Plymouth Research and Development

NHS University Hospitals Plymouth NHS Trust

Standard Operating Procedure

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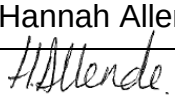
Title:	Preparation and maintenance of an Investigator Site File		
Approver		Document No:	P20
Name:	Hannah Allende	Version No:	V1.0
Signature:		Effective Date:	Aug-2022
Date:	05-Aug-2022	Review Date:	Aug-2025

1. Purpose

To describe the procedure for preparing and maintaining an Investigator Site File (ISF) throughout the lifetime of a study.

Essential documents, stored in the ISF, individually and collectively permit evaluation of the conduct of a study and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, research team, sponsor and monitor with the standards of Good Clinical Practice (GCP) and with all applicable regulatory requirements.

2. Scope

This Standard Operating Procedure (SOP) relates to all research studies at University Hospitals Plymouth NHS Trust (UHP). The preparation and maintenance of a Pharmacy Site File (PSF) and Study Master File (TMF) is not described here, refer to SOP CT40 and P9.

3. Responsibilities

Chief Investigator (CI)/ sponsor must provide participating sites with all essential study documents required to conduct the study, including amendments.

Principal Investigator (PI) is overall responsible for maintaining study documentation in line with ICH E6(R2) Section 8, Essential Documents for the Conduct of a Clinical Study, see appendix 1. Upkeep activities of the ISF may be delegated to other members of the research team.

Study Coordinator (SC) is responsible for leading on the day-to-day management of the ISF and ensure nominated staff working on the study contribute and support its maintenance as directed.

All research staff should support ISF maintenance for studies they are delegated to work on and must retain and file all key email correspondence related to the study.

4. Documents needed for this SOP

- ISF index
- Note to File template

5. Related documents

- SOP SC2 Research archiving
- SOP P9 Preparation and maintenance of an TMF
- SOP CT40 Pharmacy Clinical Study Site File *(held by Pharmacy Clinical Trials team)*

6. Acronyms

CI: Chief Investigator

GCP: Good Clinical Practice

ICH: International Council for Harmonisation

ISF: Investigator Site File

MHRA: Medicines and Healthcare products Regulatory Agency

PI: Principal Investigator

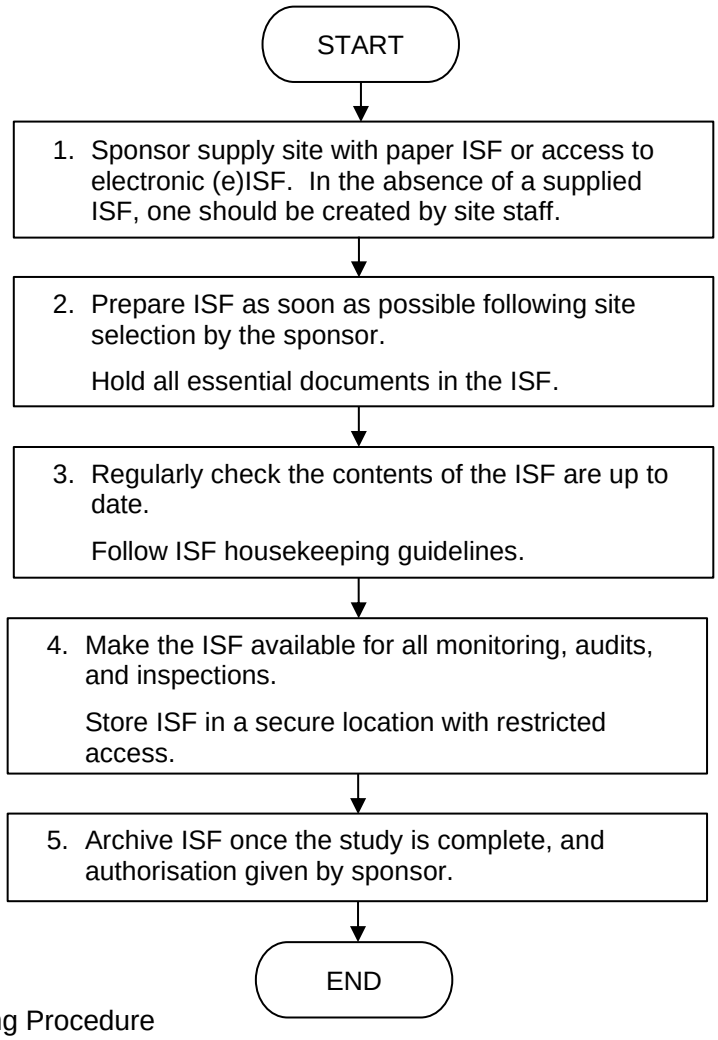
PSF: Pharmacy Site File

SOP: Standard Operating Procedure

TMF: Study Master File

UHP: University Hospitals Plymouth NHS Trust

7. Process map(s)/ flow chart(s)



8. Procedure

Step	Action	Responsibility
1	Supply site with paper ISF or provide training (if required, and access to electronic (e)ISF. In the absence of a supplied ISF, one should be created by site staff. **N.B.** The Sponsor must provide a copy of the eISF at the end of the study for archiving.	Sponsor.
2	Prepare ISF as soon as possible following site selection by the sponsor. It should be kept and maintained until the end of the study and archived thereafter in accordance with the archiving agreements made at the beginning of the study. Hold all essential documents outlined in Appendix 1 in the ISF and update as appropriate throughout the study. Use ISF Index template when one is not provided by the sponsor.	PI, SC and delegated study team.
3	Regularly check the contents of the ISF are up to date, any essential documents not found should be requested from study sponsor. Follow ISF housekeeping guidelines: • Label ISF with study number/ name, sponsor name, PI name and if more than one binder is used, numbering should be in place. • File in a timely manner, in accordance with the ISF index and in chronological order. • File amendment history indicating the changes and the dates they are implemented. • All final/ latest approved versions must be completely filed, superseded versions marked as superseded, with initials and date of the staff member superseding. • Retain and file relevant correspondence for the study. • Essential documents may be filed in a central location, outside of the ISF i.e., correspondence, CVs, GCP certificates, superseded documents, temperature logs, lab certificates and ranges. A file note must be available in the ISF explaining where to find centrally filed documentation. • Large volumes of documents such as correspondence or completed consents forms may be stored in separate binders, however, a file note must be added to the ISF section indicating location held.	PI, SC and delegated study team.

Step	Action	Responsibility
	• No sections in the ISF should be left blank, a file note should be added providing an explanation. • ISF may be split into several sections if documentation is relevant to more than one department i.e., a separate pharmacy binder in pharmacy. If split: – Documentation requires filing at minimum in one location. – Duplication of documentation is only required for documents that are relevant for both locations i.e., protocol. – Typically, the PSF may contain the protocol, drug supply manuals, all IMP-related documentation. • To save paper and archiving space, the following may be considered when printing documentation for the ISF: – Printing on both sides. – Printing with maximum 2 pages per sheet except for documentation to be provided to participants or health care professionals and CRFs, these must be printed in original size.	
4	Make the ISF available for all monitoring visits, audits and inspections by the sponsor or Medicines and Healthcare products Regulatory Agency (MHRA). Store the ISF in a safe and secure location with access only by authorised staff. Locally signed or generated documents held in the ISF must remain in the ISF. Occasionally, the sponsor may request the original signed documents, this should be discussed with the Research Governance Manager or deputy before sending. If it is agreed original documents can be sent to the Sponsor, a verified copy must remain in the ISF.	PI, SC and delegated study team.
5	Archive the ISF in accordance with SOP SC2. Where no patients signed a consent form, and no patients were screened check with the sponsor if it is permissible to discard the file contents in a confidential manner. If this is acceptable, then a list should be maintained of those studies of which the ISF has been discarded.	PI, SC delegated study team, and Research Archivist.

9. Changes from last revision

None.

Appendix 1: ISF Essential documents for the conduct study, based on ICH E6(R2)

I. Before the study commences

During the planning stage the following documents should be generated and should be on file before the study formally starts.

Title of Document	Purpose
Investigator Brochure (IB)	To document that relevant and current scientific information about the investigational product has been provided to the PI.
Signed Protocol and Amendments, if any, and sample Case Repot Form (CRF)	To document investigator and sponsor agreement to the protocol/ amendment(s) and CRF.
Patient Information Sheet (PIS) and Informed Consent Document (ICD), include all applicable translations.	To document the informed consent process.
Any other written information	To document that participant's will be given appropriate written information (content and wording) to support their ability to give fully informed consent.
Study advertisements *(if used)*	To document that recruitment measures are appropriate and not coercive
Financial aspects of the study *(where required as normally outlined in the PI/ site agreement)*	To document the financial agreement between the PI/ site and the sponsor for the study.
Insurance statement *(where required)*	To document that compensation to participants for study-related injury will be available.
Signed Agreements, e.g.: – PI/ site and sponsor – PI/ site and CRO – sponsor and CRO – PI/ site and authority(ies) *(where required)*	To document agreements.
Approval/ favourable opinion of an appropriate Research Ethic Committee (REC) of the following: – protocol and any amendments – informed consent form(s) – any other written information to be provided to the participant(s) – advertisement for participant recruitment (if used) – any other documents given approval/ favourable opinion	To document that the study has been participant to REC review and given approval/ favourable opinion. To identify the version number and date of the document(s).
Regulatory approvals (i.e. MHRA, HRA)	To document appropriate authorisation/ approval/ notification by the regulatory authority(ies) has been obtained prior to initiation of the study in compliance with the applicable regulatory requirement(s).
CV and or other relevant documents evidencing the qualifications of the PI and study team	To document qualifications and eligibility to conduct study and/ or provide medical supervision of participants.
Normal values/ ranges for medical/ laboratory / technical procedures and or tests included in the protocol	To document normal values and/ or ranges of the tests.

Title of Document	Purpose
Laboratory or other Service Vendor – certification or – accreditation or – established quality control and/or external quality assessment or – other validation *(where required)*	To document competence of facility to perform required test(s), and support reliability of results.
Sample of labels attached to IMP containers/ packaging *(normally in PSF)*	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the participants.
Instructions for handling of IMP and study related materials (*if not included in protocol or IB*).	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and study-related materials.
Shipping records for IMP and study related materials *(normally in PSF)*	To document shipment dates, batch numbers and method of shipment of investigational product(s) and study-related materials. Allows tracking of product batch, review of shipping conditions, and accountability.
Certificates of analysis of IMP *(normally in PSF)*	To document identity, purity, and strength of investigational product(s) to be used in the study.
Decoding procedure for blinded studies	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining participants' treatment.
Screening and randomisation list	To document numbers screened and method for randomisation of study population.
Monitoring reports	To document that the site is suitable and compliance with the study protocol.
Study Initiation Meeting or Site Initiation Visit (SIV) report	To document that study procedures were reviewed with the PI and the study team.

II. During the clinical conduct of the study

In addition to having on file the above documents, the following should be added to the files during the study as evidence that all new relevant information is documented as it becomes available.

Title of Document	Purpose
IB updates	To document that PI is informed in a timely manner of relevant information as it becomes available.
Any revision to: – protocol/ amendment(s) and CRF – informed consent form – any other written information provided to participants – advertisement for participant recruitment *(if used)*	To document revisions of these study related documents that take effect during study.
Approval/ favourable opinion of an appropriate Research Ethic Committee (REC) of the following: – protocol amendment(s) – revision(s) of: – informed consent form any other written information to be provided to the participant – advertisement for participant recruitment *(if used)* – any other documents given approval/ favourable opinion – continuing review of study *(where required)*	To document that the amendment(s) and/ or revision(s) have been participant REC review and were given approval/ favourable opinion. To identify the version number and date of the document(s).
Appropriate regulatory approvals: – protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements.
CV and GCP certificates for new investigators or study team members	To document qualifications and eligibility to conduct study and/ or provide medical supervision of participants.
Updates to normal values/ ranges for medical/ laboratory/ technical procedures and/ or tests included in the protocol	To document normal values and ranges that are revised during the study.
Updates laboratory or other service vendor – certification or – accreditation or – established quality control and/ or external quality assessment or – other validation *(where required)*	To document that service providers and tests, remain adequate throughout the study period.
Shipping records for IMP and study related materials *(normally in PSF)*	To document shipment dates, batch numbers and method of shipment of investigational product(s) and study-related materials. Allows tracking of product batch, review of shipping conditions, and accountability.
Certificates of analysis of IMP *(normally in PSF)*	To document identity, purity, and strength of investigational product(s) used in the study.
Monitoring reports	To document site visits by, and findings of the monitor.

Title of Document	Purpose
Relevant communication: – letters – e-mail – meeting notes – notes of telephone calls	To document any agreements or significant discussions regarding study administration, protocol violations, study conduct, adverse event (AE) reporting.
Signed ICDs	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each participant in study. Also, to document direct access permission.
Source documents *(normally held in the medical notes and participant CRF file)*	To document the existence of the participant and substantiate integrity of study data collected. To include original documents related to the study, to medical treatment, and history of participant.
Completed CRFs, signed and dated as required by the PI	To document that the PI or authorised member of the PI's team confirms the observations recorded.
Adverse Events (AEs) *(normally recorded in the medical notes and participant CRF file (AE log))*	Record of AE's recorded as per protocol.
Serious Adverse Events (SAEs) and reports *(may be held in the participant CRF file)*	Notification by originating investigator to sponsor of SAEs and related reports as required.
Suspected Unexpected Serious Adverse Reactions (SUSARs)	Notification by sponsor and/ or PI, where applicable, to regulatory authorities and REC(s) of SUSARs and follow-up safety information in accordance with regulations.
Safety information	Notification by sponsor to PIs of safety information.
Interim or annual reports to REC and regulatory authorities.	Annual reports provided to REC. For CTIMPs annual Development Safety Update Reports (DSURs) reports to MHRA. Interim reports as required to Trial Steering Committee (TSC) and funders.
Screening log	To document identification of participants who entered pre-study screening.
Participant enrolment/ randomisation log	To document chronological enrolment of participants by study number. To further document that PI/ site keeps a confidential list of names of all participants allocated to study numbers on enrolling in the study this allows PI/ site to identify study participants as required.
IMP accountability *(normally in PSF)*	To document that investigational product(s) have been used according to the protocol.
Delegation log	To document signatures and initials of all persons delegated to various study related tasks.
Record of retained samples *(if any)*	To document location and identification of retained samples if assays need to be repeated.

III. After Completion or Termination of the Study

After completion or termination of the study, all of the documents should be in the file together with the following:

Title of Document	Purpose
IMP accountability	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to participants, returned by the participants, and returned to sponsor.
IMP destruction or return	To document destruction or return of unused investigational products as per sponsor requirement.
Completed participant enrolment/ randomisation log	To permit identification of all participants enrolled in the study in case follow-up is required. List should be kept in a confidential manner and for agreed upon time.
Audit certificate *(if required or available)*	To document that audit was performed.
Final Study Close Out Visit (COV)	To document that all activities required for study close-out are completed, and copies of essential documents are held in the appropriate files.
Blind breaks	Returned to sponsor to document any decoding that may have occurred.
Final report by the CI to REC and where applicable to the regulatory authorities and/ or funders	To document completion of the study.
Clinical study reports	To document results and interpretation of study and disseminate the findings to the research community and study participants.