Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

STH Researcher

Investigator Site File

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Standard Operating Procedure
Investigator Site File

This SOP has been produced in accordance with ICH/GCP Guidelines, The DoH Research Governance Framework 2005, the Medicines for Human Use (Clinical Trials) Regulations 2004 and Medicines for Human Use (Clinical Trials) Amendment Regulations 2006.

Background

All research carried out at Sheffield Teaching Hospitals NHS Foundation Trust must have a Site File which contains essential documents.. It is intended that the investigator initiates the Site File immediately upon registration of the study with the Research Department and uses it for the duration of the study. A template sile file contents page can be accessed via the STH R&D website, useful documents page or on request to the assigned STH R&D Co-ordinator.

Definition

The Investigator Site File contains the essential documents necessary for the investigator and the research team.

Section 8 of ICH/GCP guidance details the essential documents necessary for the conduct of a trial.

Essential documents are those, which individually and collectively:

- Permit the evaluation of the conduct of a trial and the quality of the data produced
- Serve to demonstrate the compliance of the investigator, research team and sponsor with the standards of Good Clinical Practice and with all regulatory requirements
- When filed in an appropriate and timely manner greatly assist in the successful management of a trial by the investigator
- Are usually audited by the sponsors independent audit function and inspected by regulatory authorities as part of the process to confirm the validity of the trial conduct and data collection.

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

Procedure

1. The Investigator is responsible for setting up, maintaining, storing and archiving the Investigator Site File. This duty may be delegated to another appropriately qualified member of the Research Team and recorded in the Delegation of Study Duties Log.

2. The Investigator sets up a site file at the time the research is registered with the Research Department.

3. The Investigator should ensure all essential documents (see Appendix 1) are filed in reverse date order unless specified otherwise.

4. The Investigator should carry out regular checks to ensure the contents are up to date.

5. The Investigator should store the Investigator Site File securely but ensure all members of the research team have access to the file to complete any delegated duties.

6. The Investigator should file documents promptly and file superseded documents in the appropriate section of the Site File.

7. The Investigator should ensure that all working documents are made available to the support services, as appropriate, using STH electronic storage (Alfresco), via their STH R&D Coordinator.

8. The Investigator is responsible for ensuring the final study report is filed in the site file at study closure.

9. The Investigator should arrange for appropriate archiving of the Site File according to the requirements of the sponsor and regulatory authority.

Appendix 1: ICH/GCP Guidelines on essential documentation

ICH/GCP Reference:	Title of Document	Purpose	Located in files of Investigator	Located in files of Sponsor
8.2	**BEFORE THE CLINICAL PHASE OF THE TRIAL COMMENCES**	During this planning stage the following documents should be generated and should be on file before the trial formally starts		
8.2.1	**Investigator's Brochure**	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2	**Signed Protocol and Amendments, if any, and sample Case Report Form (CRF)**	To document investigator and sponsor agreement to the protocol/amendment(s) and CRF	X	X
8.2.3	Information given to trial subject – Informed Consent Form (including all applicable translations) - **any other written information** **-Advertisement for Subject Recruitment (if used)**	To document the informed consent To document that subjects will be given appropriate written information (content and wording) to support the ability to give fully informed consent To document that recruitment measures are appropriate and not coercive	X X X	X X
8.2.4	**Financial Aspects of the Trial**	To document the financial agreement between the investigator/institution and the sponsor for the trial	X	X
8.2.5.	**Insurance Statement** (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6	**Signed Agreement Between Involved Parties, e.g.** - investigator/institution and sponsor - investigator/institution and CRO - sponsor and CRO - investigator/institution and authority(ies) (where required)	To document agreements	 X X X	 X X (where required) X X

8.2.7	Dated, Documented Approval/ Favourable Opinion of Institutional Review Board (IRB) / Independent Ethics Committee (IEC) of the Following: - protocol and any amendments - CRF (if applicable) - Informed consent form(s) - Any other written information to be provided to the subject(s) - Advertisement for subject recruitment (if used) - Subject compensation (if any) - Any other documents given approval/favourable opinion	To document that the trial has been subject to IRB?IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X
8.2.8	**Institutional Review Board/Independent Ethics Committee Composition**	To document that the IRB/IEC is constituted in agreement with GCP	X	X (Where required)
8.2.9	**Regulatory Authority (ies) Authorisation/Approval/Notification of Protocol (where required)**	To document appropriate authorisation approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (Where required)	X (Where required)
8.2.10	**Curriculum Vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub-investigator(s)**	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11	**Normal Value(s)/Range(s) for medical laboratory/technical procedure(s) and/or test(s) included in the protocol**	To document normal values and/or ranges of the tests	X	X
8.2.12	**Medical/Laboratory/Technical Procedures/Tests** - **certification or** - **accreditation or** - **established quality control and/or external assessment or** - **other validation (where required)**	To document competence of facility to perform required test(s), and support reliability of results	X (where required)	X
8.2.13	**Sample of Label(s) attached to Investigational Product Container(s)**	To document compliance with applicable labelling regulations and appropriateness of instructions provided to subjects		X

8.2.14	**Instructions for Handling of Investigational Product(s) and Trial-Related Materials** (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial related materials	X	X
8.2.15	**Shipping Records for Investigational Product(s) and Trial-Related Materials**	To document shipment dates, batch numbers and methods of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16	**Certificate(s) of Analysis of Investigational Product(s) Shipped**	To document identity, purity and strength of investigational product(s) to be used in the trial		X
8.2.17	**Decoding Procedures for Blinded Trials**	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18	**Master Randomisation List**	To document method for randomisation of trial population		X (third party if

				applicable)
8.2.19	**Pre-Trial Monitoring Report**	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20	**Trial Initiation Monitoring Report**	To document that trial procedures were reviewed with investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X
8.3	**DURING THE CLINICAL CONDUCT OF THE TRIAL**	In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available		
8.3.1	**Investigator's Brochure Updates**	To document that investigator is informed in a timely manner of the relevant information as it becomes available	X	X
8.3.2	**Any Revision to:** - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X
8.3.3	Dated, Documented Approval/ Favourable Opinion of Institutional Review Board (IRB) / Independent Ethics Committee (IEC) of the Following: - protocol amendment(s) - revision of: - informed consent form - any other written information to be provided to the subject - advertisement for subject recruitment (if used) - any other documents given - approval/favourable opinion continuing review of trial (where required)	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s).	X	X
8.3.4	Regulatory Authority(ies) Authorisation/approvals/notifications where required for: - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5	Curriculum Vitae for investigator(s) and sub-investigator(s)	(see 8.2.10)	X	X
8.3.6	Updates to Normal Value(s)/Range(s) for medical laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X

8.3.7	**Updates of Medical/Laboratory/Technical Procedures/Tests** - **certification or** - **accreditation or** - **established quality control and/or external assessment or** - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8	Documentation of Investigational Product(s) and Trial-Related Materials Shipment	(see 8.2.15)	X	X
8.3.9	Certificate(s) of Analysis for New Batches of Investigational Products	(see 8.2.16)		X

8.3.10	Monitoring Visit Reports	To document site visits by, and findings of, the monitor		X
8.3.11	Relevant Communications Other than Site Visits - **letters** - **meeting notes** - **notes of telephone calls**	To document any agreements or significant discussions regarding trial administration, protocol violation, trial conduct, adverse event (AE) reporting	X	X
8.3.12	Signed Informed Consent Forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13	Source Documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
8.3.14	Signed, Dated and Completed Case Report Forms (CRF)	To document that the Investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15	Documentation of CRF Corrections	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16	Notification by Originating Investigator to Sponsor of Serious Adverse Events and Related Reports	Notification by originating Investigator to Sponsor of Serious Adverse Events and Related Reports in accordance with 4.11	X	X
8.3.17	Notification by Sponsor and/or Investigator, where applicable, to Regulatory Authority(ies) and IRB(S)/IEC(S) of unexpected Serious Adverse Drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(S)/IEC(S) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2	X (where required)	X
8.3.18	Notification by Sponsor to Investigators of safety information	Notification by Sponsor to Investigators of safety information in accordance with 5.16.2	X	X
8.3.19	Interim or Annual Reports to IRB?IEC and Authority(ies)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X	X (where required)

8.3.20	Subject Screening Log	To document identification of subjects who entered pre-trial screening	X	X (where required)
8.3.21	Subject Identification Log	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22	Subject Enrolment Log	To document chronological enrolment of subjects by trial number	X	
8.3.23	Investigational Products Accountability at this site	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24	Signature Sheet	To document signatures and initials of all person authorised to make entries and/or corrections on CRF's	X	X
8.3.25	Record of Retained Body Fluids/Tissue Samples (if any)	To document location and identification of retained samples if assays need to be repeated	X	X
8.4	AFTER COMPLETION OF THE TRIAL	After completion or Termination of the trial, all of the documentation identified in section 8.2 and 8.3 should be in the file together with the following		
8.4.1.	Investigational Product(s) Accountability at site	To document that the investigational product(s) have been used according to the protocol. To document the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects and returned to sponsor	X	X
8.4.2.	Documentation of Investigational Product Destruction	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	Completed Subject Identification Code List	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	Audit Certificate (if available)	To document that audit was performed		X
8.4.5	Final Trial Close-out Monitoring Report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X

8.4.6.	Treatment Allocation and Decoding Documentation	Returned to Sponsor to document any decoding that may have occurred	X	
8.4.7	Final Report by Investigator to IRB/IEC where required, and where applicable to the regulatory Authority(ies)	To document completion of the trial	X	
8.4.8	Clinical Study Report	To document results and interpretation of trial	X (if applicable)	X

Appendix 2. Associated Documents

	Document	Research Department Network Location	Website	Database	Created by
1	Investigator Site File	S:\General\Research Governance\Project Authorisation\Templates\Site file index	Yes	No	AL/EW
2	Delegation of Study Duties Log	Directory\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	PC
3	SAE Log	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	PC
4	Study Specific SOP Form	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	PC
5	Subject Drug Accountability Log	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	PC
6	Subject Screening Log	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	PC
7	Protocol Non-Compliance form	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	PC
8	Study File note	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	PC
9	Study Specific Training Record	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	PC
10	Subject Enrolment Log	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	PC
11	Subject Tracking Log	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	PC
12	SAE report form template	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	AL
13	Pregnancy report form	S:\General\Research Governance\Project Authorisation\Templates\Site file documents	Yes	No	AL