Dorset HealthCare University NHS Foundation Trust

Standard Operating Procedure for Preparing for and Facilitating a Regulatory (MHRA) Inspection

Objectives	The objective of this SOP is to explain the purpose and facilitation of a Medicines and Healthcare Products Regulation Agency (MHRA) inspection.
Scope	Applicable to all Research & Development staff.
Responsibility	It is the responsibility of the Principal Investigator and research study staff to adhere to this SOP, in liaison with the Chief Investigator.
Related Document	None.

1 Purpose

The purpose of this Standard operating Procedure (SOP) is to explain what to expect from an MHRA inspection of Dorset HealthCare University NHS Foundation Trust research facilities, and how to facilitate the inspection.

2 Introduction

The MHRA is an executive agency of the Department of Health. This body has a routine programme of statutory Good Clinical Practice (GCP) Inspections into the conduct of Clinical Trials of Medicinal Products. The inspections are to measure compliance with the set of internationally recognised Principles for conducting Clinical Trials – Good Clinical Practice (ICH GCP Principles) and to ensure compliance with legal requirements of the EU Clinical Trials Directive (2001/20/EC) which has been transposed into UK law by the Medicines for Human Use (Clinical Trials) Regulations 2004, and came into force on 1 May 2004. NHS organisations sponsoring and hosting CTIMPs must ensure that systems are in place so that CTIMPs can be managed and conducted in accordance with both the UK Policy Framework for Health & Social Care Research (2017) and the UK Clinical Trials Regulations.

ICH GCP guideline section 1.29 defines inspection as “the act by a regulatory authority of conducting an official review of documents, facilities, records and any other resources that are deemed by the authority to be related to the clinical trial”.

A government agency may review and evaluate a facility and/or a study during a routine or “for cause” inspection. A routine inspection is a periodic inspection to determine compliance with applicable regulations and guidelines. A “for cause” inspection is conducted in response to information that has raised concerns with a clinical trial.

3 Training

Users must read and understand this SOP before carrying out this procedure.

Existing users must read and understand the Revisions section.

4 Revisions

This is the second version of this SOP.

5 Procedure

5.1 Notification of an inspection

The Research & Development Facilitator must be notified immediately of any notification of inspection from the MHRA or an external Sponsor.

They will then notify all relevant Trust personnel, including all departments who are (likely to be) identified for inspection, as appropriate. Such departments might include (but not be limited to):

- Research Team (Clinical Trials Office)
- Pharmacy
- Information & Technology (IT)
- Laboratories
- Medical Records

The Research & Development Facilitator will inform (in writing) all Chief Investigators (CIs) and Principal Investigators (PIs) of the upcoming inspection and instruct them to make suitable preparations for an inspection.

They will also notify in writing all participating sites that are involved in studies chosen for inspection.

In cases where the organisation is being inspected as a participating site, the personnel mentioned above must also be notified immediately.

5.2 Inspection Management

The inspection will be coordinated by the 'Local Coordinator; most likely the Research & Development Facilitator (or other appropriate individual as delegated by the Research & Development Facilitator). Other staff members may be drafted in to provide support as and when required. This designated individual will organise and plan the visit, acting as the point of contact before, during and after the inspection.

The Local Co-ordinator (or other appropriate designee as described above) will establish (and report to all relevant personnel) the name(s) of the inspector(s), the scope of the inspection and negotiate with the lead inspector sufficient notice 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.

This delegated individual will act as the primary contact throughout the inspection process, and coordinate the work of other staff.

5.3 Preparing for an inspection

The Local Co-ordinator (or other delegated individual as described above) will coordinate the collection of the dossier of documents requested by the MHRA prior to inspection following the current MHRA requirements.

Where the organisation is being inspected as a participating site, the external Sponsor will complete the dossier.

The contents of the dossier may include:

- Overview of Trust facilities
- Organisational charts & responsibilities summaries

- Description of archiving arrangements
- List of projects
- Standard Operation Procedures (SOP) index and copies of specific SOPs
- Investigational Medicine product (IMP) management procedures
- Laboratory Procedures
- Quality Assurance (QA) procedures
- Pharmacovigilance procedures
- Clinical Trial Management procedures

The dossier is submitted to the regulatory authority who will reply with an Inspection Plan.

The Research & Development Facilitator or designee will negotiate the inspection plan with the MHRA regarding schedules, timing, visits to facilities, interviews and so on, and shall communicate the final inspection plan to all staff affected by it for specific inspection preparation.

The Local Study Co-ordinator (or other appropriate individual delegated by the Research & Development Facilitator) will organise an inspection pack to include: Trust visitor badges/name badges request form, “confidential” ink stamps, note books and document log templates.

This individual will ensure that one room is available for the sole use of the inspection. Only documentation relevant to the inspection should be available in the room.

This individual will ensure that (if required) each department identified in the inspection plan designates rooms and a main contact person for the inspection.

Prior to inspection all members of each department identified in the plan will carry out a quality check on all relevant documentation and ensure that all files and documents are easily accessible. The Research & Development Facilitator (or delegated individual) will oversee and facilitate this activity as appropriate.

Documentation to be inspected may include:

All Departments

- Trial master or trial site files
- Contracts
- Staff training records, job descriptions and CVs
- Organisational charts
- SOPs
- Computer system validation documents

Investigator site

- Case report forms
- Source documentation
- Patient information sheets and informed consent forms
- Delegation logs

Laboratories

- Lab procedures
- Equipment maintenance and calibration servicing routines

Pharmacy

- Pharmacy trial files
- Pharmacy Procedures
- Drug accountability logs
- Temperature logs
- Drug shipment documents
- QP release certificates (if applicable)

5.4 Initial inspection contact

On arrival at the Trust, the Inspectors will be met by the R&D department and provided with a visitor's identification badge.

The Research & Development Facilitator (or other individual delegated by the Research & Development Facilitator) confirms the identity of the inspectors and the reason for inspection (routine or for cause).

Throughout the inspection at least one member of the R&D Department will:

- accompany the Inspectors when moving around the Trust
- take notes during interviews
- act as 'runner', retrieving and photocopying documents

A pre-inspection (opening) meeting will be held with the Inspectors and all relevant parties to:

- Discuss the agenda and schedule of the inspection to arrange availability of appropriate staff.
- Confirm arrangements for designated inspection rooms.
- Request a de-briefing from the Inspectors at the end of each day to help assess progress, discuss unresolved questions, provide outstanding requested information and plan the next day's agenda.
- Establish timing of exit interview at the end of an inspection

At least one member of the inspected department must accompany the Inspectors at all times.

The Department Manager of the department under inspection must be available to review documentation prior to being provided to Inspectors.

A member of each department must be designated to retrieve and photocopy documents (Runner).

5.5 During an Inspection

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)

An inspector will be looking for a number of things during the inspection process, including, but not limited to:

<u>Source Data</u>

- Records should be accurate, complete, legible and timely (ICH 4.9.1)

- Data should be consistent with the source documents, or discrepancies explained (ICH 4.9.2)
- Document all deviations from protocol and explain (ICH 4.5.3)
- 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.

Recorded in patient notes

- Signed and dated copy of consent form and patient information leaflet
- Documented Consent process
- 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 Files (Trial Master Files and Trial Site Files)

- 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, details of any insurance or indemnity arrangements 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 (likely to be 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
- Comprehensive listing of all essential documents to be kept in a Trials Master File and a Trial Site File are listed in section 8 of ICH GCP E6(R1).

5.6 Documentation Requests

When the Inspectors request documentation for review, the runner notes the document requested on a log and retrieves it for review by the Chief Investigator, Department Manager or R&D staff as appropriate.

The Local Co-ordinator authorises the document as being within the scope and authority of the regulatory authority e.g. SOPs and site and master file documents.

The following documents will not be made available:

- financial information
- audit reports
- personnel records except CVs and training records

The runner will obscure any confidential information e.g. financial information, if required, without defacing the original, a copy will be taken and the runner will stamp 'confidential' on each sheet.

The original document will be returned to the file as soon as possible.

The runner will provide a copy to the reviewer for management review.

If agreed, the runner will provide the document(s) to the inspectors in the designated room.

A duplicate set of all documents given to the inspectors should be maintained.

At the conclusion of the inspection the documentation may be retained by the inspectors.

5.7 Interview requests

When the inspectors request an interview with a Trust employee, as a minimum requirement one member from the R&D Management team (Research & Development Facilitator or designee) must be present at each interview with a staff member.

- The interviewee will assume a friendly, cooperative, confident and professional attitude and will respond in a concise, factual and accurate manner when the inspector asks a relevant question.
- If the interviewee decides that the question is outside their area of expertise or authority or outside the scope of the Inspector's authority they must consult with the R&D representative.
- If an interviewee does not understand the question and/or the context they must ask the inspector for clarification.
- If the interviewee realises they have provided erroneous information they must take immediate corrective action when appropriate and have such an action acknowledged/noted by the inspector.
- The interviewee must not attempt to answer "what if" questions and other hypothetical questions.

5.8 Daily debriefing session

At the close of each day the Inspectors, and members of the Research Management team as appropriate, hold a debriefing session to assess progress, discuss unresolved questions, provide outstanding requested information and plan the next day's agenda.

The designee from the R&D department disseminates the outcomes of the daily debriefing sessions as appropriate.

5.9 Close-out of the inspection

A close-out meeting will be scheduled at the end of the inspection with the Inspector(s) and appropriate R&D team members. Those departments and studies directly involved with the inspection will also be invited to attend.

The inspectors will provide verbal feedback summarising observations and findings made during the inspection.

The Trust representatives must ensure that there is a clear understanding of the findings and also ensure that any erroneous findings are corrected at the time.

A date when a report can be expected and when the Trust is expected to respond will be confirmed.

Investigators and Departmental Managers, where appropriate, will provide feedback from the close out meetings to their teams with input from the Research & Development Facilitator or Research Monitor where appropriate.

5.10 Inspection reports

On receipt of the Regulatory Authority Inspection report the Research & Development Facilitator (or appropriate designee) will work with the Manager of each department and Investigators identified to provide an appropriate response to address the observations within the time frame provided.

The final MHRA report is reviewed, agreed and signed off by the Research & Development Facilitator (and Chief Investigator where required), and is sent to the Regulatory Authority.

The Research & Development Facilitator and Research Monitor (or other appropriate designee) will manage the strategy to address the findings with the MHRA report.

The MHRA inspection certificate is filed as appropriate in the R&D Department.

6 Appendices

There are no appendices to this SOP.

7 Responsibilities

Chief Investigator/Principal Investigator/Research Team – will be available for interviews and make available relevant documentation to the inspectors

The nominated Local Co-ordinator – will liaise with the inspectors regarding the regulatory inspection, communicate necessary information to relevant parties, and organise and plan the inspection. In absence of a research monitor, this role will be delegated to an appropriate member of the research team, for example the Lead Research Nurse.

The Research & Development Facilitator will be called upon if required.

The Local Co-ordinator will coordinate the collection of documents for the dossier, and organise and plan the inspection together with the Research & Development Facilitator.

Regulatory Inspectors – will undertake an inspection following their own SOPs, legislation and directives

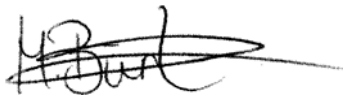
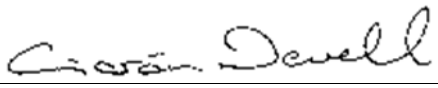
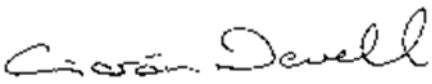
Runner – will prepare relevant documentation as requested by the inspectors

R&D staff – will take notes at inspector interviews

8 Review

This SOP should be reviewed every two years unless new guidance or legislation dictates a review any sooner.

Date reviewed: 12/04/19 Date of next review: 12/04/21

Written By	Signature	Date
Hazel Burt		12/04/19
Reviewed By	Signature	Date
Dr Ciarán Newell		12/04/19
Authorised By	Signature	Date
Dr Ciarán Newell		12/04/19