for users in the database delegation log* |
| 9.2 | CRF Design Records | *If applicable, include copies of all drafts of CRFs/documentation related to CRF design and approval process (please file the drafts and final CRF page where the questionnaires have been integrated in the database) no template necessary* |
| 9.3 | Database Specification Documentation | |
| 9.4 | Database Testing and Release Documentation<br><br>Internal User Testing<br><br>Defect List Template<br><br>System Acceptance<br><br>System Release Note | *Include copies of all database testing procedure including any findings and the final release documentation* |
| 9.5 | End User Testing | *Include the dummy data/completed CRFs used in the testing (in development)* |
| 9.6 | Data Management Plan | *Include draft and superseded versions* |
| 9.7 | Data Queries | *Include copies of data query documentation* |

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|---|---|---|
| 9.8 | Data Transfer Records or Dataset Request | *Include copies of records of all data transfers (paper and electronic) including acknowledgment of receipt* |
| 9.9 | Randomisation | *Include all relevant randomisation documentation (i.e.randomisation emails, randomisation procedures for sites and correspondence* |
| 9.10 | Recruitment | *Include copies of all recruitment documentation (i.e. accrual spreadsheet, upload of accrual data acknowledgment emails, recruitment logs, etc)* |
| 9.11 | Data Validation Plan | |
| 9.12 | Database Lock before Unblinding | |
| 9.13 | Database Lock before Archiving | *Locking of database after unblinding* |
| 9.14 | Archiving of Datasets | *Include location of archived datasets* |
| **10** | **Methodology** | |
| 10.1 | Statistics | |
| 10.1.1 | Statistician Contact List | |
| 10.1.2 | Sample Size Calculations and Software | *Verification by an independent statistician and full details of any revisions made during the trial* |
| 10.1.3 | Methods of Group Allocation | *Randomisation / minimisation, details of implementation and a file note giving the electronic location of the explicit list of randomisation allocations if applicable.* |
| 10.1.4 | Statistical Analysis Plan | |
| 10.1.5 | List of Data Files created for Analysis | *(Statistical analysis data file specifications)*<br><br>*Include details of the data file structure and coding lists* |
| 10.1.6 | Data, Analysis and Output Files | *File note the location of the data, methodology and output files used to generate each analysis* |
| 10.1.7 | Statistical Analysis Programmes Summary | *A collection of all statistical programme 'header information' with any additional comments to aid interpretation should be included* |
| 10.1.8 | Interim Statistical Report(s) | *File note giving the location of the hard copy of statistical report(s)* |
| 10.1.9 | Data Monitoring Committee (DMC) | *Include blinded DMC reports. File note the location of un-blinded DCM reports* |
| 10.1.10 | Final Statistical Report | *Include copy of the final statistical report and any relevant draft version* |
| 10.1.11 | Close Down & Merging Statistical Master File with TMF | *Include documentation and correspondence relating to merging the Statistical Master File with the Trial Master File* |

| | | |
|---|---|---|
| 10.2 | Health Economics | |
| 10.2.1 | Health Economics Questionnaires | |
| 10.2.2 | Health Economics Review and Correspondence | |
| 10.2.3 | Health Economics Analysis Plan | |
| 10.3 | Process Evaluation | |
| 10.3.1 | Process Evaluation Questionnaires | |
| 10.3.2 | Correspondence | |
| **11** | **Research Staff and Training** | |
| 11.1 | Signed and dated CVs and Good Clinical Practice Certificates | |
| 11.2 | Delegation Log | |
| 11.3 | Training Logs | *Include copies of training relating to the trial protocol, safety management plan etc.* |
| **12** | **Trial Management** | |
| 12.1 | Trial Management Group (TMG) Terms of Reference (ToR) | *Include current and superseded versions* |
| 12.2 | TMG Meetings | *Include final versions of agendas, minutes, circulations and associated documents* |
| 12.3 | Trial Steering Committee (TSC) ToR | *Include current and superseded versions* |
| 12.4 | TSC Meetings | *Include final versions of agendas, minutes, circulations and associated documents* |
| 12.5 | Independent Data Monitoring Committee (DMC) ToR | *Include current and superseded versions* |
| 12.6 | DMC Meetings | *Include final versions of agendas, minutes, circulations and associated documents* |
| 12.7 | Launch Meetings and Publicity | *Include slides, training, attendees signature lists, minutes, newsletters and any other relevant communication* |
| 12.8 | Monitoring Plan | *Include drafts/superseded versions* |
| 12.9 | Central Monitoring | *Include central monitoring findings, reports, actions follow-up and any relevant correspondence* |
| 12.10 | Audit | *Include internal, external and sponsor audit reports, actions follow-up and any relevant correspondence* |
| 12.11 | Protocol Deviations | *Include non-conformance reports and any supporting documentation* |
| **13** | **Laboratory** | |
| 13.1 | Laboratory Manuals | *Include drafts/superseded versions* |
| 13.2 | Sample Lab CRFs and Request Forms | |
| 13.3 | Normal Ranges | |
| 13.4 | Accreditation Certificates | |

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| 13.5 | Delegation of Responsibility and Signature Log | *Include all copies of signed delegation logs for laboratory staff* |
| 13.6 | Lab Sample Storage | *Include detail of processes for deviations* |
| 13.7 | Chain of Custody Logs | *Include transfer for both analysis and storage, as well as receipt and onward distribution* |
| 13.8 | Lab Supplies | *Include relevant documentation regarding lab supplies* |
| 13.9 | Correspondence | *Include all correspondence with the laboratory* |
| 13.10 | Material Transfer Agreement (MTA) | *Include a signed copy of the MTA agreement* |
| **14** | **Safety** | |
| 14.1 | Safety Management Plan | *Include drafts/superseded versions* |
| 14.2 | Serious Adverse Event (SAE) and Adverse Device Effect (ADE) Reports | *Include hard copies of all information received relating to the event* |
| 14.3 | Serious Adverse Event Reports | |
| 14.4 | Adverse Device Effect Reports | |
| 14.5 | SAE/ADE Logs and Checklists | |
| 14.6 | Notifications to Ethics and MHRA | *Include all correspondence* |
| 14.7 | Notifications to Principal Investigators | *Include all correspondence* |
| **15** | **Investigator Site Files** | |
| 15.1 | Investigator Site File | |
| **16** | **Miscellaneous** | |
| 16.1 | Correspondence | *Include any relevant correspondence that is not site specific (i.e. instructions sent out to all sites). It is advisable to break this section down into discussion areas. Ensure that all conversations are 'closed' (i.e. that all queries and questions have all been resolved and the discussion is auditable. If necessary, follow up until you have a resolution filing element of the discussion as they are sent or received until a resolution is reached (at which point you may be able to remove some of the interim communication)* |
| 16.2 | File Note Log | |
| 16.3 | Superseded File Notes | |

# Trial Master File Contents (Non-regulated studies)

## Insert study title/acronym

**Guidance:**
Delete text in *red italics.*
Amend highlighted text with study specific information.
Rows coloured grey may not be applicable to every study and can be removed if not applicable.

| Section Number | Documentation | Comments |
|---|---|---|
| **1** | **Protocol and Key Documents** | |
| 1.0 | Signed current protocol | |
| 1.1 | Signed superseded protocols | *Ensure superseded versions are clearly marked and that details of any amendments are included in subsequent protocols* |
| 1.2 | Sample Case Report Forms (CRFs) | *Include clearly marked superseded versions* |
| 1.3 | Participant Documentation | *Include Participant Information Sheets (PIS), consent forms, treatment or diary cards, recruitment advertisements etc.* |
| 1.4 | GP Letter | *Include clearly marked superseded versions* |
| 1.5 | Patient Identification form and Patient recruitment / screening form | |
| 1.6 | Study Registrations | *Include all systems in which the trial has been registered e.g. clinicaltrials.gov, EudraCT, ISRCTN* |
| **2** | **Finances** | |
| 2.1 | Initial Funding Application | *Include copies of notification of intent to fund, research application form, fund confirmation letter* |
| 2.2 | Correspondence with the Funder | *Include copies of relevant correspondence* |
| 2.3 | Funding and Expenditure Reports | *Include copies of progress report* |
| 2.4 | Financial Agreements | *Include copies of financial agreement with other parties e.g. funder agreement* |
| **3** | **Insurance and Sponsorship** | |
| 3.1 | Sponsor Insurance Certificate | *Include copies of current and superseded certificates throughout the duration of the study. File note for NHS sponsor* |
| 3.2 | Confirmation of Sponsorship | |
| 3.3 | Sponsor Documentation | *File note to detail the location of R&D/Sponsor documentation* |
| 3.4 | Risk Assessment | |
| **4** | **Agreements** | |

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|---|---|---|
| 4.2 | Collaboration Agreements | *Arrange for additional sub-sections to arrange if various collaboration agreements are in place.* |
| 4.3 | Site Agreements | |
| 4.4 | Other Agreements | |
| **5** | **Ethical and Regulatory Approvals** | |
| 5.1 | Original application | *Authorised IRAS form* |
| 5.2 | Research Ethics Committee Letter of Approval | *Favourable Opinion* |
| 5.3 | Health Research Authority Initial Assessment Letter | |
| 5.4 | Health Research Authority Letter of Approval | |
| 5.5 | Licensing and Other Approvals | *Include any other approvals (i.e. ARSAC, CAG)* |
| 5.6 | Annual Progress Reports to Ethics Committee | |
| 5.7 | End of Study Notification and Report | *Include any acknowledgment, response and publications* |
| 5.8 | Correspondence | *Include correspondence with ethics committee and regulatory authority throughout the approval process.* |
| **6** | **Other Approvals** | |
| 6.1 | R&D Approval | *Confirmation of Capacity and Capability* |
| **7** | **Amendments** | |
| 7.1 | Log of Amendments | |
| 7.2 | Version History Log | *Version history log contains versions and implementation dates of trial specific documentation modified to support amendment submissions* |
| 7.3 | Amendments | *Applications for any amendments to be filed. Ensure amendment tool, cover letters (where required), all documents submitted with dates and version numbers, and approvals are included* |
| **8** | **Data Management** | |
| 8.1 | Database User List | *(Database Delegation Log)*<br>*Location of database e.g. website address*<br>*Access instructions*<br>*Log of who has access to which functions on the database. Permissions should be approved by the database programmer for new staff. Include database training certificates for users in the database delegation log* |
| 8.2 | CRF Design Records | *If applicable, include copies of all drafts of CRFs/documentation related to CRF design and* |

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| | | *approval process (please file the drafts and final CRF page where the questionnaires have been integrated in the database) no template necessary* |
| 8.3 | Database Specification Documentation | |
| 8.4 | Data Management Plan | *Include draft and superseded versions* |
| 8.5 | Data Queries | *Include copies of data query documentation* |
| 8.6 | Data Transfer Records or Dataset Request | *Include copies of records of all data transfers (paper and electronic) including acknowledgment of receipt* |
| 8.7 | Randomisation | *Include all relevant randomisation documentation (i.e.randomisation emails, randomisation procedures for sites and correspondence* |
| 8.8 | Recruitment | *Include copies of all recruitment documentation (i.e. accrual spreadsheet, upload of accrual data acknowledgment emails, etc)* |
| 8.9 | Data Validation Plan | |
| 8.10 | Database Lock before Unblinding | |
| 8.11 | Database Lock before Archiving | *Locking of database after unblinding* |
| 8.12 | Archiving of Datasets | *Include location of archived datasets* |
| **9** | **Methodology** | |
| 9.1 | Statistics | |
| 9.1.1 | Statistician Contact List | |
| 9.1.2 | Sample Size Calculations and Software | *Verification by an independent statistician and full details of any revisions made during the trial* |
| 9.1.3 | Methods of Group Allocation | *Randomisation / minimisation, details of implementation and a file note giving the electronic location of the explicit list of randomisation allocations if applicable.* |
| 9.1.4 | Statistical Analysis Plan | |
| 9.1.5 | List of Data Files created for Analysis | *(Statistical analysis data file specifications)*<br><br>*Include details of the data file structure and coding lists* |
| 9.1.6 | Data, Analysis and Output Files | *File note the location of the data, methodology and output files used to generate each analysis* |
| 9.1.7 | Statistical Analysis Programmes Summary | *A collection of all statistical programme 'header information' with any additional comments to aid interpretation should be included* |

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| 9.1.8 | Interim Statistical Report(s) | *File note giving the location of the hard copy of statistical report(s)* |
| 9.1.9 | Data Monitoring Committee (DMC) | *Include blinded DMC reports. File note the location of un-blinded DCM reports* |
| 9.1.10 | Final Statistical Report | *Include copy of the final statistical report and any relevant draft version* |
| 9.2 | Health Economics | |
| 9.2.1 | Health Economics Questionnaires | |
| 9.2.2 | Health Economics Review and Correspondence | |
| 9.2.3 | Health Economics Analysis Plan | |
| 9.3 | Process Evaluation | |
| 9.3.1 | Process Evaluation Questionnaires | |
| 9.3.2 | Correspondence | |
| **10** | **Research Staff and Training** | |
| 10.1 | Signed and dated CVs and Good Clinical Practice Certificates | |
| 10.2 | Delegation Log | |
| 10.3 | Training Logs | *Include copies of training relating to the trial protocol, safety management plan etc.* |
| **11** | **Study Management** | |
| 11.1 | Study Management Group (SMG) Terms of Reference (ToR) | *Include current and superseded versions* |
| 11.2 | SMG Meetings | *Include final versions of agendas, minutes, circulations and associated documents* |
| 11.3 | Study Steering Committee (SSC) ToR | *Include current and superseded versions* |
| 11.4 | SSC Meetings | *Include final versions of agendas, minutes, circulations and associated documents* |
| 11.5 | Independent Data Monitoring Committee (DMC) ToR | *Include current and superseded versions* |
| 11.6 | DMC Meetings | *Include final versions of agendas, minutes, circulations and associated documents* |
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