Management of Research 07 : Managing MHRA Inspection

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

All staff should regularly check the Research & Development Webpage 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 Staff must ensure that they are adequately trained in the new procedure and must make sure that all copies of superseded version are promptly withdrawn from use unless notified otherwise by the SOP Controller.

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http://www.gloshospitals.nhs.uk/en/About-Us/Research--Development/

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The Gloucestershire Hospitals NHS Foundation Trust wishes to acknowledge York Hospitals NHS Foundation Trust and University Hospitals Bristol NHS Foundation Trust who gave permission to use their templates in the development of these SOPs.

Version History Log

This area will be updated with details of all changes made to the SOP whether due for full review or not.

Version	Details of Change	Date Implemented
1.0	Original SOP	14/02/2017
2.0	Rebranding to GHNHSFT and updating contact details	31/03/2018

This SOP will be reviewed every two years unless changes to any relevant legislation require otherwise.

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R&D SOP MR 07 –MHRA inspection preparation
version 2   Implementation date: 31st March 2018   Review date: 1st November 2019

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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, 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, 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

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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, fraud or serious breaches).

Any organisation where CTIMP work is carried out may be inspected. This may be, for example, a 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 lab 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;
- Trust R&D office 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 where externally-sponsored CTIMPs are hosted.

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 Senior Member of the Trust with the responsibility for R&D is 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 Senior Member of the Trust with the responsibility for R&D and the R&D Office immediately.

4.1 Actions on notification of MHRA Trust Systems Inspection

When the Trust Site receives notification of MHRA inspection, the Senior Member of the Trust with the responsibility for R&D should be immediately informed. The Senior Member of the Trust with the responsibility for R&D will inform the Chief Executive of the Trust and the Director of Clinical Strategy along with additional senior management, as appropriate, and the R&D Team. The Senior Member of the Trust with the responsibility for 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 the R&D team and representatives of other involved departments, which, for a whole system inspection will typically include:
- Pharmacy
- Laboratories
- Information & technology (IT)
- Radiology
- Facilities (in relation to equipment maintenance)
- Medical records
- Data Management
- Archive Facility
- Lead Research Nurses (representing the clinical teams)

4.2 The Inspection Dossier – arranging inspection date

The Senior Member of the Trust with the responsibility for R&D   (or their delegate) will co-ordinate collection of a dossier of documents requested by the MHRA prior to inspection. The list of documents required will vary but is likely to be extensive.

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 Senior Member of the Trust with the responsibility for R&D (or their delegate).

Following submission of the dossier, the MHRA Inspection Team will consider this and produce a draft inspection programme. Unless the inspection is 'for cause', the original notification will probably have given dates between which the inspection is likely to take place. When the draft inspection programme is sent to the Senior Member of the Trust with the responsibility for R&D, it will give actual scheduled dates.

The draft programme will specify areas to be visited and trials to be examined in detail, with slots for interviewing individual investigators or teams. The Senior Member of the Trust with the responsibility for R&D   (or their 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.

4.3 Prior to the inspection

When the final inspection programme is available all investigator teams and support departments 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 to ensure that they are in a position to provide the required documentation in a timely fashion during the inspection.

Files held in the R&D R&D Office 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 / Pharmacy File
- Contracts
- Staff training records, job descriptions and CVs
- Organisational charts
- SOPs [Note: R&D 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 team can arrange or provide sessions for staff in preparation for an inspection, if required.

4.3.3 Practical arrangements

The Senior Member of the Trust with the responsibility for R&D   (or their 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:
   i. In all rooms remove or lock away all unpublished material including organisational specific documentation of any kind;
   ii. 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
   iii. Outside the door of the inspectors' room provide a small table with 'in' and 'out' trays
   iv. 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
   v. 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). At this point the ICT will notify Sponsors and TUs which of their trials have been selected for inspection.

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 Senior Member of the Trust with the responsibility for R&D   (or their 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 Senior Member of the Trust with the responsibility for 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 Senior Member of the Trust with the responsibility for R&D   (or their 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 team; 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
- An interviewee may request to consult relevant SOPs or guidance documents 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

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 Senior Member of the Trust with the responsiblity for R&D (or their 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 Senior Member of each Trust with the responsibility for 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 will provide feedback from the close out meeting to research teams as necessary (for example if no team representatives has been able to attend).

4.4.6 The Inspection Report

On receipt of the Inspection Report the Senior Member of the Trust with the responsibility for R&D (or their delegate) will coordinate 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 Senior Member of the Trust with the responsibility for R&D (or their delegate) and those who have contributed responses. The Senior Member of the Trust with the responsibility for R&D (or their 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'.

4.4.7 Corrective and Preventative Action (CAPA)

The inspection report will be reviewed periodically following the inspection to ensure that corrective actions are implemented as per the responses on the report. The

R&D team will be responsible for undertaking this and for preparing and maintaining an appropriate CAPA file.

5 Related SOPs and Documents
All SOPs

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R&D SOP MR 07 –MHRA inspection preparation
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Management of Research 06: Research Studies Involving Sue Ryder

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http://www.gloshospitals.nhs.uk/en/About-Us/Research--Development/

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Version	Details of Change	Date Implemented
1.0	Original SOP	09/04/2014
1.1	Temporary version reflecting new changes on 18th June 2014	18/06/2014
2.0	Reviewed and Updated along with reorganisation into the Gloucestershire R&D Consortium suite of SOPs	26/08/2016
3.0	Review of contracting processes	08/09/2017
4.0	Rebranding to GHNHSFT and updating of contact details	31/03/2018

This SOP will be reviewed every two years unless changes to any relevant legislation require otherwise

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R&DSOP MR 06 – Research involving Sue Ryder
Version 4.0   Implementation date: 31st March 2018   Review date: 1st March 2019

Contents

1. Introduction, background and purpose

This SOP has been produced to outline the approval process for research studies that recruit from or have involvement with Sue Ryder, Leckhampton Court, Cheltenham.

For studies involving other Sue Ryder hospice sites advice needs to be sought from the Sue Ryder Research Governance Group.

2. Who should use this SOP?

This SOP should be used by:

- Gloucestershire Hospitals NHS Foundation Trust, Research and Development Department (Trust R&D)
- The Chief & Principal Investigator (contracted to Gloucestershire Hospitals NHS Foundation Trust (GHNHSFT) but based at Sue Ryder intending to conduct research involving Sue Ryder , Leckhampton Court, Cheltenham)
- The Principal Investigator's research team
- Sue Ryder Research Governance Group

3. When this SOP should be used?

This document should be referred to and considered as soon as practically possible within the setup phases / approvals processes in relation to studies recruiting NHS patients treated under contract with Sue Ryder.

4. Categories of study

This SOP is applicable to the following types of study differentiated by sponsor:

a)   Commercial pharmaceutical industry sponsored studies
b)   Gloucestershire Hospitals NHS Foundation Trust sponsored studies
c)   Third party sponsored studies (non-commercial)
d)   Student projects sponsored by an academic institution (with supervisory / study design buy-in from a GHNHSFT-employed Consultant)

4.1 Sponsorship of a study by Sue Ryder

In the event of Sue Ryder sponsoring their own research study, it will be the responsibility of Sue Ryder to undertake all feasibility and administrative setup complying with their Research Governance Group related processes. In this circumstance, when sponsorship duties are fulfilled and the study submitted for review, it will be the responsibility of GHNHSFT R&D Department staff to

undertake research governance processes to issue NHS permission for the research to commence.

5. Contractual Relationships

This SOP recognises that patients receiving care at Sue Ryder, Leckhampton Court, Cheltenham, are NHS patients being treated under contract with Sue Ryder Care (SRC). This means that contractual relationships for research studies that involve patients at Sue Ryder can often be complicated.

Because of this the need for, and type of contract required, should be discussed as early as possible in the feasibility phase of any discussions between R&D and SRC. In most cases, the NIHR model Clinical Trial Agreements (mCTA) are recommended – mCTAs are available for both Commercial and Non-Commercial Studies. Examples of arrangement could include:

- For externally sponsored studies recruiting only from Sue Ryder, and NIHR mCTA between the Sponsor and SRC should be used.
- For any study where there is a transfer of finance between SRC and The Trust (in addition to any funding confirmed in the sponsor/host mCTA) and additional non-commercial mCTA will be adapted to describe the arrangements between SRC and the Trust.
- For externally sponsored studies where recruitment is occurring in both SRC and the Trust an mCTA may be used to describe the arrangement between the Sponsor and either other party (SRC or Trust) with an additional agreement in place with the third party to describe any further arrangements between sites. The decision on which party signs the main agreement will be based on the activity each site will be undertaking.
- Where the responsibilities/delegated duties for both recruiting sites is the same, a Tripartite agreement between the Sponsor, Trust and SRC may be adapted.
- For studies sponsored by The Trust and recruiting in SRC, a modified mCTA will be used in all cases, developed in discussion with SRC

The need for, and type of agreement, will be decided on a study by study basis in discussion with SRC and any relevant external sponsors.

Any agreement that describes a flow of finance between any parties must be included as an appendix that details the payment schedule and amounts for the duration of the study.

6. Recruitment Figures

NIHR Portfolio adopted projects involving Sue Ryder that involve a Principal Investigator contracted to GHNHSFT will recruit patients with accruals attributed to GHNHSFT and entered onto EDGE.

7. Sue Ryder internal processes

Sue Ryder operates a monthly Research Governance Group at which research studies are usually considered at a stage when feasibility is assured and HRA paperwork is complete. It is recommended that a draft contract is submitted to this group with all related setup paperwork.

This SOP recognises that some studies will need to be expedited through Sue Ryder meeting processes. For instance, if an urgent study (such as one adopted to the National Institute of Health Research Portfolio of priority research) emerged within a week of the last Sue Ryder Research Governance Group meeting taking place, and where the remainder of the month presented a delay on the approvals process, that such studies will be emailed to the Sue Ryder Research Governance Group for an approval in principle prior to being presented at the next Research Governance Group for information.

8. Other SOPs and documents

To be used in conjunction with this document, a number of SOPs are in place that relate to the setup / approval process for studies reviewed by GHNHSFT R&D Department including:

- R&D SOP RDVL 02 – Application to the trust for Sponsorship of a CTIMP
- R&SD SOP MR 01 Hosting CTIMPs and other Clinical studies
- R&D SOP MR 03 - Trial management system using EDGE
- R&D SOP MR 04 – Monitoring Research Studies
- R&D SOP MR 05 – Distribution of commercial income