GIG CYMRU NHS WALES Bwrdd Iechyd Prifysgol Caerdydd a'r Fro Cardiff and Vale University Health Board	**Reference Number:** UHB 126 **Version Number:** 2 **Date of Next Review:** 07 Jul 2018 **Previous Trust/LHB Reference Number:** RD02

RESEARCH DOCUMENTATION & FILE MANAGEMENT: STANDARD OPERATING PROCEDURE

Introduction and Aim

Substantial amount of documentation is generated before, during and after undertaking any research project. It is important that such documentation is complete, legible and easily accessible at any time for monitoring, audit or inspection. The aim of this standard operating (SOP) is to provide guidance on the documentation that should be retained in the course of research and how it should be maintained.

Objectives

- To outline the procedure for setting up, managing and maintaining a Trial Master File (TMF) and Investigator Site File (ISF) and to outline the essential documentation required.
- To detail the responsibilities of Chief Investigators (CIs)/ Principal Investigators (PIs) in relation to the filing of research data and other study-related material.
- To promote compliance with the Clinical Trial Regulations, Data Protection legislation and records management requirements.

Scope

This procedure applies to all individuals undertaking or involved in UHB Sponsored or Hosted research studies within the UHB where the individual has any responsibility for setting up and maintaining project files, This includes those individuals:

• holding substantive or honorary contracts/titles with the UHB;
• holding 'letters of access' to UHB;
• undertaking clinical research involving UHB patients or staff; undertaking clinical research on UHB premises

It is also relevant for any project conducted within the NHS, which needs to comply with the Research Governance Framework.

Equality Impact Assessment	An Equality Impact Assessment has been carried out on the Research Governance Policy, under which this procedure falls. No adverse impact has been identified.
Documents to read alongside this Procedure	Research and Development Suggested Trial Site File Index (FR-RG-015). Archiving Clinical Study and Research Study Data SOP UHB 121
Approved by	Research Governance Group
Accountable Executive or Clinical Board Director	Medical Director
Author(s)	Research Governance Co-ordinator

Summary of reviews/amendments

Version Number	Date of Review Approved	Date Published	Summary of Amendments
1	25/10/2011	26/07/2012	Reviewed and updated document superseding previous Trust version ref RD02
2	07/07/15	23 Sept 2015	Document updated to new UHB format and the following changes were made • Title change from “Research Files and Filing” to “Research Documentation and File Management” to more accurately reflect SOP content • Removal of reference to label for Patient Medical Notes (FR-RG-013) • Addition of Section 1, Regulatory Background • References to !SR-RG-013, ISR-RG-014 &ISR-RG-015 removed as forms combined and replaced by Appendix A • Addition of Section 3 Essential Documentation and Section 4 Source Documentation

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1. REGULATORY BACKGROUND

1.1 The Medicines for Human Use (Clinical Trials) Regulations 2004 requires researchers to comply with the principles of ICH Good Clinical Practice (GCP) in clinical trials of Investigational Medicinal Products (CTIMPs).

1.2 The Research Governance Framework for Health & Social Care in Wales (para 2.3.3) states the principles of Good Clinical Practice apply to all research involving patients, not just clinical trials.

1.3 Although it is only a legal requirement to maintain a TMF for CTIMPs, the principles should still apply for the filing of study related documentation for ALL research projects within the NHS, which have to meet the Research Governance Framework, and any other clinical investigations which may have an impact on the safety and well-being of human participants.

2. RESPONSIBILTIES

2.1 The Principal Investigator (PI) or Chief Investigator (CI) is responsible for maintaining the 'essential documentation' for the research. Where the UHB is Sponsor and the CI is based within the UHB, the CI will be responsible for management of the Trial Master File (TMF) (see below). This responsibility may be delegated to other members of the research team (provided such delegation is clearly recorded).

2.2 The PI or CI will also be responsible for ensuring that accuracy, completeness, legibility and timeliness of data reported to the Sponsor in Case Report Forms (CRFs) and in all required reports.

2.3 The Sponsor is responsible for maintaining any 'Sponsor specific essential documents' in conformance with regulatory requirements.

3. ESSENTIAL DOCUMENTATION

3.1 ICH GCP (para 1.22) defines documentation as *"all records, in any form (including, but not limited to, written, electronic, magnetic and optical records, and scans, xrays, and electrocardiograms) that describe or record the methods, conduct and/or results of a trial, the factors affecting a trial, and the actions taken."*

3.2 These documents may form part of the 'essential documentation' defined in ICH GCP (para 1.23) as *"documents which individually and collectively permit the evaluation of the conduct of a study and the quality of the data produced."*

3.3 The 'essential documents' are therefore the minimum required documents to be maintained during any research project. They also serve some other important purposes:

- To demonstrate compliance of the Investigator, Sponsor and Monitor with ICH GCP and any applicable regulatory requirements;
- Assist all parties in the successful and smooth management of the research;
- Provide monitors, auditors and inspectors with the necessary information they need to confirm the validity of the research, its conduct and the integrity of the data collected.

3.4 The 'essential documents' are divided into three categories (ICH GCP paras 8.2- 8.4): see **Appendix A.**

- Before the clinical phase commences;
- During the clinical conduct of the research;
- After completion or termination of the research.

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, for clinical trials of IMPs, most of the essential documents must legally be maintained whereas, for solely observational studies, certain documents will not be applicable.

4 SOURCE DATA

4.1 Source documents are original documents and records where study data are *first* recorded e.g. hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial. Source documents are considered "Essential Documents" that allow evaluation of the clinical trial and ensure the quality of the data and serve to certify Sponsor and CI compliance with GCP and regulatory requirements. The process referred to as Source Data Verification (SDV) is an evaluation of the data recorded in the data collection tool against the source documents.

4.2 Source data can also be captured initially into a permanent electronic record. N.B. In this context 'permanent' means that all changes in the data are recorded in an audit trial (the minimum standard for this is a record of who made the change and when).

4.3 The CI/PI is responsible for the integrity of all source data and must ensure its timely filing in the appropriate section of the TMF. Such filing may either be carried out by the CI/PI or by other members of the research study team if delegated to do so.

5 TRIAL MASTER FILE (TMF) & INVESTIGATOR SITE FILE (ISF)

5.1 The Trial Master File (TMF) and Investigator Site File (ISF) represent the standard filing system for the storage of 'essential documentation.' These expressions are taken from ICH GCP, however they are not specific to CTIMPs as inclusion of the word 'trial' might suggest.

5.2 According to ICH GCP, the TMF includes all 'essential documentation' and should be set-up and maintained by the Sponsor who will store it at the Sponsor's office. The ISF is the file held by the PI and is maintained by the PI who will store it at the research site office.

5.3 Where research is sponsored by the UHB and the CI is based at the UHB, the TMF and ISF will usually be set-up, managed and located with the CI. The TMF should be established at the beginning of the trial. Where the UHB is the Sponsor, copies of the relevant sections of the TMF should be retained by the UHB R&D Office, CTU or other UHB departments as appropriate (e.g. Pharmacy). The UHB R&D office will retain electronic records relating to research governance but is not required to retain Case Report Forms (CRFs) or other source documentation as Sponsor. A TMF may consist of more than one file. If this is the case the files should be numbered (e.g. File 1 of 3), indexed and cross referenced.

5.4 For externally sponsored studies it is likely the PI will be provided with an ISF. For non-commercial studies where no study file is supplied an ISF should be set up by the PI or delegate using the ICH-GCP guideline Section 8 and the Research and Development Suggested Trial Site File Index (FR-RG-015).

5.5 The TMF/ISF should be labelled with the R&D Office Project Identification number, the protocol number and other information as determined by the study Sponsor. In the case of externally sponsored studies, the telephone number of the Sponsor and a contact name should be filed in the ISF.

6. FILE MANAGEMENT

6.1 Managing study proposals

Specific space should be allocated for the filing of proposed studies, where protocols, Investigator Brochures (IBs) and early correspondence can be stored when they are first produced or, in the case of externally Sponsored studies, received by the Directorate. The filing system should be segmented so that individual study documentation remains separate, to avoid misfiling/ loss of documents and correspondence. If the study is to proceed, all accumulated study specific material should be transferred to the ISF.

Where a decision is made not to participate in an externally commissioned study, the protocol and IB should be returned to the external Sponsor (if requested). A record should be maintained to confirm what and when information has been returned. Information of a confidential nature may need to be shredded following discussion and agreement with the Sponsor. Written proof of such destruction is sometimes required.

6.2 Responsibility

The CI or PI may delegate responsibility for the management of research documents to another Investigator, trial manager or research nurse(s). Any delegation should be recorded on the Study Delegation Log (SDL).and the person responsible should understand their role.

6.3 Format

There is a requirement to retain hard copies of all documentation. An eTMF can be maintained as a back up to the paper TMF, in which case the eTMF folder should match the structure of the paper TMF.
Currently there is little guidance relating to the storage of documents in electronic format. Electronic copies should be password-protected or stored in a password-protected folder or drive for backup purposes.

6.4 Storage

Documents contained in the TMF/ISF may be original regulatory approvals and confidential information. The files should therefore be stored in a secure place with restricted access. A locked drawer, cupboard or dedicated room is recommended, depending on the size of the project.

6.5 Quality

Essential documents should be complete, legible, accurate, unambiguous, authentic and, as appropriate, certified after verification. Sections 5.1.1 and 5.1.3 of ICH-GCP state the responsibilities of the

Sponsor for implementing quality assurance and quality control to assure the quality of essential documents.

6.6 Version Control

A system should be in place for version control of documents. It is recommended that a chronology of amendments is kept on file that records all the amendments submitted and the documents that they relate to. Old version of documents should be retained on file alongside the new versions and old versions clearly marked as no longer being used.

6.7 Archiving

Before, during and after the conduct of the research, it is useful to bear in mind the archiving of the documentation. Documentation may need to be retrieved at a future stage and so a catalogue or index of documents should be maintained to ensure this process is not burdensome.

The Chief or Principal Investigator (CI/PI) has a responsibility to ensure the safekeeping of all study related documentation and must guard against its premature destruction (please refer to Archiving of Clinical Trial and Research Study Data: Standard Operating Procedure (SOP UHB 121)

Patient medical notes are no longer digitised at the UHB; instead, the medical records are archived 18 months after the last patient contact (retained at an external archiving facility) until the retention period has expired. For the majority of patients in its care, the UHB has a duty to maintain medical notes for 8 years after the last contact; Mental Health, Child Health and Maternity records are kept for longer (between 20-25 years) depending on the patient group). Hence any source documentation residing within patients' medical notes is retained for at least 8 years after the last patient contact. Please refer to Archiving Clinical Study and Research Study Data SOP UHB121 for further information on the minimum requirements for retention of medical notes for different groups of patients.

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7. TRAINING

Education and support will be available from the UHB R&D Office for researchers who are involved in conducting UHB Sponsored CTIMPs.

8. IMPLEMENTATION

The Clinical Board R&D Leads should facilitate implementation by ensuring that all relevant research active personnel within their Clinical Boards are aware of the Procedure and the implications for their practice.

9. AUDIT

The UHB R&D Office is responsible for overseeing the operational management of Research Governance and for providing assurance of robust Research Governance arrangements in the UHB. It will be necessary to ensure that CTIMPs Sponsored by the UHB are being carried out in accordance with this Procedure. Audits may be carried out by the UHB R&D Office to ensure that all processes comply with this Procedure.

10. REVIEW

The Procedure should be reviewed every 3 years, or more regularly if important new legislation so requires.

11. REFERENCES

International Conference on Harmonisation: Harmonised Tripartite Guideline for Good Clinical Practice E6 (CPMP/ICH/135/95), European Commission (1996).
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002874.pdf

European Commission. Directive 2001/20/EC of the European Parliament and of the Council of the 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. Official Journal of the European Communities (2001), Luxembourg, L121/34-44.
http://www.eortc.be/Services/Doc/clinical-EU-directive-04-April-01.pdf

Medicines and Healthcare products Regulatory Agency. The Medicines for Human Use (Clinical Trials) Regulations 2004. Statutory Instrument 2004/1031 (2004).

The Medicines for Human Use (Clinical Trials) Amendment Regulations 2006 (Statutory Instrument 2006/1928). The Medicines and Healthcare products Regulatory Agency (2006).

The Medicines for Human Use (Clinical Trials) Amendment (No. 2) Regulations 2006 (Statutory Instrument 2006/2984). The Medicines and Healthcare products Regulatory Agency (2006).
http://www.hmso.gov.uk/si/si2006/20062984.htm

The National Assembly for Wales (2000)71, For the Record. Management of Records in the NHS Trusts and Health Authorities.

Great Britain. Data Protection Act (1998): Elizabeth II. (1998). London: The Stationery Office.

12 DISTRIBUTION

Cardiff and Vale University Health Board research personnel. The documents should be available via the Clinical Portal, Intranet and Internet pages.

13. ABBREVIATIONS AND DEFINITIONS

CI – Chief Investigator
CRF – Case Report Form
CTIMP – Clinical Trial of an Investigational Medicinal Product
CTU - Clinical Trials Unit
GCP - Good Clinical Practice
IB - Investigator's Brochure
IMP – Investigational Medicinal Product
ICH – International Conference for Harmonisation
ISF –Investigator Site File
MHRA – Medicines and Healthcare products Regulatory Agency
PI – Principal Investigator
REC – Research Ethics Committee
SDL – Study Delegation Log
SOP – Standard Operating Procedure
TMF – Trial Master File
UHB – Cardiff and Vale University Health Board

Chief Investigator – The investigator with overall responsibility for the research. In a multi site study, the CI has coordinating responsibility for research at all sites.

Principal Investigator – The investigator responsible for the research site where the study involves specified procedures requiring site-specific assessment by a Research Ethics Committee (REC). For multi site studies, there should be one PI for each research site. In the case of a single site study, the CI and the PI will normally be the same person.

APPENDIX A

ICH GCP: Essential Documentation*

*READ IN ACCORDANCE WITH PROJECT-SPECIFIC PROTOCOL

	TRIAL MASTER FILE	INVESTIGATOR SITE FILE
BEFORE STUDY COMMENCES		
Investigator's Brochure *To document that relevant and current scientific information about the Investigational Medicinal Product has been provided to the Investigator*	●	●
Signed Protocol & Amendments (if any) and Sample Case Report Form (CRF) *To document investigator and sponsor agreement to the protocol and CRF*	●	●
Informed Consent Form (inc. translations) *To document informed consent*	●	●
Patient Information Sheets *To document that subjects will be given appropriate information (content and wording) to support their ability to give informed consent*	●	●
Advertisement(s) for Recruitment *To document that recruitment measures are appropriate and not coercive*	●	●
Financial aspects of the Research *To document the financial agreement between the Investigator/Institution and Sponsor*	●	●
Insurance Statement/Certificate (if any) *To document that compensation to subject(s) for research- related injury or harm will be available*	●	●
Signed Agreements between Parties *To document agreements, liability, responsibilities and arrangements*	● (WHERE REQUIRED)	●
Dated, documented Approval/Favourable Opinion of Research Ethics Committee (REC) *To document that the research has been subject to ethical review and given approval/favourable opinion. To identify the version number of all the approved documents*	●	●
Research Ethics Committee (REC) Committee Composition *To document that the REC is constituted in agreement with ICH GCP*	● (WHERE REQUIRED)	●
Regulatory Authorisations/Approvals *To document appropriate authorisation/approval/notification by regulatory authority(ies) has been obtained prior to commencement of the research with the applicable regulatory requirement(s)*	● (WHERE REQUIRED)	● (WHERE REQUIRED)
Curriculum Vitae (CV) and or other relevant document(s) evidencing qualifications of Investigator(s) and Sub-Investigator(s) *To document qualifications and eligibility to conduct the*	●	●

research and/or provide medical supervision of subjects		
Normal value(s)/range(s) for Medical/Laboratory/Technical procedure(s) and/or Test(s) included in the Protocol *To document normal value(s) and/or range(s) of the tests*	●	●
Medical/Laboratory/Technical procedures/Tests Certification, Accreditation, Quality Control or other Validation *To document competence of facility to perform required test(s) and support reliability of results*	●	● (WHERE REQUIRED)
Sample of label(s) attached to Investigational Medicinal Product (IMP) containers *To document compliance with applicable labelling regulations and appropriateness of instructions provided to subjects*		●
Instructions for handling of IMP and trial related materials (if not in Investigator's Brochure or Protocol) *To document instructions needed to ensure proper storage, packaging, dispensing and disposition of IMP and trial related materials*	●	●
Shipping records for IMP and Materials *To document shipment dates, batch and method of shipment and tracking of batches, review and accountability,*	●	●
Certificate(s) of analysis of IMP shipped *To document identify, purity, strength of IMP to be used in the research*	●	
Decoding procedures for Blinded Projects *To document how, in case of an emergency, identify of blinded IMP can be revealed without breaking the blind for the remaining subject's treatment*	● (THIRD PARTY, IF APPLICABLE)	●
Master Randomisation List *To document method for randomisation of research population*	● (THIRD PARTY, IF APPLICABLE)	
Pre research Monitoring Report *To document that the site is suitable*	●	
Initiation Monitoring Report *To document that research procedures were reviewed with the Investigator and research staff*	●	●
DURING THE STUDY		
Investigator's Brochure Updates *To document that Investigator is informed in a timely manner of relevant information as it becomes available*	●	●
Revisions to Protocol, Informed Consent Form(s), Written Information to Subjects, Advertisement(s) *To document revisions of these research documents that take effect during the research*	●	●
Dated, documented Approval/Favourable Opinion of Research Ethics Committee (REC) for revisions to Protocol, Informed Consent Form(s), Written Information to Subjects & Advertisement(s) *To document that the amendment(s) or revision(s) have been subject to review and were given approval/favourable opinion.*	●	●

To identify the version number and date of the document(s)		
Regulatory Authority Authorisation/Approval/Notifications required for Protocol Amendment(s) and Other Documents *To document compliance with applicable regulatory requirements*	●	● (WHERE REQUIRED)
Curriculum Vitae (CV) for new Investigator(s) and/or Sub Investigator(s) *To document qualifications and eligibility to conduct the research and/or provide medical supervision of subjects*	●	●
Updates to normal value(s)/range(s) for Medical/Laboratory/Technical procedure(s)/Test(s) included in Protocol *To document normal values and ranges as revised during the research*	●	●
Updates of Medical/Laboratory/Technical procedures/Tests Certification, Accreditation, established Quality Control and/or external Quality Assessment or other Validation *To document that tests remain adequate throughout*	●	● (WHERE REQUIRED)
Documentation of IMP and research related Materials shipment *To document shipment dates, batch and method of shipment and tracking of batches, review and accountability.*	●	●
Certificate(s) of analysis for new batches of IMP *To document identity, purity, strength of IMP during the research*	●	
Monitoring Visit Reports *To document monitoring visits and findings*	●	
Other relevant communications such as letters, reports or telephone notes *To document any agreement or significant discussion regarding administration, protocol violations, conduct or adverse event reporting*	●	●
Signed Informed Consent Forms *To document that consent is obtained in accordance with GCP and protocol and date prior to participation of each subject in the research. Also to document direct access permission.*		●
Source Documents *To document the existence of the subject and substantiate integrity of research data collected. To include original documents related to the research, to medical treatment and history of the subject*		●
Signed, dated and completed Case Report Forms (CRFs) *To document that the Investigator or authorised member of the staff confirms the observations recorded*	● (ORIGINAL)	● (COPY)
Documentation of CRF Corrections *To document all changes/additions or corrections made to CRF after initial data are recorded*	● (ORIGINAL)	● (COPY)
Notification by originating Investigator to Sponsor of Serious Adverse Events (SAEs) & related Reports	●	●

To document compliance with GCP, protocol and applicable regulatory requirements for reporting SAEs and other reports		
Notification by Sponsor and/or Investigator to regulatory authority(ies) and Research Ethics Committees (RECs) of Suspected Unexpected Serious Adverse Reactions (SUSARs) and other Safety Information *To document compliance with GCP, protocol and applicable regulatory requirements for reporting SUSARs and other reports*	●	● (WHERE REQUIRED)
Notification by Sponsor to Investigators of Safety Information *To document communication of safety information to other research sites and interested parties*	●	●
Interim/Annual Reports to Research Ethics Committees (RECs) and Regulatory Authority(ies) *To document compliance with GCP, protocol and applicable regulatory requirements for periodical reporting*	● (WHERE REQUIRED)	●
Subject Screening Log *To document identification of subjects who entered pre –study screening*	● (WHERE REQUIRED)	●
Subject Identification Code List *To document that Investigator/Institution keeps a confidential list of names of all subjects allocated to numbers on enrolling in the research. Allows Investigator/Institution to reveal identity of any subject*		●
Subject Enrolment Log *To document identification of chronological enrolment of subjects by number*		●
IMP Accountability at Site *To document that IMP have been used according to protocol*	●	●
Signature Sheet *To document that signatures and initials of all persons authorised to make entries and/or corrections on CRFs*	●	●
Record of retained Body Fluids/Tissue Samples (if any) *To document location and identification of retained samples if assays need to be repeated*	●	●
AFTER COMPLETION OR TERMINATION OF THE STUDY		
IMP Accountability at Site *To document that the IMP(s) have been used according to the protocol. To document the final accounting of IMP(s) received at the site, dispensed to subjects, returned by the subjects and returned to sponsor*	●	●
Documentation of IMP Destruction *To document destruction of unused IMP(s) by Sponsor or at Site*	●	● (IF DESTROYED AT SITE)
Completed Subject Identification Code List *To permit identification of all subjects enrolled in the research in case follow up required. List should be kept in a confidential manner and for agreed time.*		●
Audit Certificate (if available) *To document that an audit was performed*	●	

Final Close out or Completion Monitoring Report *To document that all activities required for close out or completion are completed and copies of essential* documents held in appropriate files	●	
Treatment Allocation & Decoding Documentation Returned to Sponsor to document any decoding that may have occurred	●	
Final Report by Investigator to Research Ethics Committee (REC) and/or Regulatory Authority(ies) *To document completion of the research and outcomes*		●
Clinical Study Report *To document results and interpretation of the research*	●	● (IF APPLICABLE)