RESEARCH STUDY FILES AND FILING: STANDARD OPERATING PROCEDURE

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Documents to read alongside this Procedure	Research Governance Policy (UHB 099)

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1.0 INTRODUCTION

'Essential documents are those which 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, sponsor and monitor with the standards of Good Clinical Practice and with all the applicable regulatory requirements' (International Conference for Harmonisation of Good Clinical Practice, ICH-GCP, 1996).

Essential documents also serve a number of other important purposes. Filing essential documents at the investigator site in a timely manner can assist in the successful management of a study by the Investigator, Sponsor and Monitor. These documents are also those which are normally audited and inspected by the regulatory authorities or study Sponsor as part of the process to confirm the validity of the conduct of the study and the integrity of the data collected.

In the ICH-GCP guideline 'essential documents' are grouped according to the stage of the study during which they will be generated i.e.:

- before the study starts,
- during the study,
- and after completion or termination of the study.

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), SR-RG-001).

2.0 OBJECTIVE

- To outline the procedure for setting up, managing and maintaining a Trial Site File (TSF) or Project File (PF) and to outline the essential documentation required.
- To detail the responsibilities of the CI/PI in relation to the filing of research data and other study-related material.
- To promote compliance with Data Protection legislation and records management requirements.

3.0 SCOPE

This Standard Operating Procedure (SOP) applies to all Cardiff and Vale University Health Board (UHB) staff who have responsibility for setting up and maintaining project files, particularly those involved in non-commercial ('in-house') research studies falling under the Clinical Trials Regulations for which the UHB has agreed to act as Sponsor.

4.0 RESPONSIBLE PERSONNEL

Responsibility for setting up and maintaining a PF (for research studies) or a TSF (for clinical trials) usually rests with the CI or PI, but may be delegated to some of the following: Co-Investigator, Research Nurse, Research Assistant, Clinical Trial Practitioner, Data Manager/Trial Administrator, any other members of the research team not listed previously. Some aspects may be provided by the Clinical Trials Pharmacist, by the UHB Research Governance Coordinator, and by Medical Records personnel responsible for digitising patient medical notes.

5.0 ABBREVIATIONS AND DEFINITIONS

CI – Chief Investigator
CRF – Case Report Form
CTIMP – Clinical Trial of an Investigational Medicinal Product
GCP - Good Clinical Practice
IB - Investigator's Brochure
IMP – Investigational Medicinal Product
ICH – International Conference for Harmonisation
MHRA – Medicines and Healthcare products Regulatory Agency
PF – Project File
PI – Principal Investigator
REC – Research Ethics Committee
SDL – Study Delegation Log
SOP – Standard Operating Procedure
TSF – Trial Site 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.

Trial Site File – For the purposes of this SOP the term Trial Site File may be taken to include the term Project File.

6.0 PROCEDURE

6.1 GENERAL

With the large volume of documentation required for each study a well organised filing system is vital. Where there is an external Sponsor, it is likely the research team will be provided with a Trial Site File (TSF). For non-commercial studies where no study file is supplied a TSF or PF should be set

up by the research team using the ICH-GCP guideline Section 8 which has been converted into information sheets for use in the UHB (ISR-RG-013, ISR-RG-014 and ISR-RG-015). The ICH-GCP guidelines are mandatory for a clinical trial involving an Investigational Medicinal Product (IMP) for human use i.e. studies which fall under the EU Clinical Trials Directive (2001/20/EC) and corresponding Medicines for Human Use (Clinical Trials) Regulations 2004, but the pertinent issues of GCP are also relevant to all other types of studies.

The TSF should be established at the beginning of the trial. For research studies falling under the Clinical Trials Regulations, copies of the TSF are held by both the Investigator and Sponsor. Where the UHB is the Sponsor, copies of the relevant sections of the TSF should be retained by the UHB R&D Office or other UHB departments as appropriate (e.g. Pharmacy).

The CI/PI for each study within the UHB carries the primary responsibility for the conduct of the study on this site, including the establishment (where applicable) and maintenance of an appropriate TSF and ongoing management of all study related documentation.

The CI/PI is also responsible for the integrity of all source data and must ensure its timely filing in the appropriate section of the TSF. 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 and documented in the Study Delegation Log (SDL).

6.2 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 TSF.

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 applicable). 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.

6.3 TRIAL SITE FILE (TSF)

6.3.1 SETTING UP THE TSF

If a proposed study is to proceed, all accumulated study specific material should be transferred to the TSF. Where the CI/PI or research team is required to establish the TSF, this should be prepared as soon as possible after the first contact by the Sponsor or, for studies where there is no external Sponsor, as soon as an outline protocol is available. The TSF should be sub-divided into sections as shown in FR-RG-015 Research and Development Suggested Study Site File Index.

For CTIMPs, further information on the detail of each document can be found in:

- ISR-RG-013 Checklist of Essential Documents for Trial Site File and Sponsor Files Before the Clinical Phase of the Trial Commences.
- ISR-RG-014 Checklist of Essential Documents for Trial Site File and Sponsor Files During the Clinical Conduct of the Trial.
- ISR-RG-015 Checklist of Essential Documents for Trial Site File and Sponsor Files After Completion or Termination of the Trial.

Where a clinical trial is commercially sponsored, a TSF will usually be supplied by the external Sponsor. In this case, the Sponsor's TSF index must be adhered to. Similarly, a non-commercial external Sponsor may also provide a TSF, in which case their TSF index will need to be followed.

6.3.2 LABELLING THE TSF

The TSF 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 also appear on the label, or on the cover of the folder.

A TSF may consist of more than one file. If this is the case the files should be numbered (e.g. File 1 of 3) and cross referenced.

6.3.3 MAINTAINING THE TSF

The person who has been delegated the responsibility for the general organisation of the study, together with the person assigned to setting up and/or monitoring the TSF, must ensure that the necessary files are established and properly maintained.

The file should be actively maintained and updated from this time until the trial is formally closed. When it becomes available, the final report should be filed in the TSF. The three information sheets detailed in section 6.3.1 Checklist of Essential Documents for Study Site File should be referred to in order to

assist the maintenance of a GCP compliant TSF. Whenever possible, storage should be provided in secure, fireproof cupboards or filing cabinets.

6.4 QUALITY OF ESSENTIAL DOCUMENTS

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.

6.5 AT THE END OF THE STUDY

After the final study visit has been completed, all data queries have been resolved, the data have been analysed and the Clinical Study Report (for CTIMPs) or Final Report (for non-CTIMPs) produced and submitted, the following documents (where applicable) should be collated prior to archiving:

- IMP(s) accountability at site,
- Documentation of IMP destruction,
- Completed subject identification code list,
- Audit certificate or report (if available),
- Final study close-down monitoring report,
- Treatment allocation and decoding documentation,
- Final Report by Investigator to REC,
- Clinical Study Report to the Medicines and Healthcare products Regulatory Agency (MHRA).

For CTIMPs, further information on the detail of each document required at the end of a study can be found in ISR-RG-015 Checklist of Essential Documents for Trial Site File and Sponsor Files After Completion or Termination of the Trial.

Investigators and/or Sponsor institutions are required to maintain essential documents (as specified in ICH-GCP Section 8) and to “take measures to prevent accidental or premature destruction of these documents” (ICH-GCP Section 4.9.4).

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 SR-RG-001 Archiving Clinical Study and Research Study Data SOP for further information on the minimum requirements for retention of medical notes for different groups of patients.

7.0 TRAINING

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

8.0 IMPLEMENTATION

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

9.0 EQUALITY

An equality impact assessment has been carried out on the Research Governance Policy, under which this Procedure falls. No adverse impact has been identified.

10.0 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.

11.0 REVIEW

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

12.0 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.

13.0 DOCUMENT LINKS

Research and Development Suggested Trial Site File Index (FR-RG-015).

Label for Patient Medical Notes (FR-RG-013).

Checklist of Essential Documents for trial Site File and Sponsor Files Before the Clinical Phase of the Trial Commences (ISR-RG-013).

Checklist of Essential Documents for Trial Site File and Sponsor Files During the Clinical Conduct of the Trial (ISR-RG-014).

Checklist of Essential Documents for Trial Site File and Sponsor Files After Completion or Termination of the Trial (ISR-RG-015).

14.0 DISTRIBUTION

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