Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

Regulatory Inspection

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Standard Operating Procedure: STH Research Department

Regulatory Inspection

This SOP has been produced in accordance with Research Governance Framework 2005, the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments. This SOP will outline the procedures necessary to prepare, host and participate in a Regulatory Inspection by a Competent Authority at Sheffield Teaching Hospitals NHS Foundation Trust.

Background
EU Directive 2001/20/EC mandates inspection of trial and Sponsor premises to verify compliance with GCP. The European Agency for the Evaluation of Medicinal Products (EMEA) coordinates the scientific evaluation of the safety, quality and efficacy of medicinal products throughout the EU. The Competent Authority in the UK is the Medicines and Healthcare products Regulatory Agency (MHRA).

A Regulatory Inspection is performed to assess an organisation's compliance with guidelines and Regulations in the conduct of clinical research involving investigational medicinal products (IMPs) or investigational devices and to assure the Competent Authority of the validity of the study data and the protection and rights of the subjects during the conduct of that research. This is done through verifying adherence to the study plan (protocol) and study related guidance documents, to SOPs and to the GCP and Regulatory requirements for clinical trials. The Inspection will also review an organisation's facilities, staff competency and training.

Regulatory Inspections take place to examine systems and look for good control of processes and opportunities for process improvement. To do this the Inspector will select a study and "drilldown" looking at the processes involved and/or select a process and review that process in depth in a number of studies.

Definition
ICH GCP guideline section 1.29 defines inspection as "the act of regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authorities 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 the conduct of a clinical trial.

A. Trust wide Regulatory Inspection

Procedure

Initial notification of Inspection: Preparation of Dossier for the Competent Authority

1. On receipt of advance notification of an inspection by the MHRA the member of the Trust who is initially notified informs the Research Department Senior Management immediately; this will come in the form of a request for an Inspection Dossier.
   1.1. The Research Manager immediately informs the Trust Director of R&D, CRO Director, Medical Director, additional senior management, as appropriate, and Research Department Inspection Coordinator(s)[1].
2. The Research Manager or delegated Inspection Coordinator informs all STH Support Services and Facilities involved in clinical research (referred to as departments below) of the advance notification of inspection. Departments include but are not limited to:
   2.1. Research Department
   2.2. Clinical Research Facility
   2.3. Cancer Clinical Trials Centre
   2.4. Pharmacy

[1] Research Department Inspection Coordinators to be made up of appropriate members of Research Department R&D Coordination team

2.5. Information & Technology (IT)
2.6. Radiology (STH or University)
2.7. Laboratories
2.8. Medical Records
2.9. Clinical Engineering

3. The Research Manager or delegated Inspection Coordinator informs all investigators at STH involved in CTIMPs, regardless of whether STH are sponsor or host, and any Clinical Trials Units or Contract Research Organisations (CTRU/CRO) managing STH sponsored CTIMPs, of the advance notification of inspection.
4. The Research Manager and Inspection Coordinator(s) coordinates the collection of a dossier of documents as requested by the MHRA prior to inspection. The Research Manager and Inspection Coordinator(s) work closely with the departments, Investigators and any CTRU/CROs accordingly to compile an Inspection Dossier within the 30 day deadline as set by the MHRA. The contents of the dossier may include:
   4.1. Overview of Trust facilities
   4.2. Organisational charts & staff responsibility summaries
   4.3. List of Clinical Trial Processes
   4.4. List of STH sponsored and hosted non commercially sponsored CTIMPs
   4.5. Summary information of the Trust's Clinical Trial Systems
5. The Research Department submits an electronic copy of the Inspection Dossier to the MHRA as requested; a hardcopy and disk copy is retained by the Research Department.

Notification of an inspection date

6. The Research Manager liaises with the MHRA Inspectorate to agree an Inspection date.
7. On notification of an inspection date by the MHRA, the Research Manager informs the Research Department Senior Management immediately.
   7.1. The Research Manager immediately informs the Trust Director of R&D, CRO Director, Medical Director, additional senior management, as appropriate, and Research Department Inspection Coordinator(s)[1].
8. The Research Manager agrees the inspection plan with the MHRA Inspectorate including studies identified for inspection, interviewees, additional information or documentation, and any site visits.
9. The Research Manager or delegated Inspection Coordinator informs all departments involved in clinical research that they have been identified for inclusion in the Trust inspection, as appropriate. Departments that may be involved include but are not limited to:
   9.1. Research Department
   9.2. Clinical Research Facility
   9.3. Cancer Clinical Trials Centre
   9.4. Pharmacy
   9.5. Information & Technology (IT)
   9.6. Radiology (STH or University)
   9.7. Laboratories
   9.8. Medical Records
   9.9. Clinical Engineering
10. If a specific project is identified, the Research Manager or delegated Inspection Coordinator notifies the Chief Investigator and Sponsor where necessary (i.e. external institution if not STH sponsored). Where the study is an STH sponsored multicentre CTIMP, the CTRU or CRO managing the study is notified requesting they notify all participating sites.

Preparation for an inspection

11. The Research Manager acts as the primary contact throughout the inspection process, coordinating the activities of the Research Department, and keeping other identified departments and Trust managers informed of developments in preparation for the inspection.
12. The Research Manager and Inspection Coordinator(s) ensure that each identified STH Support Department has access to the appropriate training in preparation for inspection.
13. The Research Department Research Support Manager organises an inspection pack for the Research Department to include: name badges, "confidential" ink stamps, note books and document log templates.
14. The Research Manager and Inspection Coordinator(s) ensure that each identified STH Support Department designates rooms for the inspection; one room where the inspection is to be conducted, a second where all documents are to be reviewed before review by the Inspectors and

a third “breakout” room for the Inspectors; the room for inspection may also serve as the breakout room depending on availability of rooms.

15. Prior to inspection, all members of each department identified for participation in the inspection ensure that documentation is reviewed and up to date and that they are aware of the location and content of all documentation. Documentation requested for inspection may include:
    - 15.1. From all Departments involved in the Inspection
        - 15.1.1. Study and systems related documentation
        - 15.1.2. Contracts
        - 15.1.3. Staff training records, job descriptions and CVs
        - 15.1.4. Organisational charts
        - 15.1.5. SOPs
    - 15.2. From the Investigator site file
        - 15.2.1. Case report forms
        - 15.2.2. Source documentation
        - 15.2.3. Patient information and informed consent forms
    - 15.3. Laboratories
        - 15.3.1. Lab procedures
        - 15.3.2. Equipment maintenance and calibration servicing routines
    - 15.4. Pharmacy
        - 15.4.1. Dispensing log
        - 15.4.2. Drug accountability
        - 15.4.3. QP certificates
    - 15.5. Clinical Engineering
        - 15.5.1. Equipment maintenance and calibration records

Initial inspection contact

16. On arrival at the Research Department the Research Support Manager provides the Inspectors with an identification badge and informs the Research Manager and Inspection Coordinator(s) of their arrival.
17. The Research Manager and Inspection Coordinator(s) meet the Inspectors and escort them to the designated room in the Research Department for the regulatory inspection.
18. The Research Manager or delegated Inspection Coordinator confirms the identity of the Inspectors and the reason for inspection (routine or for cause).
19. The Research Manager arranges a pre-inspection meeting to be held with the Inspectors and the Director of R&D to discuss:
    - 19.1. The agenda and schedule of the inspection to provide availability to appropriate staff.
    - 19.2. 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.
    - 19.3. Establish timing of exit interview (close out meeting) at the end of the inspection.
20. The Research Manager arranges a pre-inspection meeting with the Research Department members to discuss:
    - 20.1. The agenda and schedule of the inspection.
    - 20.2. Which member of the Research Department will accompany the Inspectors at all times during the Inspection.
    - 20.3. Which two members of the Research Department not responsible for answering questions are designated to take notes during interview; one as observer to note key points and the other to note the questions asked (to ensure consistency, wherever possible these should be Inspection Coordinators).
    - 20.4. Which member of the Research Department is designated to retrieve and photocopy documents (the Runner).
21. The Inspection Coordinator(s) arranges a pre-inspection meeting with the leads of the other departments involved in the Inspection to discuss:
    - 21.1. The agenda and schedule of the inspection.
    - 21.2. Confirmation of arrangements for designated inspection rooms.
    - 21.3. Which member of the Research Department and which member of the department under inspection will accompany the Inspectors at all times during inspection of that Department.

21.4. Which member of the department being inspected will be available at all times during the Inspection. This should be the Inspection Lead for that Directorate/department where possible.
21.5. Which member of the Research Department is designated to take notes during staff interviews with the Inspectors (to ensure consistency, where possible this should be an Inspection Coordinator).
21.6. The Department Manager of the Department under inspection who will be available to review documentation prior to being provided to Inspectors.
21.7. The member of each department who is designated to retrieve and photocopy documents (Runner).

22. The Inspection Coordinator(s) arranges a pre-inspection meeting with the Principal Investigator and research teams of any of the studies chosen for inspection to discuss:
22.1. The agenda and schedule of the inspection.
22.2. Confirmation of arrangements for designated inspection rooms.
22.3. Which member of the Research Department and which member of the department under inspection will accompany the Inspectors at all times during inspection of that Department.
22.4. Which member of the research team being inspected will be available at all times to contact during the inspection (to ensure consistency, where possible this should be the Principal Investigator).
22.5. Which member of the Research Department is designated to take notes during interviews (where possible this should be an Inspection Coordinator to ensure consistency).
22.6. That the Principal Investigator or delegated senior member of the research team is available to review documentation prior to it being provided to Inspectors.
22.7. Which member of the research team is designated to retrieve and photocopy documents (Runner).

During the inspection

23. When the Inspectors request documentation for review:
23.1. The Inspection Coordinator notes the document requested on a log and requests the document from the relevant Department Manager or delegate.
23.2. The Runner retrieves the document for review from the Department Manager or delegate.
23.3. The Department Manager or delegate authorises the document as being within the scope and authority of the MHRA e.g. SOPs and site and master file documents.
23.4. The Runner provides the document to the Inspection Coordinator who records the provision of all documentation provided to the Inspectors and retains a copy for later reference.
23.5. On confirmation of documents requested by the Inspectors, the Inspection Coordinator provides the document to the Inspectors in the designated room.
23.6. Following inspection the documents are retrieved from the Inspector and returned to the file ASAP.
23.7. If the Inspectors request to be left alone at any time, documents agreed and noted (as per 23.3 and 23.5) are left with them.

24. When the Inspectors request copies of documentation:
24.1. The Inspection Coordinator notes the document requested on a log.
24.2. The Runner obscures any confidential information e.g. financial information and makes duplicate copies of all documents requested.
24.3. The Runner provides a copy to the Department Manager or delegate for management review.
24.4. The Inspection Coordinator stamps “confidential” on each sheet of the Inspector’s photocopy.
24.5. A duplicate set of all documents given to the Inspectors is retained by the Inspection Coordinator.
24.6. On confirmation from the Inspectors of documents required, the Inspection Coordinator provides the document to the Inspectors in the designated room.
24.7. At the conclusion of the inspection the documentation may be retained by the Inspectors at their request. This request will be recorded by the Inspection Coordinator.

25. When the Inspectors request an interview with a Trust employee:
25.1. It is recommended that the interviewee requests appropriate management to be present throughout the interview.

25.2. Two members of the Research Department who are not responsible for answering questions are designated to take notes during interview; one as observer to note key issues and the other to note the questions asked (to ensure consistency, wherever possible these should be Inspection Coordinators)
25.3. The interviewee assumes a friendly, cooperative, confident and professional attitude.
25.4. The interviewee does not guess, lie, deny the obvious, make misleading statements or engage in unconstructive arguments.
25.5. The interviewee responds in a concise, factual and accurate manner when the inspector asks a relevant question.
25.6. If the interviewee decides that the question is outside of their area of expertise or authority or outside the scope of the Inspector's authority they should consult with their management representative.
25.7. If an interviewee does not understand the question and/or the context they should ask the inspector for clarification.
25.8. 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.
25.9. The interviewee does not solicit opinions from the Inspector.
25.10. The interviewee does not attempt to answer "what if" questions and other hypothetical questions.
25.11. The interviewee does not contradict something said by a colleague. If necessary, the interviewee leaves the room, confirms the correct answer, and then corrects the response with the Inspector.

Daily debriefing session

26. At the close of each day the Inspectors, Research Manager and Inspection Coordinator(s) hold a debriefing session to assess progress, discuss unresolved questions, provide outstanding requested information and plan the next day's agenda.
27. The Inspection Coordinator(s) disseminate the outcomes of the daily debriefing sessions as appropriate.

Close out of the inspection

28. A close out meeting is scheduled at the end of the inspection with the Inspectors and appropriate Trust representatives (for example, Research Manager, Inspection Coordinator(s), Principal Investigators and management of other departments involved as agreed).
29. The inspectors provide verbal feedback summarising observations and findings made during the inspection.
30. The Trust representatives ensure that:
    30.1. There is a clear understanding of the findings
    30.2. Any erroneous findings are corrected at the time
    30.3. A date when a report can be expected and when the Trust is expected to respond is confirmed.
31. The Departmental Managers provide feedback from the close out meetings to their teams with input from the Inspection Coordinator(s) where appropriate.

Inspection reports

32. The Research Manager, Inspection Coordinator(s) and note taker(s) work with members of departments and the Principal Investigators involved to produce an internal inspection report. The responsible members of each department are identified and take appropriate actions to address any issues relevant to their Department within agreed timeframes.
33. On receipt of the Regulatory Authority Inspection Report from the MHRA, the Research Manager and Inspection Coordinator(s) work with the Manager of each department and Principal Investigators identified to provide an appropriate response to address the observations within the time frame provided.
34. The final MHRA report and Trust response to the MHRA is reviewed and agreed by the STH Director of R&D and CRO Director, signed off by the Medical Director and is sent to the MHRA.
35. The Research Manager and Inspection Coordinator(s) manage the strategy to address the findings with the MHRA report, reporting to the Director of R&D, CRO Director and Medical Director.
36. The MHRA inspection certificate is filed appropriately in the Research Department central files.

Training for Inspection

37. The Research Department will provide training sessions for preparation and conduct of regulatory inspections on an "as required" basis.

B. Single Trial Regulatory Inspection where Trust is host to the study

Procedure

Notification of an inspection

1. On notification from the study Sponsor, of an inspection by the MHRA, the member of the Trust who is initially notified informs the Research Department Coordinator and Research Manager immediately.
2. The Research Manager immediately informs the Research Department Senior Management.
   2.1. The Research Manager immediately informs the Director of Research, CRO Director, Medical Director, and additional senior management, as appropriate.
3. The Principal Investigator with assistance from the Sponsor delegate(s) or Research Department Coordinator informs all departments identified for inspection, as appropriate. Departments that may be involved include but are not limited to:
   3.1. Department of the Principal Investigator
   3.2. Research Department
   3.3. Clinical Research Facility
   3.4. Cancer Clinical Trials Centre
   3.5. Pharmacy
   3.6. Information & Technology (IT)
   3.7. Radiology (STH or University)
   3.8. Laboratories
   3.9. Medical records
   3.10. Clinical Engineering

Preparation for an inspection

4. The Sponsor delegate(s), the Research Department Coordinator (referred to as Inspection Coordinator from herein) or Principal Investigator, as agreed, acts as the primary contact throughout the inspection process, coordinates the Department of the Principal Investigator, and keeps the Research Department and other identified departments and management informed in preparation for the inspection.
5. The Sponsor delegate(s) or Inspection Coordinator or Principal Investigator, as agreed, ensures that each identified department has access to appropriate training in preparation for inspection.
6. The Sponsor delegate(s), Inspection Coordinator or Principal Investigator, as agreed, organises an inspection pack for the Research Team and key individuals involved in the Inspection to include: name badges, "confidential" ink stamps, note books and document log templates, as appropriate.
7. The Sponsor delegate(s), Inspection Coordinator or Principal Investigator, as agreed, ensures that each identified department designates rooms for the inspection; one room where the inspection is to be conducted, a second where all documents are to be reviewed before inspection and a third "breakout" room for Inspectors; the room for inspection may also serve as the breakout room depending on availability of rooms.
8. Prior to inspection all members of each department identified for inspection ensures that documentation is reviewed and up to date and that they are aware of their location and content. Documentation to be inspected may include:
   8.1. All Departments
      8.1.1. Study and systems related documentation
      8.1.2. Contracts
      8.1.3. Staff training records, job descriptions and CVs
      8.1.4. Organisational charts
      8.1.5. SOPs
   8.2. Investigator site
      8.2.1. Case report forms
      8.2.2. Source documentation

8.2.3. Patient information and informed consent forms
8.3. Laboratories
8.3.1. Lab procedures
8.3.2. Equipment maintenance and calibration servicing routines
8.4. Pharmacy
8.4.1. Drug accountability
8.4.2. Equipment maintenance and calibration servicing routines
8.5. Clinical Engineering
8.5.1. Equipment maintenance and calibration records

Initial inspection contact

9. On arrival at the Department of the Principal Investigator, the Sponsor delegate(s) provides the Inspectors with an identification badge. The Principal Investigator informs the Inspection Coordinator of their arrival.
10. The Sponsor delegate(s) or Principal Investigator meets the Inspectors and escorts them to the designated room in the Department for the regulatory inspection.
11. The Sponsor delegate(s) confirms the identity of the Inspectors and the reason for inspection (routine or for cause).
12. The Sponsor delegate(s) arranges a pre-inspection meeting to be held with the Inspectors, the Principal Investigator and research team, and Research Department representative (this may be Research Manager or Inspection Coordinator) to discuss:
    12.1. The agenda and schedule of the inspection to provide availability to appropriate staff.
    12.2. 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.
    12.3. Establish timing of exit interview (close out meeting) at the end of an inspection.
13. The Sponsor delegate arranges a pre-inspection meeting with the Principal Investigator and research team and leads of the other departments involved to discuss:
    13.1. The agenda and schedule of the inspection.
    13.2. Confirmation of arrangements for designated inspection rooms.
    13.3. A Sponsor delegate and if permitted at least one member of the Trust must accompany the Inspectors at all times. The Trust representative may be a member of the Research Department or a member of the department under inspection as appropriate.
    13.4. A member of the research team or department being inspected is available at all times. To ensure consistency, where possible this should be the Principal Investigator, or the Inspection Lead for the department, as appropriate.
    13.5. The Sponsor delegate(s) or a member of the research team/department under inspection is designated to take notes during interviews; where no note takers are available, the Inspection Coordinator will take notes.
    13.6. The Principal Investigator or Department Manager of the department under inspection, as appropriate, is available to review documentation prior to being provided to Inspectors.
    13.7. A member of each research team or department is designated to retrieve and photocopy documents (Runner), as appropriate.

During an inspection

14. When the Inspectors request documentation for review:
    14.1. The Sponsor delegate(s) notes the document requested on a log and either retrieves it from the Sponsor site or requests the document from the Principal Investigator or delegate.
    14.2. The Runner retrieves the document for review by the Sponsor delegate(s), or Department Manager or delegate.
    14.3. The Sponsor delegate(s) or, Department Manager or delegate authorises the document as being within the scope and authority of the regulatory authority e.g. SOPs and site and master file documents.
    14.4. The Sponsor delegate(s) provides the document to the Inspectors in the designated room.
    14.5. The document is returned to file ASAP.
    14.6. If the Inspectors request to be left alone at any time, documents agreed and noted (as per 14.3) are left with them.
15. When the Inspectors request copies of documentation:

15.1. The Sponsor delegate(s) notes the document requested on a log.
15.2. The Runner obscures any confidential information e.g. financial information and makes duplicate copies of all documents requested.
15.3. The Runner provides a copy to the Sponsor delegate(s) or, Department Manager or delegate for management review.
15.4. The Sponsor delegate(s) stamps “confidential” on each sheet of the Inspector’s photocopy.
15.5. A duplicate set of all documents given to the Inspectors should be maintained.
15.6. At the conclusion of the inspection the documentation may be retained by the inspectors.

16. When the Inspectors request an interview with a Trust employee:
16.1. It is recommended that the interviewee requests appropriate management to be present throughout the interview.
16.2. A Sponsor delegate, member of the Department, or Inspection Coordinator who are not responsible for answering questions are designated to take notes during interview.
16.3. The interviewee assumes a friendly, cooperative, confident and professional attitude.
16.4. The interviewee does not guess, lie, deny the obvious, make misleading statements or engage in unconstructive arguments.
16.5. The interviewee responds in a concise, factual and accurate manner when the inspector asks a relevant question.
16.6. If the interviewee decides that the question is outside of their area of expertise or authority or outside the scope of the Inspector’s authority they should consult with their management representative.
16.7. If an interviewee does not understand the question and/or the context they should ask the inspector for clarification.
16.8. 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.
16.9. The interviewee does not solicit opinions from the Inspector.
16.10. The interviewee does not attempt to answer "what if” questions and other hypothetical questions.
16.11. The interviewee does not contradict something said by a colleague. If necessary, the interviewee leaves the room, confirms the correct answer, and then corrects the response with the Inspector.

Daily debriefing session

17. At the close of each day the Inspectors, Sponsor delegate(s), Principal Investigator and appropriate Trust representative (for example, Inspection Coordinator) hold a debriefing session to assess progress, discuss unresolved questions, provide outstanding requested information and plan the next day’s agenda.
18. The Sponsor delegate(s) or Principal Investigator disseminates the outcomes of the daily debriefing sessions as appropriate.

Close out of the inspection

19. A close out meeting is scheduled at the end of the inspection with the Inspector, Sponsor delegates, Principal Investigator and research team, and appropriate Trust representatives (for example, Inspection Coordinator(s), Research Manager, and management of other departments involved as agreed).
20. The inspectors provide verbal feedback summarising observations and findings made during the inspection.
21. The Sponsor delegate ensures that:
21.1. There is a clear understanding of the findings
21.2. Any erroneous findings are corrected at the time
21.3. A date when a report can be expected and when the Sponsor/Principal Investigator is expected to respond is confirmed.
22. The Departmental Managers provide feedback from the close out meetings to their teams.

Inspection reports

23. The Sponsor delegate(s) and note taker(s) work with members of departments and the Principal Investigators involved to produce an internal inspection report. The responsible members of each department are identified and take appropriate actions to address any relevant items within agreed timeframes. A copy of the report is sent to the Research Department Research Manager.
24. On receipt of the Regulatory Authority Inspection Report from the MHRA, the Sponsor delegate(s) work with the Manager of each department and Principal Investigators identified to provide an appropriate response to address the observations within the time frame provided. A copy is sent to the Research Manager for review.
25. The Sponsor response incorporating the Trust response to the MHRA report is sent to the Regulatory Authority by the Sponsor delegate(s).
26. The Research Manager and Inspection Coordinator(s) manage the strategy to address Trust related findings with the MHRA report, reporting to the Director of R&D, CRO Director and Medical Directors.

Training for Inspection

27. The Sponsor delegate(s) and/or Research Department will provide training sessions for preparation and conduct of regulatory inspections on an “as required” basis.

Appendix 1
STH Related Documents

	Document	Research Department Network Location	Website	Database	Created by
1	Master file template	Directory\Research Governance\Project Authorisation\Templates\Site file index	No	No	n/a
2	Investigator Site template	Directory\Research Governance\Project Authorisation\Templates\Site file index	Yes	No	n/a
3	Document log template	S:\General\Research Governance\Inspections\! MHRA Statutory Inspection 2007\Administration docs	No	No	AL