Research & Innovation Office

Standard Operating Procedure

St Luke's Hospice

Maintaining a study site file

SOP Number	SLHSOP004	**Version Number**	1.2
Date Effective	23/06/2025	**Author**	Clare Pye Research & Innovation Manager
Related SOP's: Research Policies & procedures. V3. Dated 21/01/2025 SLHSOP-001. Informed consent. V1 dated 23/06/2025 SLHSOP002. Archiving. V1 dated 23/06/2025 SLHSOP003. Documenting Source data. V1 dated 23/06/2025		**Document Summary:** Describes the processes for the filing and storage of research documentation in the study site file.	
Approved by (name & Role)	Dr Paul Taylor Head of Research - SLH	**Date**	14/04/2025
Review date – 3yrs from date effective			

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Contents

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Acronyms

CI – Chief Investigator
PI- Principal Investigator
CTIMP - Clinical Trial of an Investigational Medicinal Product
SOP – Standard Operating Procedure
R&IO – Research & Innovation Office
SLH – St Luke's Hospice
TMF - Trial Master File
CRFs - Case Report Forms
ISF - Investigator Site File
SLH – St Luke's Hospice

Introduction

An investigator site file (also known as a study file or site file) is a standard filing system that allows the effective storage of essential study documents. Collectively, these documents should enable both the conduct of the clinical trial and the quality of the data produced to be evaluated. Essential documents are defined as: "those documents which individually and collectively permit evaluation of the conduct of the 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 GCP and with all applicable regulatory requirements".

Under the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended (the Regulations), it is a legal requirement to maintain essential documentation for all clinical trials of investigational medicinal products (CTIMPs).

Additionally, under the Research Governance Framework, the principles of Good Clinical Practice (GCP), including essential documents maintenance, should be applied to all research involving patients, other clients, staff, and their data.

Purpose

To describe procedures for maintaining essential documentation within a study file.

Note that not all documents will be required for every project - the contents of the study file will therefore differ according to the nature of the study and you should interpret this information in the context of your own project. Similarly, the version control procedure is an example that may be followed, if required, or amended to meet specific project requirements.

Roles and responsibilities

It is the responsibility of the Research & Innovation Office (R&IO) to make Hospice R&I SOPs available to all research active staff working on Hospice approved research studies.

It is the responsibility of the study Chief Investigator (CI), local Principal Investigator (PI) or R&IO to ensure that up-to-date copies of Hospice R&I SOPs are available to research staff.

All SOPs can be accessed on the Hospice website.

It is the responsibility of the study CI, local PI and R&IO to ensure that research staff are aware of the research SOPs and know how to access the most up to date versions. In the Investigator Site File (ISF) a file note will need to be prepared to detail the online location of the Hospice SOPs (Appendix 1).

It is the responsibility of the study CI or PI to designate if the SOPs of another organisation are to be followed for a study and to inform the R&IO. For example those of a Clinical Research Network, Commercial sponsor or University. If there is significant conflict between the external SOP and the Hospice SOP it is the responsibility of the CI or PI to resolve these with the R&IO prior to starting the study. If external SOPs are being followed, copies of each will need to be filed in the site file.

It is the personal responsibility of all staff to follow Hospice (or the designated alternative organisations) procedural documents**.**

The Research & Innovation Office is responsible for managing Hospice R&I SOPs including their approval, dissemination and archiving. All Hospice R&I SOPs must be made available and published on the Hospice website.

Specifics of this SOP

The local CI/PI is responsible for ensuring that a study file is set up and maintained on site throughout the study. Where this task is delegated to another member of the research team such as the Research Nurse/Administrator, etc. this should be recorded in the delegation of duties log.

The local CI/PI is responsible for making the study file available for audit, monitoring or inspection by the Hospice, sponsor or regulatory authority. They must also provide the R&IO with copies of monitor/audit reports that are conducted by other parties.

For multi-site studies, the sponsor is responsible for co-ordinating all participating sites, including ensuring that they are informed of any amendments to the study and are supplied with any updated study documentation and copies of annual reports in a timely fashion. If these responsibilities are delegated to another individual or organisation, this must be documented prior to the start of the study.

Trial Master File (TMF)

The Trial Master File (TMF) is held at the main coordinating site (usually CI's site) and should allow for reconstruction of conduct in the trial for audit purposes. For multi-site studies, copies of essential documents are kept at each participating site in their own Investigator Site File (ISF).

The regulatory and approvals documents within the TMF should be maintained alongside Case Report Forms (CRFs) and source documentation. Not all documents will be of relevance to every project – the content of the TMF will therefore differ according to the nature of the study. For example, most of the essential documents must legally be maintained for Clinical Trials of Investigational Medicinal Products (CTIMPs) whereas, for solely observational studies, certain documents will not be

applicable. Therefore, the SOP should be interpreted in the context of the individual project.

Investigator site file (ISF)

A separate ISF must be established for every research project at every site at the beginning of a trial. If the trial has a commercial sponsor, a study file and instructions for organising the documentation may be provided. Otherwise, the file should include a contents page with documentation arranged in appropriate sections according to local procedure, (Appendix 2).

The Trial Master File Index (Appendix 2) provides an extensive list of essential documents that may be needed in the TMF/ISF. Not all sections and documents will be applicable for every project (i.e. masters student), it is the responsibility of the PI to ensure the necessary documents are stored appropriately.

The ISF should be labelled with the short title, protocol number, IRAS project code, PI name and other information as determined by the study sponsor. The files should be also labelled numerically, but the total number of existing files must also be indicated i.e. File 1 of 1, File 1 of 2.

Study details and key contact information should be available at the front of the ISF, including the study team and contact details.

If any documents are stored separately from the ISF i.e. research CVs and GCP certificates, a file note should be placed in the relevant section detailing the location of the documents.

All correspondence should be retained; however, only critical documents should be stored in the study file as a hard copy. These would include agreements or significant discussion regarding trial administration, protocol violations, trial conduct and adverse event reporting.

The ISF must remain up to date at all times. It should be regularly added to and maintained by the PI or delegated individual. It is best practice to file new information and documents when they are received. Regular maintenance and checking of documents should be done.

At the end of the study, the ISF must be archived. Please see 'SLHSOP - 002 Arching' for archiving information.

All study-related documentation should be stored securely in a restricted-access area and should not be removed from Hospice premises unless this is required by the protocol.

If an electronic ISF is being used in addition or instead of a physical ISF, the PI or delegated individual must inform the R&IO of its location and details on how it can be accessed.

Any or all of the documents in the ISF, or referenced in the ISF but stored elsewhere, may be subject to, and should be available for monitoring, audit or inspection by the Hospice, sponsor or regulatory authority.

To assist researchers in compiling a study file, the following template documents can be requested from the Research & Innovation Office:

- Study information/ contact page
- Investigator CV template
- Delegation of Duties Log
- Adverse event/ serious adverse event forms
- Protocol deviation log
- Screening and enrolment log

Version Control

All documents that are submitted for approval (MHRA, ethics, sponsor, HRA) should be subject to systematic version control, with the version and date indicated in the document header/footer. A suggested method of version control, which may be adjusted in line with local conventions, is as follows:

Prior to seeking the relevant approvals, the first draft of a document is labelled 'v0.1' and dated. Subsequent drafts are labelled 'v0.2, v0.3…' etc. and dated. A 'Draft' watermark may also be placed in the background of the document (In Word: Format/Background/Printed Watermark).

Once a final version of the document has been produced, it is labelled 'v1.0' and dated, and if a watermark has been added, this is removed; this is the version that is submitted for the relevant approvals.

If any of the reviewing bodies request alterations to a document prior to granting approval, this is labelled 'v1.1, v1.2…' etc. and dated whilst being drafted and reviewed internally. The revised version re-submitted for approval is labelled 'v2.0' and dated.

During the course of the project, if minor amendments/non-substantial amendments (as defined by HRA https://www.hra.nhs.uk/approvals-amendments/amending-approval/ are made to a study document, this is re-versioned by incrementing the decimal place only – 'v2.1, 2.2…' etc. and dated. Note that while there is no requirement to notify the main REC of non-substantial amendments, it is best practice to provide updated study documents for information to the bodies that have approved them.

If substantial amendments (as defined by HRA) are made to a study document, this is re-versioned by incrementing the whole version number on the document submitted for approval each time a new amendment is submitted – 'v3.0, v4.0…' etc. and dated. Any substantial amendments to documents should be approved by the

relevant authorities **prior** to implementing any proposed changes. New versions of documents and their corresponding approvals should also be supplied to the R&IO.

There is no requirement for the version number on all study documents to match. Every document should be versioned independently, and only re-versioned if changes have been made to them. If there are documents that are very similar, i.e. multiple patient information sheets, the title should be repeated in the document header/ footer to avoid confusion.

Only one up to date version of any given document should be in use at any one time, and the version number and date should match those listed in the ethics favourable opinion/ most recent amendment approval letter.

Once approvals have been given for a new document, a copy of the older version of the document must be filed in the ISF. The previous version must be crossed through, marked as superseded and initialled and dated. All other copies should be destroyed.

Where study documents are numerous and/ or frequently amended and/ or sent out to a number of participating sites, a version control document checklist should be kept in the ISF and updated during the amendment process.

References

UK Policy Framework for Health & Social Care Research (2023): UK Policy Framework for Health and Social Care Research - Health Research Authority

NIHR Trial Master File Toolkit - Trial Master File | Clinical Trials Toolkit

ICH Topic E 6 (R2) Guideline for Good Clinical Practice - https://www.ema.europa.eu/en/ich-e6-r2-good-clinical-practice-scientific-guideline

Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments - https://www.legislation.gov.uk/uksi/2004/1031/contents

MHRA: Good Clinical Practice for Clinical Trials - https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials

Appendices

Appendix 1 – File note

File note for the storage and location of on-line Study site file.

Study Name:			
SLH study number:			
CI/PI			
Description: The site file for the above-mentioned study will be filed **(insert link)**			
	Print Name:	**Signature:**	**Date:**
CI/PI			

Appendix 2 – Trial Master File/Investigator Site File

Research Governance

Trial Master File* / Investigator Site File*

*delete as appropriate

This guidance applies to all research registered within St Luke's Hospice, Sheffield regardless of design or location.

The Trial Master File / Investigator Site File should contain the essential documents, which individually and collectively permit evaluation of the conduct of a research trial. The contents of the file serve to demonstrate the compliance of the investigator and the research team with the standards of Good Clinical Practice (GCP) and to the requirements of the UK Policy Framework for Health and Social Care Research.

The CI will keep a Trial Master File. The local PI will keep an Investigator Site File. In the case of a single centre study there will often be a single file for both CI and PI, in this case this file will be a Trial Master File.

The documents contained in the file are those that will be audited as part of the research governance process to confirm the validity of the trial conduct.

Those sections which do not apply to an Investigator Site File (where this file is not also acting as a Trial Master File) are greyed out in the ISF column. Some sections and sub-sections may not apply to all projects (i.e. masters students).

Guidance Notes:

Correspondence Sections: Separate topics of correspondence should be spilt into individual wallets. Consider whether a file note would be useful to describe the topic and outcomes.

File Notes: File notes should be used to describe important events / decisions and also to summarise documents or correspondence contained in the file if required.

Trial Master File* / Investigator Site File*

SLH study number:	SLHXXX	
IRAS Number:*		
Trial Registration number: *		
REC Reference:		
MHRA Reference: *	CTA No:	EudraCT No:
Study Title:		
Chief Investigator:		
Principal Investigator:		
Sponsor:		
Funder:*		

*N/A depending on study

Emergency Contacts:

	Name	Telephone Number	Email
Chief* Investigator			
Principal* Investigator			
Sub Investigator*			
Research Nurse*			
Pharmacy*			
Out of Hours*			

R&IO*			

0.0	**Contents**		
		TMF	ISF
0.1	Contents Page		
0.2	Current Version Control Tracking Spreadsheet		
Core Study Documents (current approved)			
		TMF	ISF
1.1	Protocol		
	Protocol signature page *		
1.2	Participant Information Sheet(s) *		
1.3	Informed Consent Form(s) *		
1.4	Information for GPs or consultants *		
1.5	Letters to Participants *		
1.6	Questionnaires *		
1.7	Participant Card / Diary *		
1.8	Adverts for Recruitment *		
1.9	Interview Schedule *		
1.10	Other REC approved documents		
2.0	**Independent Scientific Review**		
		TMF	ISF
2.1	Report / Evidence of Independent Scientific Review *		
2.2	Sponsor Protocol Review Checklist *		
2.3	Sponsor Risk Assessment *		
2.4	Statistical Review *		
3.0	**Ethics and HRA**		
		TMF	ISF
3.1	Research Ethics Committee Approval letter		
3.2	HRA/University Approval letter		
3.3	Application forms *(original REC form or IRAS form, as applicable)*		
3.4	Amendments split by submission number (e.g. SA01) *(individual wallets to include: application form, approval from REC and HRA)*		
3.5	**CARG Documents**		
3.6	Annual Progress Reports (*copy of the progress report, submission cover letter/email and/or REC acknowledgement letter)**		
3.7	Annual Safety Reports *(copy of the submission cover letter/email and/or REC acknowledgement letter)**		
3.8	Relevant correspondence with the REC Committee *		
3.9	Relevant correspondence with the HRA *		

4.0	**Regulatory Documents**		
		TMF	ISF
4.1	MHRA Notice of No Objection *		
4.2	Subsequent / Final MHRA Application package, including documents submitted to MHRA that are not filed elsewhere *		
4.3	MHRA Grounds for Non-Acceptance *		
4.4	Original MHRA Application package, including documents submitted to MHRA that are not filed elsewhere *		
4.5	MHRA Amendments split by submission number (e.g. SA01) *(individual wallets to include: application form, approval from MHRA)**		
4.6	Current Investigator Brochure / SmPC / IMP Dossier / Technical File / CE-marked device instructions for use *		
4.7	DSUR *(copy of the DSUR and submission cover letter)**		
4.8	Gene Therapy Advisory Committee documents *		
4.9	Relevant correspondence with the MHRA *		
5.0	**Research Governance Documents**		
		TMF	ISF
5.1	**SLH Research Management approval form** **SLH Capacity & Capability Approval letter (as applicable)** **SLH Low risk email confirmation email***		
5.2	**SLH Amendment Approval Letters/email***		
5.3	Confirmation of Capacity and Capability and Amendment approval from participating sites *(if this is maintained in a separate file, there should be a File Note to detail location)**		
5.4	Clinicaltrials.gov / ISRCTN Registration *		
5.5	**Insurance Certificate / Indemnity arrangements**		
5.6	Support Services information / approvals *		
5.7	ARSAC documentation / IRMER documentation *		
6.0	**Financial Management**		
		TMF	ISF
6.1	**SLH Signed site agreement**		
	Other signed financial agreements, service agreements, technical agreements, material transfer agreements, and collaboration agreements *		
	Laboratory Agreement *		
	Agreements with participating sites *(if this is maintained in a separate file, there should be a File Note to detail location)**		
6.2	SoECAT Summary *(as this is a large excel spreadsheet, the remainder of the document is available electronically)**		
6.3	Funding application forms *		
6.4	Confirmation of funding *		

7.0	**Investigator, Facilities and Research Team**		
		TMF	ISF
7.1	Chief Investigator CV		
7.2	Local Principal Investigator CV		
7.3	Co-investigators CVs		
7.4	Team members GCP Certificates		
7.5	Team member SOP Training Records and evidence of other training, as required by the study		
7.6	PI Responsibilities		
7.7	Delegation log template		
7.8	Delegation log *(this should include signature log of all members of the research team and list of tasks and responsibilities delegated to co-investigators)*		
7.9	**Honorary Contracts / SLH Letters of Access**		
8.0	**Participant Information**		
		TMF	ISF
8.1	Original signed consent forms *		
8.2	Participant screening, enrolment and/or tracking log templates *		
8.3	Completed participant screening log *		
	Completed participant enrolment log *		
	Completed participant tracking log *		
8.4	Sample tracking log (for stored or shipped samples) template *		
8.5	Completed sample tracking log (for stored or shipped samples) *		
8.6	Record of tapes and transcripts of interviews and focus groups *		
8.7	Completed Case Report Forms *		
8.8	SAE reports *		
8.9	SAE log *		
8.10	SUSAR reports *		
8.11	SAE Trend Analysis *		
9.0	**Project Management**		
		TMF	ISF
9.1	Terms of reference and minutes or other records of Trial Steering Committee (TSC) *		
	Terms of reference and minutes or other records of Trial Management Group (TMG) *		
	Terms of reference and minutes or other records of Data Monitoring and Ethics Committee (DMEC) *		
9.2	Study Specific Standard Operating Procedures (SOPs) *		
9.3	Laboratory Accreditation certificate *		
9.4	Normal laboratory values *		
9.5	Template of all Case Report Forms / data collection sheets *		
9.6	Sponsor approval *		

9.7	Details of the study database		
10.0 Pharmacy / IMP Management (file note for location if separate pharmacy file held)*			
		TMF	ISF
10.1	Pharmacy Arrangements (dispensing guide) *		
10.2	Randomisation schedule/Treatment allocation procedures*		
10.3	Code Break procedures/SOP *		
10.4	Prescribing arrangements/ template prescription*		
10.5	Completed IMP prescriptions*		
10.6	Dispensing log*		
10.7	Drug Accountability log template*		
10.8	Drug Accountability records (including completed accountability logs, drug shipment, patient compliance records and drug destruction records)*		
10.9	Template of approved drug label(s)*		
10.10	IMP storage arrangements (including temperature log)*		
11.0 Monitoring and Auditing			
		TMF	ISF
11.1	CI Management and Monitoring Arrangements*		
	Sponsor Management and Monitoring Arrangements*		
11.2	Study specific monitoring templates*		
11.3	Records of internal team monitoring *		
11.4	Completed monitoring reports for participating sites *(if this is maintained in a separate file, there should be a File Note to detail location)*		
11.5	Protocol non-compliance reports and log*		
11.6	Protocol non-compliance reports and log for participating sites *(if this is maintained in a separate file, there should be a File Note to detail location)**		
11.7	Site Initiation Documents*		
12.0 Study Closure			
		TMF	ISF
12.1	Archiving arrangements / confirmation of archived documents*		
12.2	Dissemination: plans for/record of*		
12.3	End of study declaration to REC *		
	End of study declaration to MHRA*		
12.4	Final Report to REC*		
	EudraCT report or Final Report to MHRA*		
	Email to MHRA confirming EudraCT upload*		
13.0 Correspondence			

		TMF	ISF
13.1	All relevant trial related correspondence other than as listed elsewhere. Please detail the section to which the correspondence pertains and consider a file note to summarise discussions.		
14.0	**Superseded Documents**		
		TMF	ISF
14.1	Copy of all superseded study documents should be filed in order of the contents page above.		

If applicable