STANDARD OPERATING PROCEDURE FOR PREPARING AND PARTICIPATING IN A MEDICINES AND HEALTHCARE PRODUCTS REGULATORY AGENCY (MHRA) INSPECTION

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DOCUMENT HISTORY

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1.0	Allyson Bailey	01/06/2015	N/A – adapted from TASC SOP 17, Version 2
2.0	Julie Aitken	29/08/2018	Minor changes for clarity and to reflect current practice.

1. PURPOSE

This document describes the procedure used in NHS Fife for preparing for and participating in an MHRA inspection of a Clinical Trial of an Investigational Medicinal Product (CTIMP) and complies with the principles of Good Clinical Practice (GCP).

It is the responsibility of all researchers using this SOP to ensure they are using the latest version of it. The latest version is available via the Research & Development (R&D) pages on the NHS Fife Intranet (www.nhsfife.org/research) or for guidance, contact the R&D Office (fife-uhb.randd@nhs.net).

2. APPLICABILITY

This SOP applies to all members of staff associated with and managing CTIMPs.

3. POLICY

3.1 The MHRA has a routine programme of Good Clinical Practice (GCP) inspections to ensure compliance with the principles of GCP (ICH GCP Principles) and the legal requirements of the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. In addition, the MHRA can conduct "for cause" inspections in response to information that has raised concerns about a clinical trial.

MHRA Inspectors may visit a particular organisation to look at one trial (for example, a participating site as part of a broader inspection of a multi-site trial's co-ordinating organisation) and they may also visit to carry out a 'whole system' inspection, when they will review an organisation's facilities, staff competency and training to assess its ability to conduct CTIMPs to appropriate standards.

An inspection of the organisation's whole system may include any part of the organisation and any aspect of its operations having a bearing on CTIMP work. It is therefore necessary to ensure that NHS Fife has the systems, processes and procedures in place to participate in such an inspection.

3.2 **Chief Investigator (CI)/Principal Investigator(PI)/Research Team** - must be available for interviews and make relevant documentation available to the Inspectors.

3.3 **Inspection Coordinator (IC**) will:
- respond to the MHRA confirming receipt of the initial Notification of Inspection
- send the GCP Inspection Dossier to MHRA following authorisation from the Assistant R&D Director
- liaise with the MHRA Inspectors regarding the inspection
- communicate necessary information to relevant parties
- organise and plan the inspection

3.4 **Inspection Preparation Team (IPT)** - will coordinate the inspection process.

4. PROCEDURE

4.1 ONGOING PREPARATION

4.1.1 The R&D office will maintain and regularly update an Inspection Preparation File containing a 'draft' GCP Inspection Dossier (see section 4.2.3) including a list of staff responsible for reviewing/updating the various sections.

4.1.2 Investigators opening new studies are required to sign either a Principal Investigator Responsibilities Form (Doc Ref 11-02) or Chief Investigator Responsibilities Form (Doc Ref 11-03) prior to Local Management Approval being issued (See SOP 11 - Process of Local Management Review and Approval of all Research Undertaken in NHS Fife). This includes reference to their responsibilities in the event of an inspection.

4.2 NOTIFICATION OF INSPECTION BY THE MHRA

4.2.1 The Sponsor will be formally notified by the MHRA that the organisation or site has been selected for an inspection. Notification of a routine MHRA inspection will generally be given 2-3 months in advance.

Where NHS Fife is a host site for a CTIMP, notification of inspection will generally be received by the local CI/PI but may come to the Medical Director, R&D Office, Research Nurse(s) or other member(s) of staff. The original recipient must ensure that the Assistant R&D Director and any other relevant people/departments are informed of the impending inspection as soon as possible.

4.2.2 An individual from NHS Fife will be nominated by the Assistant R&D Director to act as the IC who will be responsible for liaising and communicating with the MHRA.

4.2.3 The notification from the MHRA will include a request for information, in the form of a GCP Inspection Dossier and a GCP Inspection Dossier Clinical Trials Spreadsheet. A GCP Inspection Dossier template and the GCP Inspection Dossier Clinical Trials Spreadsheet are available from the MHRA website: https://www.gov.uk/good-clinical-practice-for-clinical-trials. The website also provides a GCP Inspection Dossier Checklist which must be used to ensure the Dossier is complete.

The IC must coordinate the preparation of the GCP Inspection Dossier which must be submitted electronically to the GCP Inspection Dossier Mailbox - GCP.Inspectiondossier@mhra.gsi.gov.uk within 30 days of receipt of the notification of inspection.

4.2.4 The submitted Inspection Dossier will be considered by the MHRA who will then produce a draft inspection programme. This will specify the areas to be visited and trials to be examined in detail, with slots for interviewing individual investigators and/or research teams. The IC will liaise with the MHRA to agree the final programme.

4.2.5 The IC will organise the IPT which will generally be made up of R&D Department staff and representatives of other involved departments, which, for a whole system inspection of NHS Fife will typically include:

- Assistant R&D Director
- IC
- R&D Director
- Senior Clinical Trials Pharmacist
- Senior Clinical Trials Pharmacy Technician
- R&D Senior Research Nurse
- R&D Research Coordinator
- Information Governance representative
- Laboratories representative
- Radiology representative
- Medical Records representative
- Scribes/Observers

This group will be supplemented by appropriate members of the research team(s), depending on the focus of the inspection (e.g. whether the inspection relates to a specific study or is a general inspection) and would possibly lead to the inclusion of:

- Local CI/PI & Co-investigators
- Trials Research Nurse(s)

4.2.6 Once the final inspection programme is available the IC must individually inform all investigator teams and Support Departments that they will be involved and request written acknowledgement that they are aware of this.

All staff should be made aware that the programme may need to be changed during the inspection to enable other trials or other departments to be brought into its scope. Therefore, a Board wide communication (via Dispatches and R&D 'Need to Know' email to the 'Researcher Distribution List') must be issued by the R&D Support Officer so that all research teams and Support Departments are aware of the inspection dates and are aware that they may be called upon to make themselves available to the Inspectors during that time.

4.3 PREPARATION FOR INSPECTION

4.3.1 The IC or delegate is responsible for general housekeeping arrangements for the visit (*e.g.* ensuring the availability of meeting rooms, access to photocopiers, providing refreshments for Inspectors).

4.3.2 The IPT should ensure that all relevant staff are prepared prior to the inspection by providing training/mock interviews and giving staff the opportunity to raise any concerns or issues regarding the inspection.

4.3.3 All staff, when informed of their involvement in an inspection, must ensure that:
- they are available on the inspection date(s)
- all documents relating to the study or studies being inspected are complete, up to date and available, including evidence of training
- any information required by the IC (e.g. security procedures for accessing departments) is made available when requested.

4.4 DOCUMENTATION REQUIRED FOR THE INSPECTION

4.4.1 All research teams are aware that study documentation should ***always*** be inspection ready. However, teams may take the opportunity to review their files and training records to ensure that they are in a position to provide the required, complete documentation in a timely fashion during the inspection. Additional consideration should be given to any requirement for the review of electronic data.

Files held in the R&D Department or within Support Departments such as Pharmacy must be similarly reviewed.

The R&D Support Officer must be notified of any requirement to access documentation from the Archive Facility as soon as possible.

4.4.2 Documentation for inspection may include but is not be limited to:
- Trial Master File (TMF)/Investigator Site File/Sponsor File. These should contain all essential documentation relating to the trial.
- Case Report Forms (CRFs): these should be complete and legible. These should be reviewed before inspection to ensure that any queries are resolved.
- Patient hospital records/source documentation: all requested source documentation must be available for review on the day of inspection.
- Pharmacy/drug accountability records: all records pertaining to drug accountability must be complete, accurate and legible.

- Patient information leaflets/informed consent forms: all original consent forms should be available for review.
- Training records: All Staff Training Records should be complete with an up to date CV, Job Description and dates of GCP training included.
- R&D Policies, SOPs and Work Instructions
- Support Department SOPs
- Equipment maintenance and calibration records
- Sponsor Risk Assessment(s) for specific trial(s)
- Trial databases for specific trials
- Temperature records

4.5 DURING THE INSPECTION

4.5.1 The Inspectors are likely to hold an opening meeting to explain the purpose of their visit and outline the plan for the inspection. The IC will be responsible for inviting relevant members of the organisation to attend; this invitation will include the Chief Executive and other members of senior management as deemed appropriate, members if the IPT and members of any research teams or Support Department staff involved in the inspection.

4.5.2 During their visit, the MHRA Inspector(s) must be accompanied at all times to any relevant departments and interviews and meetings must not be conducted in areas that are used to store research documentation.

4.5.3 Interviewees should answer questions honestly and succinctly to the best of their knowledge. Information should not be volunteered and questions should not be answered unless the answer is known. If the answer is not known, it should be agreed with the Inspector that the answer will be clarified at a later date. Interviewees can update or clarify information given during an interview at any time throughout the inspection via the IC.

4.5.4 During an interview, the MHRA Inspector(s) may request a specific document or piece of information. Any such request must be conveyed to the appropriate personnel and the documentation delivered to the Inspector(s).

4.5.5 The IC must keep a list of any documentation requested by the Inspector and a duplicate set of documents given to the Inspector should be kept. Internal audit reports will not routinely be reviewed but may be requested. Confidential information e.g. financial information will be obscured without defacing the original and a copy stamped ‘confidential’ will then be provided to the Inspector.

4.5.6 Scribes and observers are allowed during interviews but recording of interviews is not permissible.

4.5.7 At the close of each day the Assistant R&D Director may host a debriefing session to which all staff who have been involved in the day’s inspection activities will be invited. This will be an opportunity to assess progress, discuss unresolved questions, provide outstanding requested information and plan the next day’s agenda.

4.6 CLOSE OUT MEETING AND INSPECTION REPORT

4.6.1 At the end of the inspection, a closeout meeting will take place and the Inspector(s) will provide verbal feedback of the findings to appropriate IPT members and those Investigators that were directly involved with the inspection. Within 30 days this will

be followed with a detailed written report from the MHRA which will typically list findings as 'critical', 'major' or 'other'. Critical findings must be addressed before an Inspection Statement can be issued. "Major" and "Other" findings should be addressed prior to any subsequent inspection.

4.6.2 A response to this written report is required within the timelines specified by the MHRA, but usually 30 calendar days. The IC and IPT should action and manage this response as appropriate.

4.6.3 A dialogue may be held between the MHRA and the IC to clarify the report findings and the proposed Corrective and Preventative Actions (CAPAs). The final written response to the MHRA should document CAPAs and the response timeline and must be signed by the R&D Director and those who have contributed responses.

4.6.4 When the MHRA is satisfied with the response it will issue a GCP Inspection Statement and cover letter/email to formally close the inspection.

4.6.5 All documentation, including the MHRA Inspection Statement and records of the outcomes of the inspection should be kept by the NHS Fife R&D Department and any other departments involved in the inspection.

4.6.6 A copy of the MHRA Inspection Statement must also be provided to the NHS Fife Research Governance Group.

4.7 POST INSPECTION FOLLOW-UP

4.7.1 An overview of the MHRA inspection should be disseminated to relevant parties by the IC or delegate. Any CAPAs in relation to inspected trials should be addressed by the CI and the research team. Any CAPAs in relation to Sponsor systems and/or SOPs should be addressed with the relevant staff.

4.7.2 Appropriate closure of all CAPAs will be overseen by Assistant R&D Director.

5. ASSOCIATED DOCUMENTS

SOP 11 - Process of Local Management Review and Approval of all Research Undertaken in NHS Fife
Doc Ref 11-02 - Principal Investigator Responsibilities Form
Doc Ref 11-03 - Chief Investigator Responsibilities Form

6. ABBREVIATIONS

CAPA	Corrective Action and Preventive Action
CI	Chief Investigator
CTIMP	Clinical Trial of Investigational Medicinal Product
GCP	Good Clinical Practice
IC	Inspection Coordinator
ICH-GCP	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Use – Good Clinical Practice
IPT	Inspection Preparation Team
ISF	Investigator Site File
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
R&D	Research and Development

SOP Standard Operating Procedure
TMF Trial Master File

7. REFERENCES

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI - Ethical Principles for Medical Research Involving Human Subjects.
(https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/)

Medicines for Human Use (Clinical Trials) Regulations 2004.
(http://www.legislation.gov.uk/uksi/2004/1031/contents/made)
It is assumed that by referencing the principal regulations, all subsequent amendments made to the principal regulations are included in this citation.

MHRA Guidance - Good Clinical Practice for Clinical Trials
(https://www.gov.uk/guidance/good-clinical-practice-for-clinical-trials).