

## University of Hertfordshire

# AUDIT AND INSPECTION

## Clinical Trials Support Network (CTSN)

Standard Operating Procedure for the Audit and Inspection of UH  
sponsored/co-sponsored Clinical Trials

<b>SOP Number:</b> SOP-23-01	<b>Effective Date:</b> 05 June 2018
<b>Version Number:</b> 1.0	<b>Review Date:</b> 3 years (or as required)

### 1. BACKGROUND

This is a University of Hertfordshire standard operating procedure. UH acknowledges WHHT R&D which has allowed UH to use the SOPs developed by WHHT where possible, modified for local implementation.

An audit is:

*“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, analysed and accurately reported according to the protocol, sponsor’s Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirements.” (ICH GCP 1.6)*

Throughout the audit, general information exchange between the auditor and the person(s)/institution being audited is acceptable and essentially is used as an evaluation tool. Any results obtained from an audit should be used to train staff and improve upon the quality of research conducted.

An inspection is:

*“The act by a Competent Authority of conducting an official review of documents, facilities, records, quality assurance arrangements and any other resources that are deemed by the authority to be related to the clinical trial and that may be located at the site of the trial, at the sponsor and/or Contract Research Organisation’s (CRO’s) facilities or at other establishments that the Competent Authority sees fit to inspect”. (ICH 1.29)*

An inspection is a formal process that has legal implications if non-compliance with the regulations is found. It is therefore imperative that all trial related documentation is maintained and continually updated in readiness for an inspection.

Where there are potential conflicts between different collaborating organisations’ SOPs, project level working instructions should be developed, to determine precedence.

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## **2. PURPOSE**

The aim of this Standard Operating Procedure (SOP) is to describe to research staff the process for preparing for an audit or inspection either by the sponsor/co-sponsor, CTSN or by the Competent Authority (CA) for clinical trials that fall under the UK Medicines for Human Use (Clinical Trials) Regulations 2004 (SI 2004/1031) and the European Clinical Trials Directive (EUCTD). The SOP will cover the processes necessary to prepare, host and participate in a regulatory inspection by the Competent Authority.

Both audits and inspections take place to examine 'systems' and look for good control of processes and opportunities for process improvement.

## **3. APPLICABLE TO**

This applies to all staff involved in clinical research sponsored/co-sponsored by UH, including, but limited to: Chief Investigators, Principal Investigators, Research Fellows, Consultants, Statisticians, Clinical Trial Pharmacists, Research Managers, Research Nurses, Clinical Trial Practitioners, Allied Health Professionals, Trial co-ordinators/Managers, Clinical Studies Officers, Data Managers and Research Assistants.

## **4. RESPONSIBILITIES**

The Chief/Principal Investigator, research personnel, and personnel from other departments involved in the audit/inspection such as pharmacy, laboratory (departments should be fore-warned if the inspector intends to visit), should be available to answer questions and to attend the final meeting before the auditor/Inspector leaves the site.

## **5. PROCEDURE**

**Please notify the CTSN of any planned inspections.**

### **WHO?**

The following Personnel, where appropriate, should be available to answer questions and to attend the final meeting before the Inspector leaves the site:

- Chief/Principal Investigator and research personnel
- Personnel from other departments involved in the audit/inspection such as pharmacy, laboratory (departments should be fore-warned if the auditor/inspector intends to visit)

### **WHEN?**

An audit is an informal and planned process and can take place prior to, during or after the patient recruitment phase. An internal audit is often undertaken prior to an external inspection. A regulatory inspection is very often notified, (usually 14 days in Europe), however there are exceptions if the Competent Authority has concerns for patient safety or grounds to suspect that improper practices are occurring at a site. Under these circumstances, a "triggered" inspection will take place whereby inspectors have the legal right of entry to inspect premises at any time without notification.

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**HOW?**

Prior to an inspection taking place a co-ordinator should be appointed to organise and plan the visit. All records must be made available (direct access) for monitors, auditors and regulatory authorities (ICH 4.9.7.) It is important to address the following:

- Identify who will be the 'hosting organisation' (for multicentre trials)
- Establish the name(s) of the inspector(s), the scope of the inspection and agree all dates in advance. It is essential that sufficient notice should be given to those expected to attend the inspection, with dates for availability of all involved agreed well in advance. The hosting co-ordinator should be given a timetable of events and all roles and responsibilities agreed. For commercial trials that have been assigned an external monitor, they will act as a key liaison between the sponsor (if commercial company) and the Investigator's study team, providing support to ensure that the personnel and site are ready for an inspection.
- Identify and book suitable accommodation for the inspection to be conducted in, including space for all trial documents to be reviewed. Ensure that the room is tidy before the inspection.
- Provide photocopying facilities
- Organise refreshments such as tea/coffee/biscuits but no lunch or extras as this can be viewed as an enticement
- Respond to requests for specific documents, visits to specific departments eg labs, pharmacy. Point of note – The FDA have a different approach to auditing. You won't be allowed to give them refreshment, and they have a 20 minute rule. If you cannot produce any documentation or information within 20 minutes of being asked, they will assume that it doesn't exist and will not accept it after this time.
- Provide Inspection training/mock interviews for staff to prepare for an inspection and document in their training records.

An inspector will be looking for a number of things during the inspection process including:

**Essential Documents**

*'...those documents which permit evaluation of the conduct of the trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and the monitor with the standards of GCP and with regulatory requirements' (ICH8.1)*

**Source Data**

- Records should be accurate, complete, legible and timely (ICH4.9.1)
- Data should be consistent with the source documents, or discrepancies explained (ICH 4.9.2)
- Document all deviations from protocol and explain (ICH4.5.3)
- Any changes should be initialled, dated and signed
- Document all dose/therapy modifications, visits and tests not conducted
- Data verification will check CRF's for completeness, looking at data queries, lab results, ECG's, X-rays etc., protocol details/ number in notes, date of birth, vital signs, all visit dates, medical examinations, concomitant medication and changes, adherence to study specific procedures.

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Essential documents should be retained for 2 years following last approval of marketing application in the ICH region (ICH4.9.5).

### **Recorded in patient notes**

- Signed and dated copy of consent form and Patient Information Leaflet
- Record of confirming consent at each visit
- Laboratory results, X-ray results etc. related to participation in the clinical trial
- Title of the trial including the drug to be received
- Visit dates
- Concomitant medicines taken
- Any adverse events
- A letter informing the GP that the patient has been enrolled in the clinical trial

### **Investigator File**

- Approval and correspondence- ethics approval with all correspondence between ethics and Trust, MHRA notification and MREC approval
- Laboratory – normal ranges, reports and procedures
- Documentation – Protocol and amendments (signed and dated), Information leaflet and consent form (all current updated versions), previous version of protocols, indemnity and all correspondence between sponsor and investigator, sample CRF
- Personnel – CV's (signed and dated) of those working on study, training record (such as GCP)
- Drugs – Shipping record, drug receipt (possibly held in pharmacy), sample of labels, accountability, security and dispensing log
- Patient Details – Screening/enrolment/identity logs, randomisation log, SAE reports
- Signed and dated completed Informed Consent Forms (originals)
- Decoding procedure for blinded trials
- Interim or annual reports to Ethics Committee of the trial status
- Any monitoring documentation
- Signature/delegation list

### **It is important that:**

- Documents are up to date, reviewed and staff familiar with location and content
- There is a clear Audit trail
- Relevant documents bear dates and version numbers
- A Tracking log is kept, if documents are updated (evidence of distribution and receipt)
- Patient hospital notes should include up to date annotations, copy of consent form, General Practitioner (GP) letters, laboratory results, X-ray results etc. related to participation in the clinical trial
- There are Pharmacy/drug accountability records

### **Evidence of Compliance**

- SOPs/Guides/Work instructions/trial procedures manuals etc
- Centre Delegation Log - old versions should be kept to reflect past and present staff
- Trial Master Files

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- Investigator Centre Files
- Databases
- Archiving
- Contracts
- Training records/CV's
- SOP's for related departments
- Equipment
- Security
- Emergency out of hours procedures

### Close-out of the inspection

At the end of the inspection a close out meeting will take place and the inspector will provide verbal feedback of the findings, followed by a detailed written inspection report. Each finding will be labelled, 'Critical, major, minor or For Note'. Each finding is referred to the particular regulation/guideline to which it is attributed. **A reply to the report is required.**

Dissemination of Inspection findings should be used to evaluate research practices and assist in staff training. Improving upon the quality of research conducted by implementing solutions to remedy the findings should be a priority after an inspection.

### Systems Audit

A systems audit is an assessment of a sample of clinical trials to verify the compliance of procedures and system set up within UH to conduct clinical trials. The systems audit will identify any deficiencies within the existing system that leads to non-compliance with sponsor, GCP, regulatory and UH requirements.

The audits will be carried out by the CTSN on a selected number of projects based on risk assessment methods.

## 6. RELATED DOCUMENTS

- ICH Harmonised Tripartite guideline for Good Clinical Practice (1996)
- gSOP-06 TMF/Site File
- gSOP-28 Management of Source Data
- gSOP-41 CRF Completion

## 7. APPENDICES

- Appendix 1 – Definitions

## 8. VERSION HISTORY/REVISIONS

Version Number	Effective Date	Reason for Change

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**9. AUTHORSHIP & APPROVAL**

**Author**

**Signature**

**Date**

**Pro-Vice Chancellor (Research & Enterprise) Approval**

**Signature**

**Date**

**10. AGREEMENT**

Please detach and retain in your training files

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**I have read and understood the contents and requirements of this SOP (gSOP-23-01) and accept to follow by UH policies in implementing it.**

<p><b>Recipient</b></p> <p>Signature: .....Date:.....</p> <p>Name &amp; Position: .....</p>
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## Appendix 1 – DEFINITIONS

**Case Record Form (CRF)** - a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject”.

**Chief Investigator (CI)** - A Registered Physician, Dentist, Pharmacist or Registered Nurse who has overall responsibility for the conduct of the trial.

**Clinical Trial** - A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or control) to evaluate the effects of those interventions on health outcomes.

**Clinical Trial of Investigational Medicinal Product (CTIMP)**

A study that looks at the safety or efficacy of a medicine/food stuff/placebo in humans as defined by the Medicines for Human Use Regulations (2004).

**Good Clinical Practice (GCP)** - as defined in the Regulations.

**International Conference on Harmonisation (ICH)** – Produced a series of guidelines in 1996, E6 being the guideline on Good Clinical Practice, otherwise known as (ICH-GCP).

**Investigational Medicinal Products (IMP)** - means a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial. This includes a medicinal product which has a marketing authorisation but is, for the purposes of the trial -

- used or assembled (formulated or packaged) in a way different from the form of the product authorised under the authorisation,
- used for an indication not included in the summary of product characteristics under the authorisation for that product, or
- used to gain further information about the form of that product as authorised under the authorisation

**Principal Investigator (PI)** - A Registered Physician, Dentist, Pharmacist or Registered Nurse who has responsibility for the conduct of the trial at a host site.

**The Medicines & Healthcare products Regulatory Agency (MHRA)** - UK Competent Authority responsible for regulation of clinical trials.

**The Regulations** - Medicines for Human Use (Clinical Trial) Regulations 2004 transposed the EU Clinical Trials Directive into UK legislation, as Statutory Instrument 2004 no 1031. This became effective on the 1st May 2004. An amendment to implement Directive 2005/28/EC was made to the Regulations as Statutory Instrument 2006 no 1928.

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