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RESEARCH AUDIT
Standard Operating Procedure

Introduction and Aim

As a legal Sponsor organisation (an institution that takes responsibility for initiation, management and/or financing of a clinical trial), Cardiff and Vale University Health Board (UHB) is responsible for auditing research practice and assuring adherence to current legislation and guidelines.
As such, it is necessary to audit research for which, the UHB is the Sponsor against the standards of the Research Governance Framework for Health and Social Care in Wales (2nd Edition) and the Medicines for Human Use (Clinical Trials) Regulations 2004 (and subsequent amendments) where applicable and against the quality systems of Good Clinical Practice intrinsic to the Regulations.
This standard operating procedure (SOP) is to assist researchers in understanding the audit process, so they are prepared should they be selected for internal audit or external audit/ inspection.

Objectives

- To describe the audit procedures of the R&D office acting on behalf of the UHB as Sponsor organisation.
- To describe the processes for selecting studies for audit, the procedures for carrying out audits; and reporting audit results to Investigators.
- To describe the requirements for Investigators to respond to audit reports and implement corrective actions.

Scope

This procedure applies to staff in all locations including those with honorary contracts.

Equality Health 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 Governance Policy (UHB 099) Serious Breach SOP (UHB 235) Investigating and Handling Allegations of Research Misconduct SOP (UHB145)
Approved by	Research Governance Group

Accountable Executive or Clinical Board Director	Medical Director
Author(s)	Clinical Research Monitor

Disclaimer

If the review date of this document has passed please ensure that the version you are using is the most up to date either by contacting the document author or the Governance Directorate.

Summary of reviews/amendments

Version Number	Date of Review Approved	Date Published	Summary of Amendments
1	08/04/14	23/06/14	New document
2	17/10/17	30/11/17	Transferred into current UHB SOP template, addition of objectives and scope sections. Glossary updated Appendix 2, Template audit report updated. Reference documents updated

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GLOSSARY

ABBREVIATIONS AND DEFINITIONS

CAPA – Corrective and Preventative Action
CI - Chief Investigator
CTIMP - Clinical Trial of Investigational Medicinal Product
GCP - Good Clinical Practice
ICH - International Conference for Harmonisation
IMP - Investigational Medicinal Product
PI - Principal Investigator
R&D - Research & Development
ReDA – Research Database Application
RGF - Research Governance Framework
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 co-ordinating responsibility for the research at all sites. The main application for ethical review should be submitted by the CI.

Principal Investigator - The investigator responsible for the research site where the study involves specified procedures requiring site specific assessment by the local R&D Office. 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.

External Sponsor – This means any Sponsor other than Cardiff and Vale UHB. An External Sponsor may be a Commercial organisation (e.g. a Pharmaceutical company) or a Non-Commercial organisation (e.g. another Local Health Board, NHS Trust or University, including Cardiff University).

1. PURPOSE

This Standard Operating Procedure (SOP) describes the audit procedures of the R&D Office, acting on behalf the UHB.

It describes the processes for selecting those studies for audit, the procedures for carrying out audits; and the reporting of audit results to Investigators. It also describes the requirements for Investigators to respond to R&D audit reports and implement corrective actions.

The SOP primarily covers the procedures to be followed for

- UHB sponsored CTIMPS
- UHB sponsored non-CTIMPS (including interventional studies such as surgical trials or trials involving devices).
- Externally sponsored studies hosted at the UHB

The purpose of research audit within the scope of this SOP is to verify that systems are in place to ensure:

- The rights and well-being of human subjects are protected

- The reported study data is accurate, complete, and verifiable from source documents.

- The conduct of the study is in compliance with the approved study protocol/amendments, with Research Governance Framework for Health and Social Care (RGF), the applicable regulatory requirements and UHB policies and SOPs.

2. PROCEDURE

2.1 Routine Audit Selection

UHB sponsored studies

Audits of UHB sponsored CTIMPS and non CTIMPS interventional studies such as surgical trials or trials involving devices will follow a risk-based approach. During the sponsor assessment process, a Risk Assessment Form (RAF) will be completed which categorises studies into 3 areas of risk:

Type A = comparable to the risk of standard medical care
Type B = somewhat higher than the risk of standard medical care
Type C = markedly higher than the risk of standard medical care

Routine audits will be performed with priority to Type C studies followed by Type B and Type A. The following will be excluded: Studies closed to recruitment, studies in set up and studies that have recently been audited or inspected. The R&D Office will select a representative sub-set of studies to be audited which will be documented in the annual R&D audit schedule.

For non CTIMPs studies sponsored by the UHB, the R&D office will select a representative sub-set of studies to be audited which will be documented in the annual R&D audit schedule.

Externally sponsored studies

CTIMPs and non-CTIMPs studies that are externally sponsored will not be included within the programme of routine audit, unless there are particular audit/inspection findings in relation to quality management systems that warrant it. The responsibility for auditing externally Sponsored studies lies with the Sponsor, in accordance with GCP and the applicable regulatory guidelines. Sponsors will be requested to supply copies of any audit reports of hosted studies to the R&D office for oversight.

To ensure that the research quality of projects hosted at the UHB is in accordance with the Research Governance Framework (RGF), the Medicines for Human Use (Clinical Trials) Regulations 2004 (and subsequent amendments) where applicable and Good Clinical Practice, the R&D department require CI/PIs to self complete a Research Audit Tool for non commercial CTIMPs studies on an annual basis.

2.2 Audit Preparation

The auditor will draft an audit plan using a template (see Appendix 1) and develop audit tools (questionnaire and checklists) according to the aim of the

audit. The audit activities to be undertaken will be proportionate to the risks associated with the study.

The audit plan will:

- Define scope and objectives for audit
- Provide timelines for audit conduct
- Identify where and when the audit will take place
- Identify requirements to be audited against
- Identify areas to be audited
- List documents and records to be reviewed.
- List responsibilities i.e. list who is responsible for each stage of the audit process.

The study documentation contained within the R&D study file and ReDA will be reviewed ahead of the audit. If any issues highlighted from this review these should be discussed with the research team at the audit meeting.

The auditor should contact the CI/PI (as applicable) to arrange a convenient appointment and ensure they are aware of the documents which will be required at the audit (e.g. hospital notes, TMF and completed case report forms). Generally four weeks notice will be given in order to allow time for preparation, unless the audit is “for cause”.

If an externally sponsored study is to be audited the sponsor should be contacted by the auditor to inform them the audit is to take place.

2.3 Audit Activities

The auditor will need to meet the appropriate members of the research team by way of an opening meeting to inform them of the remit of the audit and also to ask any relevant questions to address the audit aim.

The auditor should review the study documentation and complete the audit checklist, according to the audit remit as outlined in the audit plan. The review should consist of (but not exclusive to):

- review of the Trial Master/ Investigator Site File
- adherence to study specific and UHB SOPs
- review of consent process
- adherence to protocol e.g. inclusion/exclusion criteria
- research team – delegation log, training, honorary contracts
- event reporting (amendments, adverse events, serious breaches of protocol)
- progress with recruitment

Once the audit is complete, the auditor will provide verbal feedback to the study team. The CI/PI is expected to be present if the findings are critical or major. Any serious breaches in GCP or the study protocol identified during audit should be reported to the Sponsor as described in the UHB notification of serious breaches of GCP or the study protocol SOP.

2.4 Reporting

After the visit, the auditor will prepare an audit report (Appendix 2**).** All findings identified during the audit will be documented and categorised as follows:-

- CRITICAL - where non compliance with GCP standards is affecting the integrity of the clinical trial or patient safety and immediate corrective action is required.
- MAJOR - Where non compliance with GCP standards has the potential to affect the clinical trial or patient safety if not corrected in a timely fashion
- OTHER- minor non compliances with no significant impact on the outcome of the trial or patient safety.

The audit report will be discussed with the lead manager for audit in R&D and the categorisation of findings identified during the audit agreed. The auditor will aim to send the report to the CI/PI and clinical trial pharmacist (if applicable) within two weeks of the audit. The report should be reviewed and agreed by the investigator. If however a critical non-compliance is identified the auditor will forward an initial report within 48 hours to the R&D Manager and R&D Director for review and agreement of the proposed CAPA plan. This is to ensure the CAPA plan to address the critical non-compliance can be implemented as soon as possible.

It is the CI/PI's responsibility to ensure action is taken to correct any identified gaps in compliance. If any advice or assistance is required the auditor will be able to help with this. The CI/PI and clinical trial pharmacist (if applicable) is expected to respond to the audit report within 1 month and corrective actions made within an agreed time frame. The auditor should ensure that the agreed actions have been completed. When all actions have been completed the auditor will inform all parties in writing that the audit is complete.

A copy of the final audit report should be filed electronically in the R&D study file. The final audit report will be copied to the relevant Directorate R&D Lead and sponsor (if applicable).

2.5 Follow up/Escalation

Where there are one or more critical findings or multiple major findings a meeting will be arranged with the research team to ensure appropriate corrective and preventative actions are implemented.

The auditor should follow up with the CI/PI and clinical trial pharmacist (if applicable) to ensure the actions have been completed in the agreed timescales. A follow up visit will be scheduled if appropriate to ensure corrective actions have been taken.

Evidence of continued non-compliance or failure to address the audit findings in the agreed timelines will be escalated to the R&D Director. Failure to complete CAPAs within the agreed timescales will be escalated through the Research Governance Group, and may be considered as possible research misconduct. If the non compliance is deemed to be research misconduct then such cases will be managed using the Research Misconduct SOP (UHB 145)

A summary of key findings will be presented to the Research Governance Group.

2.6 For-cause audit

Where there are concerns in relation to the conduct of a study a for-cause audit may be required as part of an investigation to better understand the root of the concern(s). Incidents, serious breaches of GCP, internal/external audits or inspections may also prompt for-cause audits of other studies within the investigator's portfolio of research. Findings from the for-cause audit may help to establish the extent of the concern.

The process outlined in sections 2.2 Audit Preparation, 2.3 Audit Activities, 2.4. Reporting and 2.5 Follow up/Escalation as above should be followed.

3. TRAINING

Education and support should be available from the UHB R&D Office for researchers who are involved in conducting clinical research studies. UHB R&D Office staff should receive relevant training (internal and external as necessary) in order for them to become competent auditors.

4. IMPLEMENTATION

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

5. 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.

6. REVIEW

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

7. REFERENCES

Research Governance Framework for Health and Social Care in Wales (2nd Edition).

UK Clinical Trials (Medicines for Human Use) Regulations 2004 (and subsequent amendments)

ICH GCP Guideline E6 (R2) dated 9 Nov 2016

8. RELATED SOPs and DOCUMENTS

Managing Breaches of GCP or the Study Protocol, SOP (UHB 235)

Investigating and Handling Allegations of Research Misconduct Misconduct, SOP (UHB 145)

Applying for Cardiff and Vale NHS University Health Board Sponsorship Guideline - GR-RG-008

9. APPENDICES

Appendix 1- Example Audit Plan

Objectives
The objective of this audit is to ensure compliance with <if IMP study> Medicines for Human Use (Clinical Trials) Directive 2004, incorporating amendments (2006) from the EU Directive 2005/28/EC on GCP <if non-IMP study> Research Governance Framework for Health and Social Care, 2nd edition. For all studies, we will be looking for adherence to Good Clinical Practice as outlined in the ICH Harmonised Tripartite Guideline for Good Clinical Practice. The final audit report will document findings against these guidelines.

Project Title
R&D Ref No:
PI
Type of study
Clinical trial IMP
Audit site
Date of audit

Essential documents to be available during the audit

- Protocol
- Consent form and Participant Information Sheets
- Ethics approvals and correspondence
- R&D approval and correspondence
- Regulatory approvals and correspondence (eg MHRA, GTAC etc) (IMP study only)
- General Study Correspondence.
- Training documents
- SOPs
- Serious Adverse Events reports
- Pharmacy/Product-Related (IMP study only)
- Monitoring and Audit documentation
- Source data (i.e. patient notes)

Audit Timeline

On the day, the auditor(s) will introduce themselves and explain the planned procedure for the day. It would be useful if a separate room could be organised for the auditors to review the documents. The patient notes as requested by the auditor must be made available for source data verification.

Once the audit is complete, the auditor(s) will briefly go through the findings with the study personnel, and PI if present. A formal report will be provided within two weeks of the audit.

The CI/PI and clinical trial pharmacist (if applicable) is expected to respond to the audit report within 1 month and corrective actions made within an agreed time frame. The auditor should ensure that the agreed actions have been completed. When all actions have been completed the auditor will inform all parties in writing that the audit is complete.

Appendix 2 – Example Audit Report Template

RESEARCH GOVERNANCE AUDIT REPORT

TRIAL DETAILS			
R & D Reference: Trial Name: IRAS: EudraCT no: Sponsor:			
Principal Investigator:			
Date of audit:			
Trial personnel present:	Auditor:		

1. APPROVALS (auditor check of R&D records prior to site audit)	Yes	No	Comment
Ethical Approval			
a. Is there a record of full approval from the main REC?			
b. If the study has been amended has REC been granted for substantial amendments?			
MHRA Approval			
c. Is there a record of full approval from the MHRA?			
d. Have all substantial amendments been notified to and received approval from the MHRA?			
R&D Approval			
e. Is there a record of initial R&D approval? f. Have all applicable amendments been notified to and received approval by R&D?			
Comments			

2. TRIAL STAFF	Yes	No	N/A
a. Has R&D received a copy of the study delegation log prior to audit ?			
b. Do all members of the trial team listed on the delegation log have evidence of up to date GCP			
c. Do all members of the research team who have access to patients, their organs, tissues, data or access to NHS staff, information and facilities hold an in date UHB employment, contract/ UHB NHS honorary contract, honorary research contract or letter of access?			
Comments:			

3. RECRUITMENT STATUS

	Total
Planned	
Screened	
Excluded	

	Total
Enrolled	
Completed	
Ongoing	

Comments:

4. DATA PROTECTION	Yes	No	N/A
a. Are the paper records stored in a locked filing cabinet?			
b. Is all personal information held on a secure server?			
c. Is study data stored on a password protected computer?			
d. If yes to the question c above, is there a list of people with passwords?			
e. Is all personal information anonymised as early in the study as possible?			

Comments:

5. CONSENT-10% of patient medical records will be audited to ensure compliance. However a minimum of 5 patient medical records will be audited in all cases.	Yes	No	N/A
a. Is there a full record of all research participants' written informed consent and/or where appropriate written carer assent?			
b. Is a copy of the consent form and PIL always placed in the patients' medical notes?			
c. If a protocol amendment necessitated a re-consenting process was this done in a timely manner for example at the next visit as defined in the protocol?			
d. If someone takes consent other than the Principal Investigator is there a clear record of the delegation of this role?			
e. Is there a clear documented record of consent training for any individual who does not obtain consent as part of their normal duties?			
f. Is there a system in place for ensuring that the current approved information sheet and consent form is used?			
g. Has current out of hours contact information been provided to patients?			
h. Does all material given to patients have ethical and R&D approval to be used?			
i. Has the GP has been informed of the participants' involvement in the study if applicable?			

Comments:

6. SAFETY	Yes	No	N/A

a. Have any SAEs/SUSARs been recorded?			
b. Are all reported SAEs/SUSARs verifiable against source documents?			
c. Have all SAEs/SUSARs been reported within the required timelines to the Sponsor and R&D office			
d. Have any serious breaches of GCP or the study protocol been identified at this site?			
e. Have safety and progress reports been submitted to the NHS Research Ethics Committee and MHRA (if applicable)			

Comments:

ACTIONS IDENTIFIED

Action Points	Who	Completed	Ongoing

SUMMARY OF FINDINGS AND CLASSIFICATION

CRITICAL - where non compliance with GCP standards is affecting the integrity of the clinical trial or patient safety and immediate corrective action is required.

MAJOR - Where non compliance with GCP standards has the potential to affect the clinical trial or patient safety if not corrected in a timely fashion

OTHER- minor non compliances with no significant impact on the outcome of the trial or patient safety.

Author of report

Name:

Signature:	Date:

The signed report is to be filed in the R&D Study file, copy to PI and pharmacy if applicable

Table 1- INVESTIGATOR SITE FILE CONTENTS- * see comments below			
Before Clinical Phase of Trial Commences	**Yes**	**No**	**N/A**
1. Investigator's Brochure or Summary of Product Characteristics			
2. Signed current Protocol (including amendments if any) and Sample CRF			
3. Sample Patient Information 4. Informed Consent Form 5. Information Sheet 6. Other written information			
7. Financial aspects of trial (as detailed in agreements)			
8. Insurance statement			
9. Signed agreement between UHB and Sponsor			
10. Signed Agreement between UHB and Investigator (COMA)			
11. Research Ethics Committee approval and REC composition			
12. MHRA approval			
13. R&D approval			
14. CV s and/or other documents evidencing qualifications of CI/PI and research team			
15. GCP Training Certificates			
16. Normal values/ranges for procedures and/or tests included in the protocol			
17. Laboratory Accreditation Certificates			
18. Record of protocol specific training received by research team			
19. Medical/lab/technical procedures/tests SOPs			
20. Instructions for handling IMP and trial-related materials			
21. Decoding procedures for blinded trial			
22. Trial initiation and HQAV reports			
During the Trial	**Yes**	**No**	**N/A**
1. Investigator Brochure or SPC updates			
2. Dated, documented approval from REC of revisions to: Protocol/amendments and CRF 3. Informed Consent Form 4. Additional written subject info			
5. Regulatory Authority approvals/notifications where required for protocol amendments and other documents			
6. CVs for any new investigator and sub-investigators			
7. Updates to normal value(s)/ranges for medical/laboratory 8. technical procedures tests included in the protocol			
9. Updates of medical/laboratory/technical procedures/tests			
10. Relevant Communications 11. Letters			

12. Meeting Notes 13. Notes of telephone calls			
14. Signed Informed Consent Forms			
15. Signed, dated and completed case report forms (CRF)			
16. Notification by originating investigator to sponsor of serious adverse events and related reports			
17. Notification by Sponsor and/or investigator where applicable, to regulatory authorities and REC of unexpected serious adverse drug reactions and of other safety information			
18. Notification by Sponsor to investigators of safety information			
19. Interim or annual reports to REC and authorities			
20. Subject Screening Log			
21. Subject Identification Code list			
22. Investigational product accountability at the site *(if accountability done by pharmacy please complete as n/a)*			
23. Delegation Log/Signature Sheet			
24. Record of retained body fluids/tissues sample if any			
25. Monitoring visit reports			
On Completion /Termination of the Trial	**Yes**	**No**	**N/A**
1. Investigational Product Accountability at Site *(if accountability done by pharmacy please complete as n/a)*			
2. Completed Subject Identification Code List			
3. Final report to REC and MHRA			
4. Close down Visit report			
5. Clinical Study Report			
Comments: .			