RD&I	NHS University Hospitals Plymouth NHS Trust **STANDARD OPERATING PROCEDURE**

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Researcher Audit Guidance

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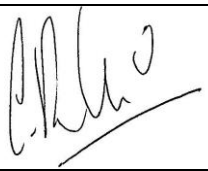
Signature:	
Date:	21st Jan 2019

1 Purpose and Scope

To describe the procedures relating to the preparation of the study site, prior to the conduct of a site audit by a Sponsor.

An audit is a systematic and independent examination of trial-related activities and documents that determines whether a trial or its related activities were conducted, and the data recorded, analysed and accurately reported according to the protocol, Sponsor's SOPs, UK Policy Framework for Health and Social Care Research (2017), Good Clinical Practice, and the applicable regulatory requirement(s).

Who will perform the Audit?
A member(s) of the Sponsor's staff, trained in audit, will undertake an audit which may either be routine or for cause audits. The auditors must be independent of the Sponsor's staff responsible for setting up and managing the clinical trial program. Commonly, the Sponsor may contract out audit to an external reviewer.

The investigator should try to discover:

a) whether the audit is for cause or whether it is a routine audit;

b) the research study that will be audited;

c) the number of auditors in attendance and if possible their names and titles; and

d) whether it is possible to obtain the medical records of patients for the study in question.

The Audit Timetable
The Sponsor / Auditor will inform the Study Monitor that an audit is to take place with a suggested date and agenda. The Monitor immediately informs the Investigator. Alternatively, the Sponsor / Auditor may contact the Investigator directly to inform him/her that an audit is to take place.

Once the audit date has been agreed, the Monitor may contact the Investigator or his/her Clinical Trial Manager (CTM) to make an appointment for a pre-audit visit at the study site. If a pre-audit visit is scheduled, during the visit, the Monitor will give the Investigator a full briefing regarding what will happen on the day of the audit and who needs to be present.

Note: The Monitor is also being assessed and so will also want to ensure that the study is going well, the protocol is being followed, the Case Report Forms (CRFs) are properly completed and up-to-date, and that the study files are all in order.

If a pre audit visit is not conducted, it is recommended that the monitor schedule a teleconference with the PI and his team in order to review the agenda and the audit process.

In scope: research hosted by, and/or sponsored by UHPNT.

Definitions

PI	Principal Investigators
CI	Chief Investigator
CTIMP	Clinical Trial of an Investigational Medicinal Product
CRF	Case Report Form - is the data collection tool used by a study sponsor of a clinical trial to collect data from each trial participant. All data on each participant in a clinical trial are held and/or documented in the CRF, including adverse events. The data is normally held in a pseudonymised format i.e. a name is replaced with a unique participant study number.
GCP	Good Clinical Practice
ECG	ElectroCardioGram
GP	General Practitioner
HCA	Health Care Assistants
Audit	A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s).
Audit Report	A written evaluation by the sponsor's auditor of the results of the audit.
Audit Trail	Documentation that allows reconstruction of the course of events
HRA	Health Research Authority
MHRA	Medicines and Healthcare products Regulatory Agency
REC	Research Ethics Committee
RD&I	Research Development & Innovation
RO	Research Office
SOP	Standard Operating Procedure
UHPNT	University Hospitals Plymouth NHS Trust

2 Who should read this document?

All staff involved in conducting research e.g. Chief Investigators (CI), Principal Investigators (PI), Research Nurses & Midwives, Health Care Assistants (HCA), RD&I Managers and Clinical Trial Administrative staff

3 Procedure to Follow

3.0 Responsibility

Under the UK Policy Framework for Health and Social Care Research (2017), a legal Sponsor organisation is an institution that takes responsibility for initiation, management and/or financing of a clinical trial.

3.1 Role of the auditor

It is the auditor's primary role to collect evidence of research practice and compare it against the requirements of Research Governance, Good Clinical Practice and applicable regulatory requirement(s). The auditor is responsible for documenting observations and conclusions, safeguarding audit documents, records and reports, assessing whether requirements are being met, and developing reports incorporating recommendations for change or adherence.

3.2 Auditor Qualifications

The auditor should be independent to the research team/research systems to conduct audits appropriately. An auditor should be qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented (ICH GCP 5.19.2).

Audit of a trial can be initiated at any stage during the trial process, that is, from the time of RD&I approval to open a trial until the time the sponsor gives approval for the archived trial data to be destroyed.

3.3 Prior to the Audit

The Investigator associated with the study should notify personnel who need to be aware that an audit is to take place. The following provides an example of who may need to be informed:

- Department Head
- Co-investigator(s)
- Clinical Trial Manager / Research Nurse or Midwife
- Study Administrator
- Pharmacy
- Laboratory
- Technical Departments (X-Ray, ECG, etc.)

- Medical Records Personnel

The Investigator should call a meeting of those involved to ensure that everyone in the team is aware of the following:

- That there is to be an audit
- The purpose of the audit
- When the audit is to take place, who should be present, and/or be available.

Conduct a thorough review of the following prior to the audit:

- Study Procedures
- Study Protocol
- CRFs
- Source Data
- Study Documentation
- Study Status
- SAEs
- Protocol Deviations

3.4 Preparation for the Audit

The purpose of a sponsor's audit is to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements (ICH-GCP 5.19.1).

Compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements, verification and assurance that the well-being, rights, and safety of trial subjects are protected, and that the clinical trial data are credible and have good quality, should be an ongoing effort throughout the study. Considering this, the study site should be ready for sponsor audits at any time.

Therefore, the preparation for an audit should have the main purpose of double checking if everything is ready and well-organized in order to facilitate the audit process.

a) Check that suitable facilities are made available for the Auditor. The Auditor will need to have an office or a quiet area in which to work, meet people and examine records. The Auditor may request that the monitor or someone else be with him during the audit to help with translations. Access to a photocopier may also be a necessary requirement. Ensure that all the requested documentation is available for the Auditor.

b) Ensure that all trial team personnel are available on the day of the audit.

c) Ensure that the Investigator Site File (ISF) is up to date:
    - Make sure that you have a copy of the most recent Investigator's Brochure (if applicable) and a signed copy of the final protocol, including any protocol amendments.

- Locate the letter of approval from the Research Ethics Committee (REC) and check that it refers to the final version of the protocol for the study.
- Identify any protocol amendments and locate the REC approval letters for these. Record dates of implementation of each protocol amendment and check that the date supersedes the date of approval.
- Check that there is documentation to confirm that any other information required by the REC has been supplied e.g. notification of Serious Unexpected Adverse Events.

d) Ensure the list of study personnel/delegation of responsibilities is up to date, accurately reflects all personnel who have been involved in the study regardless of how minor their roles were, and the activities they performed in the trial match the activities the PI delegated to them. Check that the *Curriculum Vitae* (CVs) and/or résumés are on file for anyone undertaking assessments, completing CRFs, and/or obtaining informed consent.

e) Ensure that there is documentation of adequate training (e.g., on the protocol, specific assessments to be performed, etc.) for members of the study team (all team members should have signed off on the study specific training log in the ISF that they have read the study protocol for example).

f) Make sure that the log of subjects enrolled in the study is up to date and complete. If a log of subjects screened is being kept, make sure that this is also current.

g) Inspect all completed informed consent forms and check that these have been signed and dated by the subject (or the subject's legal representative) and the person taking consent. Check that the date of the consent is prior to any study-related procedures.

h) Review the eligibility criteria for all subjects who have entered the study. Make detailed notes regarding any subject who does not satisfy the study inclusion criteria and verify if authorization was given by the sponsor to enrol such patients, and that the REC was informed of the protocol deviation.

i) Check that each CRF has been fully completed and that all data are legible.

j) Check the CRFs for inconsistencies regarding medical history, diagnoses, concomitant medications and dates of visits.

Verify that all corrections in the CRF have been signed and dated. Where the reason for the correction is not obvious, provide a brief explanation.

k) For each subject in the study, check the files and records etc. for evidence of Adverse Events (AEs) and ensure that details of all Adverse Events have been recorded in the CRF.

Together with the Monitors on an ongoing basis throughout the trial, the sites should determine whether or not the AEs observed are defined as serious. They

should refer to the protocol for AE definitions and ensure that all Serious Adverse Events are reported to the Sponsor.

Confirm that there is no outstanding documentation relating to any Adverse Events and check that all events have been followed up adequately.

l) If drug accountability is being undertaken by the Investigator, check that all medication packs are accounted for.

If a pharmacy is dispensing medications and/or drugs, visit the pharmacy and ensure that dispensing and return records are complete and available.

m) Ensure the Investigator and each member of the study team are aware that the Auditor will be looking for evidence that each person dealing with the study, particularly the Investigator, can clearly identify the extent of their knowledge and degree of participation throughout the whole study.

3.5 **During the Audit**

The Auditor enters his/her name and the date(s) of the audit on the Site Monitoring Log located in the ISF.

a) Initial Meeting - The Auditor meets with the PI, CTM, and other important study site staff for a general discussion/ overview of the study, which may include the following items:

- Purpose of the audit.
- Site infrastructure, ongoing studies, and capacity.
- Availability of site SOPs.
- Investigational product receipt, storage, and dispensing procedures.
- Site's source documentation/medical charting process and the location of study documents.

b) The Auditor may request a facility tour to view examination rooms, testing equipment, and investigational product storage area.

c) Most Auditors will conduct the site audit, mainly working with the CTM and sometimes they will also request to speak with the investigators. The Auditor normally asks questions and seeks clarification if there is uncertainty about any aspect of the site's files and/or procedures. Many issues may be misunderstandings rather than actual deficiencies.

d) The Auditor will probably review:

- Enrolment status.
- Investigator Site File - Essential documents are verified for completeness and compliance with GCP guidelines and local regulations.

- Subject's Records - The records are reviewed in detail, comparing CRFs with source documentation to ensure that information is complete and accurate, and verifying that evaluations are performed according to the protocol. The auditor will verify that the patients reviewed meet all protocol inclusion/exclusion criteria, and that any deviation has been informed to the sponsor and REC. The auditor will also review the Informed Consent Forms (ICFs) in detail to ensure the ICFs used have been approved by the REC, and that the informed consent process was correctly performed and documented. The investigational drug records, accountability, storage will probably be reviewed as well.

e) Closure meeting: the Auditor will meet with the PI, CTM, and any other important study site staff to discuss general observations and findings during the audit, and also to inform the site of the next steps after the audit.

3.6 Audit Findings

Once the practical audit has been completed the Facilitator will develop a summary and make preliminary recommendations to assist with research conduct.

The Facilitator will:

- List any gaps in compliance with any supporting evidence
- Cross-reference with regulatory requirements

3.6.1 Grading of findings

Monitoring visit findings are graded using the following criteria:

Critical: a finding defined as one with the capacity to directly undermine the integrity of the entire study. For example findings:

- where evidence exists that the safety, wellbeing, rights or confidentiality of study subjects has been (or has had significant potential to be) jeopardised.
- where reason has been found to cast serious doubt upon the accuracy and/or credibility of study data.
- where approval for the study has not been sought from one or more regulatory agency/body or granted from one or more regulatory agency/body (e.g. Ethics committee, MHRA) but the study has commenced regardless.
- where procedures not covered/included on the consent form are being performed or where new procedures have been introduced into the study protocol but where participants who had consented prior to their introduction have not been asked to re-consent.
- where following study approval, significant amendments have been made to the study protocol or documentation but no new request for approval has been submitted.

Major: A finding defined as one that compromises the integrity of a certain component(s) of the study, for example:

- where there has been failure to comply with the regulatory requirements e.g. failure to assess and report SAEs and/or SUSARs accurately and to the correct bodies.
- where there has been a significant unjustified departure from GCP e.g. failure to provide participants with a copy of their consent form or Participant Information Sheet.

Other: Any other inspection findings, defined as those where the integrity of the study is not directly compromised but which represent an absence of due diligence on behalf of study staff towards the conduct of the study. For example findings:

- which demonstrate that no definite document management/organisation processes are in place at site / no investigator site file exists.
- where there has been failure by study staff to inform the relevant authorities of amendments to start and stop dates or study specific documents.

3.7 Audit Results

Where there are many areas of improvement to develop, the Facilitator and/or RGM will arrange a meeting with relevant research staff to discuss the recommendations or gaps in compliance. This can be used to develop solutions to any problems identified through the audit.

3.8 Corrective and Preventative Action Plan (CAPA)

After receipt of the Audit report, the Research Facilitator and/or RGM will review the report and compile with the research team a CAPA to address any audit findings, this will which will be disseminated to the Chief/Principal Investigator and study team for auctioning.

The CAPA will include:

- A list of identified gaps in compliance
- Any corrective measures that can be taken
- Preventative actions in the form of recommendations for change in practice to conform to regulation
- A date for completion of actions

3.9 Follow-up actions

It is the Chief Investigator's responsibility to ensure action is taken to correct any identified gaps in regulation compliance. If any advice or assistance is required the Research Facilitator will be able to help with this.

4 Document Ratification Process

The review period for this document is set as ***default of three*** years from the date it was last ratified, or earlier if developments within or external to the Trust indicate the need for a significant revision to the procedures described.

This document will be approved by the ***RD&I Manager or their Deputy***.

Non-significant amendments to this document may be made, under delegated authority from ***a Senior RD&I manager***, by the nominated author. These must be ratified by ***a Senior RD&I manager***.

Significant reviews and revisions to this document will include a consultation with ***appropriately knowledgeable staff***. For non-significant amendments, informal consultation will be restricted to ***staff*** who are directly affected by the proposed changes.

Dissemination and implementation

4.1. Dissemination of this SOP

4.1.1. New SOPs and new versions of existing SOPs: The Research Governance Manager will be responsible for ensuring authorised SOPs are uploaded on the RD&I intranet site. Internal Trust Staff are expected to use the RD&I intranet site to access latest versions of SOPs and to check the website regularly for updates.

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

- Inclusion in the Trust weekly e-bulletin Vital Signs
- Direct email to Trust Researchers and or teams

4.2. Training in this SOP

4.2.1. All staff whose activities are subject to this SOP should ensure that they read and understand the content of the SOP.

5 Reference material

ICH E6 Good Clinical Practice (GCP) and subsequent addendums.
http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

Appendix: Example of an Audit Appointment Letter to Investigator — Appendix 1

Dr. Name

Address

Date

Dear Dr. Name,

As an investigator participating in the [protocol/study name], your site has been selected for an audit by [Sponsor name].

As the Sponsor of the study, [Sponsor name] maintains a confidential compliance program for of its clinical trials. This program is part of the [Sponsor name] to assure compliance with corporate policies and protocols, as well as current local regulatory directives, law, guidelines and ethical considerations of the Declaration of Helsinki.

It is our intention that the compliance assurance-audit process be mutually beneficial to you and to [Sponsor name]. The MHRA and other Regulatory Authorities often inspect Investigators who have contributed to the conduct of "pivotal" studies. Our audit will also serve to help you be prepared in the event of such an inspection.

During the next few weeks I will telephone you or your study coordinator to arrange an appointment to visit your facility. During my visit, it would be helpful if a clinical trial manager / research nurse could be available to take me on a tour of your facility, and answer questions regarding patients' charts and the conduct of the study at your site. I will need access to the study medication and any equipment used during the conduct of the study.

Please have the following available for review:

Investigator's site files containing required study documents including:

1. Investigator's Brochure.
2. Final approved protocol and amendments.
3. Protocol agreement.
4. REC approval documents.
5. Investigator and Co-investigator curriculum vitae.
6. Laboratory normal ranges and certification, if applicable.
7. Case report forms, patient charts and medical records, source documents, signed consent forms, reports of deaths and serious adverse events, patient assignment sheets and correspondence with monitors, where applicable.
8. All records pertaining to the blinding, receipt, dispensing and return of the study drug.

I would also like to request a brief meeting with you and your investigational team at the conclusion of the audit to discuss the findings.

Thank you in advance for your cooperation and preparation. Should you have any questions about my visit to your office, please feel free to contact me by phone [telephone number], fax [fax number] or email [email address].

Confirmation of my visit date and time will be sent by fax and email prior to the audit.

Yours sincerely,

[Auditor's Name]

[Title]

Audit No.

6 Amendment History

Version Number:	Jan 2019
Date Of Amendment:	2.1
Details Of Amendment:	Updated Trust and Dept. name. Reduce signature requirement to single senior RD&I Manager. Updated references to the UK Policy Framework for Health and Social Care Research (2017).

Version Number:	2.0
Date Of Amendment:	Aug 2017
Details Of Amendment:	Updated SOP template and numbering system. Reviewed and updated SOP.