York and Scarborough Teaching Hospitals NHS Foundation Trust R&D Unit
Standard operating Procedure
R&D/S53

Managing MHRA Inspections (Clinical Trials of Investigational Medicinal Products)

IT IS THE RESPONSIBILITY OF ALL USERS OF THIS SOP TO ENSURE THAT THE CORRECT VERSION IS BEING USED

All staff should regularly check the R&D Unit's website and/or Q-Pulse for information relating to the implementation of new or revised versions. Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded versions are promptly withdrawn from use unless notified otherwise by the SOP Controller.

The definitive versions of all R&D Unit SOPs appear online. If you are reading this in printed form check that the version number and date below is the most recent one as shown on the R&D Unit website: www.research.yorkhospitals.nhs.uk/sops-and-guidance-/ and/or Q-Pulse

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	Date:	17th June 2019
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	Date:	17th June 2019

This SOP will normally be reviewed every 3 years unless changes to the legislation require otherwise

Version History Log

This area should detail the version history for this document. It should detail the key elements of the changes to the versions.

Version	Date Implemented	Details of significant changes
1.0	28th November 2011	
2.0	26th March 2014	Removal of references to the North and East Yorkshire R&D Alliance. Changes to remove Head of R&D and minor changes to procedures following experience of two previous Trust inspections.
3.0	22nd August 2017	General update
4.0	15th July 2019	Review to check all procedures still relevant and appropriate. Minor typographical errors corrected. Change of link to R&D website.

Contents

1 Introduction, Background and Purpose

This SOP relates specifically to clinical trials of investigational medicinal products (CTIMPs) and the regulatory inspection regime to which they are subject.

ICH GCP section 1.29 defines inspection as 'The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies)'

Under the UK Clinical Trial Regulations the Medicines and Healthcare Products Regulatory Agency (MHRA) is the 'competent authority' mandated to carry out regulatory inspections. This is to assess compliance with the law and is concerned with both the validity of the study data and the protection given to study participants. This is done through verifying adherence to the study protocol, study related guidance documents, SOPs, GCP and relevant legislation. 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). They may also visit to do a 'whole system' inspection, when they will review an organisation's facilities, staff competency and training and assess its ability to conduct CTIMPs to appropriate standards. Most inspections will include a combination of staff interviews, document reviews and facilities visits.

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. Example processes that may come under scrutiny include regulatory submissions, laboratories, investigational medicinal product (IMP) management, contract management, project management, trial-file management, quality assurance, training, computer systems, monitoring, pharmacovigilance, medical advisors, data management, statistical analysis, report writing, archives and the management of investigator teams.

The MHRA will verify how these processes work in practice to ensure that:

- robust procedures are in place
- the rights, wellbeing and safety of trial participants are protected
- the trial is conducted in accordance with UK Clinical Trial Regulations and the principles of GCP
- appropriate Standard Operating Procedures (SOPs) are in place and that these are clearly documented and adhered to
- trials have all the necessary approvals prior to commencing – including ethics committee, HRA, MHRA and any specific approvals that may be relevant such as that relating to use of ionising radiation – with checking of this and formal approval on behalf of the organisation by its R&D Office.
- adequate pharmacovigilance is in place

MHRA may review and evaluate a facility and/or an individual trial during either a routine or a "for cause" inspection. A routine inspection is as the

name implies; a “for cause” inspection is a triggered inspection conducted in response to information that has raised concerns with a clinical trial (e.g. suspicion of significant regulatory non-compliance, scientific misconduct or fraud).

Any organisation where CTIMP work is carried out may be inspected. This may be, for example, an NHS Trust, a University or a GP practice. Particular attention is given to sites that sponsor CTIMPs; however host sites and parts of organisations providing particular CTIMP services (e.g. university departments providing laboratory or data management services) may also be scrutinised.

2 Who Should Use This SOP

This SOP is aimed at:

- Chief Investigators (CIs), trial co-ordinators, and other professional or administrative research staff, in the investigator team or in support departments, working on CTIMPs sponsored or co-sponsored by the Trust;
- Principal Investigators (PIs) and other professional or administrative research staff in the investigator team or in support departments, at Sites where multi-site studies sponsored or co-sponsored by the Trust are being run;
- R&D Unit personnel, who manage the sponsorship of CTIMPs on behalf of the Trust;
- PIs, research staff and staff in all involved service departments in the Trust involved in any aspect of CTIMP work.

3 When this SOP Should be Used

This SOP outlines the procedures necessary to prepare for, host and participate in an MHRA inspection.

4 Procedure(s)

For Trust systems inspections the Head of R&D would be the MHRA’s initial contact point.

Should any member of staff be directly notified of any other MHRA inspection planned to take place within the Trust (e.g. by a study Sponsor, CRO, or directly by the MHRA) they should inform the Head of R&D immediately.

4.1 Actions on notification of MHRA Trust Systems Inspection

When the Trust Site receives notification of MHRA inspection, the Head of R&D should be immediately informed. The Head of R&D will inform the Chief Executive of the Trust, additional senior management as appropriate, the R&D Unit and the responsible personnel required to input into the inspection dossier. The Head of R&D (or delegated individual) will establish as soon as possible, and lead, an Inspection Coordination Team (ICT), to act as the

primary contact network throughout the inspection process, to coordinate all departments and personnel and keep senior management informed.

The ICT will generally be made up of R&D Unit Personnel and representatives of other involved departments, which, for a whole system inspection of an acute trust will typically include:

- Pharmacy
- Laboratories
- Information & technology (IT)
- Radiology
- Facilities (in relation to equipment maintenance)
- Medical records
- Data Management
- Archive Facility
- Lead Research Nurse (representing the clinical teams)

4.2 The Inspection Dossier – arranging an inspection date

The Head of R&D will co-ordinate collection of a dossier of documents requested by the MHRA prior to inspection.

There will be a strict deadline for provision of this dossier and all research staff and ICT members in the organisation being inspected are required to respond in a complete and timely manner to requests for information from the Head of R&D (or delegate).

The R&D Unit will at all times hold a 'draft' dossier and a list of staff responsible for reviewing/updating the various sections when a request is received by the MHRA.

Following submission of the dossier, the MHRA Inspectorate will consider this and produce a draft inspection programme.

The draft inspection programme will specify areas to be visited and trials to be examined in detail, with slots for interviewing individual investigators or teams. The Head of R&D (or delegate) will liaise with MHRA to agree the final programme; there may be some limited leeway for negotiation on dates to accommodate holidays or other commitments. However all investigators or other staff required for interview should appreciate that this leeway is limited and they must make every effort to make themselves available as required for this statutory inspection. Usually sufficient notification is given to allow for this.

4.3 Prior to the inspection

All research studies taking place in the Trust are expected to be run to a high standard and should be 'inspection ready'. As such, a notification of MHRA inspection should not have a significant impact on the running of research departments, the workload of research teams or patient recruitment into trials.

When the final inspection programme is available all investigator teams and support departments known to be visited will be individually informed. This notification will include the contact details of the Lead Administrator identified for the inspection (see Section 4.3.3).

All staff should be aware that the programme may be changed during the inspection so that other trials, or other departments are brought into its scope. As such, a Trust wide communication will be issued 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.

4.3.1 Documentation

All research teams are aware that their 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 documentation in a timely fashion during the inspection. Additional consideration should be given to any requirement to review electronic data.

Files held in the R&D Unit or support departments such as Pharmacy should similarly be reviewed.

Any documentation required to be obtained from the Archive facility should be notified to the Trust's Research Archivist as soon as possible.

Documentation to be inspected may include:

- Trial Master File / Investigator Site File / Sponsor File
- Contracts
- Staff training records, job descriptions and CVs
- Organisational charts
- SOPs [Note: R&D Unit SOPs will be made available to Inspectors on the website but any Sponsor or Study-Specific SOPs used for a particular trial will need to be provided by the investigator team]
- Computer system validation documents
- Case Report Forms (CRFs)
- Source documentation (e.g. Patient Notes, x-rays, lab reports)
- Patient Information Sheets and Informed Consent Forms
- Laboratory/radiology procedures
- Equipment maintenance and calibration servicing routines
- Pharmacy Drug accountability
- Temperature records

4.3.2 Training

It is appreciated that the prospect of an MHRA inspection can be daunting for those involved so the R&D Unit can arrange or provide sessions for staff in preparation for an inspection if required.

4.3.3 Practical arrangements

The Head of R&D (or delegate) with the support of the ICT will:

1. Identify administrative support for the inspection – a Lead Administrator and at least two assistants – brief them fully and provide them with an annotated inspection programme showing their tasks during all phases of the inspection.

2. Book rooms for the inspection:
   - One for the inspectors' use, for document review and report writing etc.; this should, if possible, be located near the Lead Administrator's office and photocopying facilities;
   - A room for temporary storage of documentation relevant to the inspection – near the Lead Administrator's office;
   - Two rooms for interviews - near the inspectors' room / Lead Administrator's office;

- Larger rooms for the opening and closing meetings;
- Specific room bookings as required, for programmed interviews of larger groups of people or in support departments.

3. Arrange the room furnishings appropriately including:
   - In all rooms remove or lock away all unpublished material including organisational specific documentation of any kind;
   - In the inspectors' room provide:
     a. A desk for each inspector
     b. A telephone
     c. Sufficient desk/table space to hold a significant number of files that may be accumulated for document review sessions
     d. A side table for refreshments
   - Outside the door of the inspectors' room provide a small table with 'in' and 'out' trays
   - In the room assigned for document storage, provide sufficient empty lockable storage cabinets – number to be determined and according to the volume of documentation in the trials in the planned inspection programme
   - Procure equipment for the inspection, including:
     a. Visitor name badges for use by the inspectors when in the Trust
     b. Approximately 6 note books for staff taking notes in the interview sessions
     c. Document logging sheets for use by the Lead Administrator
     d. Arrange catering requirements for the duration of the inspection

4.3.4 Location of documentation for inspection

Documentation for trials on the inspection programme will be relocated temporarily so the material is to hand for inspectors' document review sessions, which may take place at various stages of the inspection, between interview sessions.

As soon as possible after investigator teams or support departments are notified that their trial is on the programme they should email the Lead Administrator (details will be on the notification) to give an estimate of the amount of space their trial documentation will need in the temporary storage facility (in terms of whole / part drawers in a standard filing cabinet).

All investigator teams / support departments are responsible for ensuring all their trial files and documents are brought to the Lead Administrator to be placed in the temporary storage facility before the start of the inspection.

The Lead Administrator is responsible for keeping a log of all files in temporary storage and for putting a numbered labelling system in place (e.g. file 1 of 5) and for labelling all filing cabinet drawers.

This movement to temporary storage should be done at latest on the last working day prior to the inspection. Files relating to less active trials are requested to be moved earlier if possible, to assist the Lead Administrator. If,

for more active trials, it is essential to keep some material until the actual inspection day, this should be discussed with the Lead Administrator.

4.4 On the Day(s) of Inspection

On the first, and every subsequent day of the inspection the Lead Administrator or a designated assistant should meet the inspectors at the organisation's main reception desk. S/he should check the inspectors' photo identification cards and give them organisation visitor name badges for use while on the premises.

The Head of R&D (or delegate) will ensure that arrangements are in place for the inspectors to be escorted by a member of staff whenever they move around the organisation.

4.4.1 Opening Meeting

The inspectors are likely to hold an opening meeting to explain the purpose of their visit and outline the plan for the inspection. The Head of R&D will be responsible for inviting relevant members of the organisation to attend; this invitation list will include the Chief Executive and other members of senior management as deemed appropriate, members of the ICT, and members of any investigator teams or support department staff involved in the inspection.

4.4.2 Interview Sessions

All members of staff must present themselves for inspection interviews in a timely manner. If unforeseen and urgent matters prevent this they should contact the Lead Administrator immediately to reschedule at the earliest possible convenience.

The Head of R&D (or delegate) will ensure that arrangements are in place for all interviews to be attended by a 'scribe'. This will be a member of staff who will take notes of the interview in one of the designated inspection notebooks. These notebooks will be retained by the R&D Unit; the contents may be used for debriefing staff after the inspection and/or for making improvements to clinical trial practice and procedure in the Trust.

Staff should note the following guidance in relation to inspection interviews:

- If an interviewee does not understand the question and/or the context s/he should ask the inspector for clarification
- The interviewee should answer the questions posed openly and honestly
- An interviewee may request to consult relevant SOPs or guidance documents, study documentation etc. during the interview in order to provide the required information
- If the interviewee realises (either during or after the interview) s/he has provided erroneous information then s/he should immediately correct this and have this noted by the inspector
- If an interviewee decides that a question is outside their area of expertise or authority they may request time to consult others or seek further information after the interview.

4.4.3 Providing documents for the inspectors

The Lead Administrator is responsible for managing provision of documents and copy documents to the inspectors.

When the Inspectors request documentation for review, the Lead Administrator, or an assistant will:

- note the details on a document log;
- obtain the document from the temporary storage facility or request a member of staff in the relevant department to locate it and provide it – to the Administrator; not directly to the inspectors;
- give the document (or a copy of the document) to the Inspectors in the inspectors' room;
- keep a note on the document log of exactly what has been provided and any documents unable to be provided together with a reason for this;
- return the document to the temporary storage facility as soon as the Inspectors have completed their review. This includes documents obtained direct from departments, which will be returned at the end of the inspection when the temporary storage facility is cleared.

It may be more convenient to use the 'in' and 'out' trays outside the inspectors' room to pick up the inspectors' requests for documentation and leave documents for them to collect. Any confidential documents should be retained securely by the Lead Administrator until they can be handed personally to the requesting inspector.

4.4.4 Debriefing

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

4.4.5 Close out of the inspection

The inspectors will hold a close out meeting at the end of the inspection. The Head of R&D will be responsible for inviting appropriate members of the organisation to attend, as for the opening meeting. All who are invited are strongly recommended to attend if they can, since this is a valuable learning opportunity for all staff involved in clinical trial work.

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

The ICT provide feedback from the close out meeting to research teams as necessary (for example if no team representatives have been able to attend).

4.5 The Inspection Report

On receipt of the Inspection Report the Head of R&D (or delegate) will co-ordinate the organisation's response with the support of the ICT. All staff are required to respond to requests for contributions in a complete and timely manner, since the deadline for response set by the inspectors must be met.

The final MHRA Report will be reviewed and signed off by the Head of R&D (or delegate) and those who have contributed responses. The Head of R&D (or delegate) will submit the Trust's inspection response to the MHRA and will be responsible for providing any additional information or clarifications as required.

Once the MHRA has reviewed the inspection response and confirmed that the Trust has provided corrective and preventative actions that are considered acceptable, the inspection will be formally closed. The MHRA will issue a 'GCP Inspection Statement'

4.6 Corrective and Preventative Action (CAPA)

An appropriate CAPA file will be prepared by the Research QA Manager (or delegate) and maintained post inspection.

It is essential that the corrective and preventative actions required following the inspection are implemented. The Head of R&D (or delegate) will be responsible for periodically reviewing the CAPA plan to ensure that corrective actions are implemented as per the responses on the report.

5 Related SOPs and Documents

All York and Scarborough Teaching Hospitals NHS Foundation Trust SOPs