Standard Operating Procedure

ESSENTIAL RESEARCH DOCUMENTS

SETTING Trustwide

AUDIENCE Research staff responsible for developing, using and maintaining essential research study documentation for research sponsored by UH Bristol.

Standard Operating Procedure (SOP)

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Approved by:	Trust Research Group		
Date for review:	November 2017		

Date reviewed	Version number	Version Date	Effective Date	Reason for change	Author/Responsible person	Authorised by
Original SOP	V1.0	19/10/15	03/11/15	n/a	Diana Benton	Diana Benton
November 2016	V1.1	25/11/16	20/12/16	Minor updates and clarifications. Inserted standard dissemination text at end of SOP.	Jess Bisset	Diana Benton

1. Purpose

The purpose of this document is to describe essential trial documentation to be maintained in a Trial Master File and Investigator Site File. The key reference document used to develop this SOP is E6 Good Clinical Practice: Consolidated Guidance. This SOP focuses on the requirements for a clinical trial of an investigational medicinal product (CTIMP); however most elements will be relevant to all research conducted in the NHS.

2. Scope (areas/people in and out of scope should be defined)

In scope: Documentation for research sponsored by UHBristol**.** Trial documentation for CTIMPs sponsored by other organisations where the minimum standards described are not met.
Out of scope: Documentation for research sponsored by organisations other than UHBristol.

3. Abbreviations

CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
DMS	Document Management System

ICH GCP	International Conference on Harmonisation Good Clinical Practice
ISF	Investigator Site File
TMF	Trial Master File

4. Procedure

4.1 Essential Documentation

The Trial Master File (TMF) is a collection of documentation that allows the conduct of a clinical trial, the integrity of trial data and compliance of a trial with Good Clinical Practice (GCP) to be evaluated, facilitating the reconstruction of the trial.

It is the sponsor's responsibility to ensure that a TMF is set up and maintained. In practical terms, elements of the TMF may be held in more than one location. For example, the R&D office, the Chief Investigator's office/team and the Pharmacy Department may each be appropriate locations for sections of the TMF. There must however be a record in each location of where the other sections are stored. Documents may be held on paper or electronically. It is acceptable to have electronic filing, as long as it complies with the requirement for security and confidentiality, and can be easily located. Locations/formats of documents should be agreed between the sponsor and the CI and documented at the start of the study. Where UH Bristol is Sponsor this will be documented on the Study Set Up and Management Plan.

The Investigator Site File (ISF) is a collection of documents held at site, under the responsibility of the Principal Investigator. There may be duplicates of the same document held both in the ISF and the TMF, as defined in the index pages of those files.

Appendix 1 details the essential documentation to be maintained in the TMF for a clinical trial of an investigational medicinal product for UH Bristol sponsored trials. Whilst the whole suite of documents may not be relevant to all types of research, the list appended provides a good guide. It should be noted that this list is not exhaustive and therefore any additional documentation relating to the conduct of the study and not listed should also be retained. If an external trials unit is contracted to co-ordinate a UH Bristol sponsored study and has their own TMF and ISF templates, these will be reviewed and agreed (as applicable) for use by UH Bristol prior to the study commencing.

Appendix 2 details the list of documents that should be included in the ISF for both a CTIMP and Non-CTIMP at each participating site.

4.2 Initiation of the TMF and Storage

The TMF should be established as soon as possible, and it is the responsibility of the CI (unless delegated) to ensure that the file is maintained at all times. The TMF should be filed in a location that is accessible by all members of the research team, but also that is secure, in order to maintain confidentiality.

4.3 Amended Documents

During the course of a trial, it may be necessary for documents to be amended. Good practice is to file the most recent and current version at the front of the section in which that document is filed. Previous, superseded versions should be retained later in the section, crossed through and marked as superseded. Approvals for all amended documents should also be filed in the TMF and/or ISF where applicable. For electronic documents, a 'superseded' folder may be created in which to

store previous document versions.

4.4 Archiving

Please refer to the Archiving of Research Documentation SOP.

5. Dissemination and training in the SOP

5.1 Dissemination of this SOP

5.1.1 New SOPs and new versions of existing SOPs: The Research Operations Manager will be responsible for ensuring authorised SOPs are uploaded to the DMS in line with Trust policy and on the R&I website as described in the SOP "Authorship, review, revision and approval of research procedural documents produced by Research & Innovation". Internal Trust Staff are expected use the DMS to access latest versions of SOPs and to check the website regularly for updates, as communicated in the Training SOP.

Notice of new or amended procedural documents that have undergone a major amendment will be given via the following routes:

- Inclusion in the R&I e-bulletin (monthly);
- Direct email to Research Leads, Research Unit Managers and Band 7 staff for onward cascade ;
- Direct email to Chief Investigators of CTIMPs sponsored by UHBristol;
- Direct email to the Head of Research Governance at the University of Bristol (as relevant).

6. Training in this SOP

6.1.1 All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP.
6.1.2 The training log within the Investigator Site File/Trial Master File should be completed to document that members of staff have read and understood the content of the SOP and its amendments.

7. References

ICH Harmonised Tripartite Guideline for Good Clinical Practice (1996)
http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R1_Guideline.pdf

Joint Research Compliance Office, Imperial College London
http://www3.imperial.ac.uk/clinicalresearchgovernanceoffice/standardoperatingprocedures

8. Appendices

- **Appendix 1 Trial Master File Contents**
- **Appendix 2 Investigator Site File Contents**

RELATED DOCUMENTS	UHBristolR&I Archiving of Research Documentation SOP
AUTHORISING BODY	Trust Research Group
SAFETY	None
QUERIES	Contact Research Operations Manager or Research Management Facilitators on 0117 342 0223

CTIMP Trial Master File Contents

Notes for the use of this template: Where it would not be expected for a party to hold a copy of a particular document, this is indicated with a greyed area. Whether documents are stored in paper or electronic format should be clearly detailed; where documents are held in both formats this should be marked with 'P+E'.

This may be adapted for use in other types of research, as required.

ICH GCP reference	Title of document	Held by Investigator	Held by R&I (sponsor) Electronic (E) or Paper (P)	Held by Pharmacy	Held by Labs	Not applicable
Section 1: Funding						
8.2.4	Grant applications (if applicable)					
	Grant award letter/Financial agreement with funder					
	Costings					
	Invoices/payments - funder					
Section 2: Sponsorship						
	Sponsor study risk assessment					
8.2.9	Signed Sponsorship letter					
Section 3: Approvals and permissions						
HRA						
8.2.7	HRA applications (including REC if applicable)/notifications					
8.2.8	HRA approval letters					
8.2.9	REC membership list					
8.3.11	Correspondence					
MHRA/regulatory agency						
8.2.9	CTA or other regulatory applications/notifications					
8.3.11	Regulatory agency approval letters (MHRA)					
	Correspondence					
Other agency approvals (e.g. CAG, GTAC, HSCIC)						
Section 4:	**Study documents**					
	Log of amendments to study documents					
	Sponsor authorisation of study documents and amendments					
8.2.2, 8.2.7	Protocol and amendments					
	Information sheets and amendments					
	Consent forms and amendments					
	CRF and amendments					
	Clinical Trial Registration					
Section 5: Contracts						
8.2.6	Signed agreement between involved parties (if applicable)					
	• Summary of contractual relationships (if required)					
	• Collaboration agreements					
	• Service Level Agreements					
	• IMP supplier					
	• Sub contracts					

ICH GCP reference	Title of document	Held by Investigator	Held by R&I (sponsor) Electronic (E) or Paper (P)	Held by Pharmacy	Held by Labs	Not applicable
8.2.5	Insurance statement (if applicable)					
Section 6: IMP/Device information						
8.2.1	Summary of product characteristics/Investigator's Brochure and updates					
8.2.13	Sample Labels					
8.2.14	Instructions for handling of investigational products and trial-related materials (if not included in protocol or Investigator's Brochure)					
8.2.15	Shipping records for investigational product(s) and trial related materials					
8.2.16	Certificate(s) of analysis of investigational product(s) shipped					
8.3.8	Documentation of investigational product(s) and trial-related materials shipment					
8.3.9	Certificate(s) of analysis for new batches of investigational products					
8.4.1	Investigational products accountability at site (collate at end of trial)					
8.4.2	Documentation of investigational product destruction (collate at end of trial)					
Section 7: HR						
8.2.10	Chief Investigator and main site staff CVs/Contracts					
8.2.10	Relevant training records (GCP, professional and protocol)					
8.3.5	Main site CVs for new investigators/sub-investigators					
Section 8: Sites						
8.2.6	Signed site agreements					
8.2.9	NHS permission Letter (R&D approval) – if relevant					
	Capacity & Capability confirmation (if applicable)					
	Site(s) green light					
	Any other correspondence/information including submission pack sent to sites.					
Section 9: Trial Management						
8.2.12	Study specific standard operating procedures					
8.3.25	Record of retained body fluids/tissue samples (if any)					
8.2.11 8.3.6	Normal/reference value(s)/range(s) for medical/laboratory/ technical procedure(s) and/or test(s) included in the protocol and any updates					
8.3.7 8.2.12	Medical/laboratory/technical procedures/tests. Including validation, accreditation, certification or quality control and updates					
8.2.17	Unblinding procedures for blinded trials (3rd party if applicable)					
8.2.18	Master randomisation list (3rd party if applicable)					
8.3.20	Subject screening log (if required by sponsor and permission obtained)					

ICH GCP reference	Title of document	Held by Investigator	Held by R&I (sponsor) Electronic (E) or Paper (P)	Held by Pharmacy	Held by Labs	Not applicable
8.3.24	Authorisation/Delegation log for CRF entries and corrections					
8.3.14	Signed, dated and completed case report form (CRF) - originals					
8.3.15	Documentation of CRF corrections - originals					
8.4.6	Treatment allocation and decoding documentation(collate at end of trial)					
8.3.11	Miscellaneous correspondence & PR					
Section 10: Breaches and Pharmacovigilance						
8.3.11	Correspondence relating to breaches, including with regulatory authorities (as applicable)					
8.3.16	SUSAR/SAE Reports and follow up reports to sponsor					
8.3.17	SUSAR related correspondence between sponsor and MHRA/REC					
8.3.18	Notification to investigators of relevant safety information					
Section 11: Monitoring and Audit						
8.2.19/20 8.3.10 8.4.5	Completed monitoring reports and responses					
	Audit certificates (if applicable)					
Section 12: Data Management and Computer System Validation						
	Database development and sign-off					
	Computer System Validation documented checks (where applicable)					
	Data management plan and processes, including QC, lock and release					
Section 13: Reporting						
	Annual reports to funder (if required)					
8.3.19	Annual safety reports to REC and regulatory agencies					
8.3.19	Annual progress report to REC (if applicable)					
Section 14: End of study						
8.4.7	Final reports by investigator to regulatory authorities where required					
8.4.8	Clinical study/study closure report					
	Archiving					

Investigator Site file (ISF) Template

File Index

Study Information/Contact page	
Section 1	Funding
Section 2	Sponsorship
Section 3	Approvals and permissions
Section 4	Study Documents
Section 5	Contracts
Section 6	IMP/Device information (as relevant)
Section 7	Study staff
Section 8	Site specific information
Section 9	Trial management
Section 10	Breaches and Pharmacovigilance (as relevant)
Section 11	Monitoring and Audit
Section 12	Data Management
Section 13	Reporting
Section 14	End of Study

Where local pharmacy and laboratories are used accreditation certificates and normal lab ranges may be held within these departments. Where external laboratories or pharmacies are used accreditation certificates and normal ranges should be obtained and retained in the site file.

Study Information/Contact Page

Study title:

UH Bristol reference number:

IRAS number:

EudraCT number:

Sponsor details	
Name:	**Address:**
	Telephone:

Principal Investigator (PI) details	
Name:	**Address:**
	Telephone:

Chief Investigator (CI) details (if different from above)	
Name:	**Address:**
	Telephone:

Point of Contact (PoC) details	
Name:	**Address:**
	Telephone:

Start date:	**Projected end date:**

File contents

Study Information/Contact Page

Section 1: Funding/costing

- Site Financial Arrangements

Section 2: Sponsorship

- Signed copy of the sponsorship letter
- Relevant ongoing sponsor correspondence

Section 3: Feasibility, Approvals and Permissions

- Records of feasibility activities (capability and capacity)
- Statement of Activities (if applicable)
- R&D approval/NHS permission application (if applicable)
- R&D approval/NHS permission (if applicable)
- R&D correspondence
- HRA approval letter(s)
- REC membership list
- HRA correspondence
- CTA or other regulatory approvals (MHRA)
- MHRA correspondence

Section 4: Study documents

- Log of amendments to study documents (download from or refer to EDGE)
- Protocol and amendments
- Information sheets and amendments
- Consent forms and amendments
- GP letters and amendments
- Advertisements and amendments
- CRF and amendments

Section 5: Contracts

- Site agreement with sponsor OR
- Final Statement of Activities
- Site sub-contracts with service providers

Section 6: IMP/Device information (as relevant)

- Investigator Brochure or Summary of product characteristics (and updates)
- Operating instructions (device)
- Instructions for handling the IMP/trial related materials/device
- Shipping records for receipt of IMP/trial related materials/device (may be held in pharmacy)
- Shipping records for return of IMP/trial related materials/device (may be held in pharmacy)
- Certificate of analysis of IMP
- IMP accountability records (may be held in pharmacy)

Section 7: Study staff (to be updated as staffing changes)

- Site staff CVs
- Site staff training records relevant to the research (GCP, professional, protocol)
- Contractual documents (Letters of Access, Honorary Contracts)
- List of staff working on the study/delegation log

Section 8: Site specific information

- Correspondence/information relating to the site not included elsewhere

Section 9: Trial Management (subdivide if necessary)

Reference procedural information (as relevant):

- Study specific standard operating procedures
- Normal/reference value(s)/range(s) for medical/laboratory technical procedure(s) and/or test(s) included in the protocol and any updates
- Medical/laboratory/technical procedures/tests. Including validation, accreditation, certification or quality control and updates
- Procedure for randomisation
- Unblinding procedures for blinded trials

Patient-specific records

- Subject screening log
- Subject enrolment log
- Signed informed consent forms
- Confidential subject ID code list (not to be shared with sponsor without consent)
- Record of retained body fluids/tissue samples (as relevant)
- Original CRFs and amendment documentation (may be stored in a separate file if necessary)
- Decoding documentation (to be kept confidentially)
- Treatment allocation

Section 10: Breaches and Pharmacovigilance (as relevant)

- Correspondence relating to breaches of GCP (as applicable)
- SAE reports, follow up reports and correspondence to sponsor
- Copies of SUSAR related correspondence between sponsor (or site as representative of sponsor) and MHRA/REC
- Relevant safety information received from sponsor

Section 11: Monitoring and Audit

- Correspondence relating to monitoring/audit visits
- Completed monitoring reports and responses
- Audit certificates (if applicable)

Section 12: Data management

- Data Management processes
- Documentation of deviation from Data Management processes
- Correspondence

Section 13: Reporting

- Reports to sponsor (as required)
- Reports to HRA (as required)
- Reports to MHRA (as required)
- Any other reports required (e.g. funder reports)

Section 14: End of study

- Copy of final report
- Planned archiving arrangements

Study short title					
UHBristol ref no.		**IRAS no.**		**Principal Investigator**	
Sponsor				**Site**	
Site Staff Training Log (for documenting protocol training, GCP training or SOP training – can be used for groups or individuals)					

Name of SOP* **or trainee**:_____ (Use 1 sheet per person for multiple SOPs or one per SOP for multiple staff)

Date of training	Type of Training Undertaken (e.g. trainer, meeting, read document)	Name of trainee or protocol/SOP/other* (*ensure the version number and date are documented please)	Name of trainer (if applicable)	Signature (trainee)	Signature of trainer (if applicable)

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Study short title					
UHBristol ref no.		**IRAS no.**		**Principal Investigator**	
Sponsor				**Site**	
Site Staff List, Signature log and Delegation of Site Tasks					

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Name	Role in Study	Start date	End date	Tasks delegated (*use code below)	Signature	Initials	Authorisation Signature of PI	Date of authorisation

* **Please list study tasks** *(e.g. taking informed consent, study drug administration, taking blood samples, CRF completion etc).* ***NB All eligibility decisions for CTIMPs must be taken by a medically qualified individual, unless agreed in advance in writing with the sponsor and the MHRA. <u>They cannot be delegated.</u>***

1.	**06.**
2.	**07.**
3.	**08.**
4.	**09.**
5.	**10.**

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Study short title					
UHBristol ref no.		**IRAS no.**		**Principal Investigator**	
Sponsor				**Site**	
Subject Screening and Recruitment Record					

Initials	Gender		Screening date (dd/mm/yyyy)	Patient hospital number	Outcome - Please tick		1. Study / randomisation number if applicable, or 2. Reason for screen failure		Withdrawal date (dd/mm/yy)	Completed study Y/N
	Male	Female								
	☐	☐			Recruited		1.			☐Y ☐N
					Screening failure		2.			
	☐	☐			Recruited		1.			☐Y ☐N
					Screening failure		2.			
	☐	☐			Recruited		1.			☐Y ☐N
					Screening failure		2.			
	☐	☐			Recruited		1.			☐Y ☐N
					Screening failure		2.			
	☐	☐			Recruited		1.			☐Y ☐N
					Screening failure		2.			
	☐	☐			Recruited		1.			☐Y ☐N
					Screening failure		2.			
	☐	☐			Recruited		1.			☐Y ☐N
					Screening failure		2.			
	☐	☐			Recruited		1.			☐Y ☐N
					Screening failure		2.			

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Study short title					
UHBristol ref no.		**IRAS no.**		**Principal Investigator**	
Sponsor				**Site**	
Study Specific Document Log					

Study number/ Randomisation number	Date consent given (dd/mm/yyyy)	Patient Information Sheet		Signed Informed Consent Form			GP letter	
		Date copy given to patient	* Copy to medical records	* Original to site file	* Copy to patient	* Copy to medical records	Date sent to GP	* Copy to medical records

** Please tick and date when complete*

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Study short title					
UHBristol ref no.		**IRAS no.**		**Principal Investigator**	
Sponsor				**Site**	
Record of retained body fluids/tissue samples					

Patient Study Number / Randomis-ation number	Patient consent for sample collection provided? Y / N	Date sample collected (dd/mon/yy)	Sample Type	Storage location*	Storage period	
					From	To (date sample destroyed)
	☐Y ☐N					
	☐Y ☐N					
	☐Y ☐N					
	☐Y ☐N					
	☐Y ☐N					
	☐Y ☐N					
	☐Y ☐N					
	☐Y ☐N					
	☐Y ☐N					
	☐Y ☐N					

*Please specify, Building, department, location and type of storage facility

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