

STANDARD OPERATING PROCEDURE

**Preparing for and facilitating a Regulatory (MHRA)
Inspection**

R&D/S/021/1.0

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Preparing for and facilitating a Regulatory (MHRA) Inspection

1. **PURPOSE AND SCOPE**

The MHRA (Medicines and Healthcare Products Regulation Agency) 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, their amendments. 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 Research Governance Framework (2005) 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.

This SOP seeks to explain the procedure for facilitating such an inspection.

2. **ASSOCIATED DOCUMENTS**

This SOP is to be read and followed through in conjunction with all R&D SOPs and policies and procedures, and the current guidance notes provided by the Competent Authority (MHRA) on their relevant web-pages.

3. **RESPONSIBILITIES**

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

R&D Manager – will liaise with the inspectors regarding the regulatory inspection, communicate necessary information to relevant parties, and organise and plan the inspection

Inspection Readiness Group – will coordinate the inspection process

CTO Assistant Director – will coordinate the collection of documents for the dossier, and organise and plan the inspection with the R&D Manager

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 Department staff – will take notes at inspector interviews

Preparing for and facilitating a Regulatory (MHRA) Inspection**4. PROCEDURES****4.1 Notification of an inspection**

- 4.1.1 The R&D Manager must be notified immediately of any notification of inspection from the MHRA.
- 4.1.2 The R&D Manager will notify the R&D Director, CTO Director and the CTO Assistant Director. The R&D Manager also informs the Deputy Divisional Directors responsible for research governance within their respective divisions and staff of the R&D Department.
- 4.1.3 The R&D Manager informs all departments who are (likely to be) identified for inspection, as appropriate.

Such departments might include (but not be limited to):

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

- 4.1.4 The R&D Manager informs (in writing) all Chief Investigators (CIs) of the upcoming inspection and instructs the CIs to make suitable preparations for an inspection.
- 4.1.5 The R&D Manager will notify all the participating sites in writing of the inspection and will contact any participating sites that are involved in studies chosen for inspection.

4.2 Inspection Management

- 4.2.1 The inspection will be coordinated by the Inspection Readiness Group (who oversees the Trust's preparation for routine GCP inspection), which will be chaired by the R&D Director and will consist of the R&D Manager, CTO Director and CTO Assistant Director. Other staff members may be drafted in to support the group as and when required.
- 4.2.2 The CTO Assistant Director (in conjunction with the R&D Manager) will be appointed to organise and plan the visit.
- 4.2.3 In the first instance the R&D Manager will establish (and report to the group) 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.

The R&D Manager (in conjunction with the CTO Assistant Director) will act as the primary contact(s) throughout the inspection process, and coordinate the work of other R&D staff.

4.3 Preparation for an inspection

- 4.3.1 The CTO Assistant Director coordinates the collection of the dossier of documents requested by the MHRA prior to inspection following the current MHRA requirements. The contents of the dossier may include:

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- 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
- 4.3.2 The dossier is submitted to the regulatory authority who will reply with an Inspection Plan.
- 4.3.3 The R&D Manager or CTO Assistant Director shall 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.
- 4.3.4 The R&D Administrator organises an inspection pack to include: name badges, "confidential" ink stamps, note books and document log templates.
- 4.3.5 The R&D Manager 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.
- 4.3.6 The R&D Manager will ensure that (if required) each department identified in the inspection plan designates rooms and a main contact person for the inspection.
- 4.3.7 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 R&D Manager and the CTO Assistant Director 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

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- Equipment maintenance and calibration servicing routines

Pharmacy

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

4.4 Initial inspection contact

4.4.1 On arrival at the R&D Department the Inspectors will be provided with a visitor's identification badge.

4.4.2 The R&D Manager confirms the identity of the Inspectors and the reason for inspection (routine or for cause).

4.4.3 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

4.4.4 A pre-inspection meeting is held with the Inspectors and the Inspection Readiness Group to discuss:

- The agenda and schedule of the inspection to arrange availability of appropriate staff.
- 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

4.4.5 An opening meeting will be held involving all relevant parties. This meeting will discuss:

- Latest developments ascertained from the R&D pre-inspection meeting
- The upcoming agenda and schedule of the inspection.

4.4.6 Inspection meetings will be held with the leads of the other departments involved, the Inspectors and the Inspection Readiness Group as appropriate to discuss:

- The agenda and schedule of the inspection.
- Confirmation of arrangements for designated inspection rooms.
- At least one member of the inspected departments will accompany the Inspectors at all times

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- The Department Manager of the department under inspection is available to review documentation prior to being provided to Inspectors.
- A member of each department is designated to retrieve and photocopy documents (Runner).

4.4.7 Inspection meetings will be held with the Chief Investigator and research teams of any of the studies chosen for inspection, the Inspectors and the Inspection Readiness Group as appropriate to discuss:

- The agenda and schedule of the inspection.
- Confirmation of arrangements for designated inspection rooms.
- A member of the research team being inspected is available at all times. To ensure consistency, where possible this should be the Chief Investigator.
- The Chief Investigator is available to review documentation prior to being provided to Inspectors.
- A member of the research team is designated to retrieve and photocopy documents (Runner).

4.5 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)

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

Source Data

- 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

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- 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 (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
- 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).

4.6 Documentation requests:

- 4.6.1 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 Manager as appropriate.
- 4.6.2 The reviewer authorises the document as being within the scope and authority of the regulatory authority e.g. SOPs and site and master file documents.

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4.6.3 The following documents will not be made available:

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

4.6.4 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.

4.6.5 The original document is returned to the file as soon as possible.

4.6.6 The runner provides a copy to the reviewer for management review.

4.6.7 If agreed, the runner provides the document(s) to the Inspectors in the designated room.

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

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

4.7 Interview requests

4.7.1 When the inspectors request an interview with a Trust employee:

- As a minimum requirement one member from two of the following groups will be present at each and every interview with a staff member:
 - R&D Director, CTO Director
 - R&D Manager, CTO Assistant Director
 - R&D Solicitor Consultant, R&D Solicitor and Contract Manager
- The interviewee assumes 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 should consult with the R&D representative.
- If an interviewee does not understand the question and/or the context they should ask the inspector for clarification.
- If the interviewee realises they have provided erroneous information they should take immediate corrective action when appropriate and have such an action noted by the inspector.
- The interviewee does not attempt to answer "what if" questions and other hypothetical questions.

Preparing for and facilitating a Regulatory (MHRA) Inspection**4.8 Daily debriefing session**

- 4.8.1 At the close of each day the Inspectors, and members of the Inspection Readiness Group as appropriate, hold a debriefing session to assess progress, discuss unresolved questions, provide outstanding requested information and plan the next day's agenda.
- 4.8.2 The R&D Manager disseminates the outcomes of the daily debriefing sessions as appropriate.

4.9 Close out of the inspection

- 4.9.1 A close-out meeting will be scheduled at the end of the inspection with the Inspector(s) and appropriate Inspection Readiness Group members. Those departments and studies directly involved with the inspection will also be invited to attend.
- 4.9.2 The inspectors provide verbal feedback summarising observations and findings made during the inspection.
- The Trust representatives ensure that there is a clear understanding of the findings
 - Any erroneous findings are corrected at the time
 - A date when a report can be expected and when the Trust is expected to respond is confirmed.
- 4.9.3 Chief Investigators and Departmental Managers, where appropriate, provide feedback from the close out meetings to their teams with input from the R&D Manager and or CTO Assistant Director where appropriate.

4.10 Inspection reports

- 4.10.1 On receipt of the Regulatory Authority Inspection report the R&D Manager and CTO Assistant Director, work with the Manager of each department and Chief Investigators identified to provide an appropriate response to address the observations within the time frame provided.
- 4.10.2 The final MHRA report is reviewed and agreed by the R&D Director, signed off by the Clinical Trials Office Steering committee and is sent to the Regulatory Authority.
- 4.10.3 The Inspection Readiness Group manages the strategy to address the findings with the MHRA report.
- 4.10.4 The MHRA inspection certificate is filed as appropriate in the R&D Department.

5. ILLUSTRATIONS/APPENDICES

None.

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6. CHANGES SINCE LAST VERSION

Description of changes	
<i>Section Ref:</i>	<i>Brief description of change</i>