Sheffield Teaching Hospitals NHS
NHS Foundation Trust

Research Department

STANDARD OPERATING PROCEDURE

STH Researcher

Sponsor monitoring of STH-Sponsored IMP Studies

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Standard Operating Procedure: STH Researcher
Monitoring

This SOP has been produced in accordance with Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments, Research Governance Framework 2005 and ICH GCP guidelines. This SOP will outline the procedure for monitoring of STH Sponsored investigator-led clinical trials.

Background

In accordance with current legislation and guidelines, STH Research Department has a responsibility to ensure that monitoring arrangements are in place for all research studies conducted within the Trust including those where STH is acting as sponsor. This SOP focuses on STH Sponsored studies that fall under the Medicines for Human Use (Clinical Trials) Regulations 2004 and subsequent amendments where STH as Sponsor has a legal responsibility to ensure studies are subject to appropriate levels of monitoring. STH Sponsored studies falling outside the remit of the Regulations are not currently subject to monitoring visits, but study status will be monitored by the submission of reports by the Investigator as requested by Research Department. For studies with an external Sponsor, the STH Research Department satisfies itself that the appropriate monitoring arrangements are in place as part of the authorisation process.

Definition

According to ICH GCP (section 5.18) the purposes of trial monitoring are to verify that:

i. The rights and wellbeing of the human subjects are protected
ii. The reported trial data are accurate, complete and verifiable from source documents
iii. The conduct of the trial is in compliance with currently approved protocol/amendments, with GCP and with applicable regulatory requirements

Monitoring procedures are designed to ensure that data are collected and recorded accurately, that studies are managed effectively and efficiently and that study staff act in full compliance with regulatory and Trust polices.

This SOP outlines the procedures to be followed for the monitoring of IMP studies sponsored by STH.

Procedure

A. Studies not using a CTU/CRO for full project management[1]

Pre-monitoring visit procedures

1. The PI or delegate informs the R&D Coordinator as soon as the first patient is recruited into the study.
2. The R&D Coordinator(s) and PI or delegate confirm a suitable time and date for a monitoring visit. The PI confirms the availability of at least one named member of the research team to answer questions and assist the R&D Coordinator if necessary.
3. The R&D Coordinator(s) sends a letter confirming the date, time and objectives of the Monitoring Visit.
4. The PI or delegate arranges for the Investigator Site File, completed Case Report Forms (CRFs) or data collection tools, patient medical notes and any other documentation required to be available for the monitoring team on the date of the visit and arranges a suitable space for the monitoring team to work in.

[1] These will generally be single centre studies. Due to limited resources STH is unlikely to be able to agree to Sponsor multi-centre UK-based IMP clinical trials without project management and monitoring by an STH approved Clinical Research Organisation (CRO) or Clinical Trials Unit (CTU); STH will delegate responsibilities to the CRO or CTU as defined in a study specific agreement.

Monitoring visit procedures

5. The monitoring team consists of the R&D Coordinator assigned to the trial and where possible an additional suitably trained colleague.
6. During the visit the PI provides the R&D Coordinator(s) with unlimited access to the Investigator Site File, completed Case Report Form (CRF)s/data collection tools, source documents (patient notes) and other documentation as required.
7. During the monitoring visit the R&D Coordinator(s) will (as time permits):
   - 7.1. Confirm an investigator site file is in use and review the contents.
   - 7.2. Ensure all essential documents in compliance with the Research Governance Framework. GCP and relevant legislation are in place as per the investigator site file template.
   - 7.3. Review the study specific documents and any amendments.
   - 7.4. Review subject enrolment and the arrangements in place for obtaining informed consent.
   - 7.5. Confirm that all study subjects have an appropriately signed and dated Informed Consent Form (ICF).
   - 7.6. Review filing and location of ICF.
   - 7.7. Review the documentation of the subjects participation in the study in the patient medical notes.
   - 7.8. Review safety data and safety reports.
   - 7.9. Compare any Serious Adverse Event (SAE) and Suspected Unexpected Serious Adverse Reaction (SUSAR) reports at site with those in the Research Department and confirm reporting to Sponsor, MHRA and Research Ethics Committee accordingly.
   - 7.10. Review research team details e.g. CV, delegation log and training records.
   - 7.11. Review sample of CRF to evaluate accuracy and completeness of recorded data.
   - 7.12. Perform additional monitoring procedures as deemed necessary.

Post-monitoring visit procedures

8. The PI receives a monitoring visit report from the R&D Coordinator(s). The report details all findings observed during the visit and recommendations for actions that the research team should take in order to address the findings in the Summary of Findings section of the monitoring report.
9. The PI contacts the R&D Coordinator(s) to seek clarification on any of the findings or recommendations.
10. The PI completes the Investigator Comments column of the Summary of Findings section of the monitoring report detailing the actions that have been/will be taken to address each finding. The PI sends the completed report to the R&D Coordinator(s) within one month of receipt of the initial report.
    - 10.1. The PI provides evidence that the required actions have been undertaken on request.
    - 10.2. If the PI does not address the issues adequately the PI receives feedback from the R&D Coordinator and is requested to re-submit their response in writing within a specified period (standard timeline being one month)
    - 10.3. If no response or further inadequate responses are received the Director of R&D may request a further monitoring visit if appropriate or may suspend the study if appropriate, until an adequate response is received and/or the Research Department has conducted a site visit (to be decided on a case by case basis).
11. If the PI feels that the report does not accurately reflect the conduct of the study they may request further consultation with the Research Department.
    - 11.1. The PI sends a request in writing, stating the reasons for the request.
    - 11.2. The R&D Coordinator(s) confirms receipt of the request and schedules a meeting with the PI and appropriate members of the Research Department.
    - 11.3. At the meeting, the PI and Research Department aim to resolve differences of opinion.
    - 11.4. If further clarification is required advice is sought from the appropriate regulatory authorities and experts in ethics and research governance, as applicable.
    - 11.5. The Director of R&D makes the final decision on the appropriate actions to be taken.
12. Where the Research Department feels it appropriate, the R&D Coordinator arranges for a follow up monitoring visit within 6 months to re-assess the site and confirm that all findings have been addressed.

Study close out visit

13. The PI alerts the R&D Coordinator of Last Patient Last Visit (LPLV) and arrangements are made for a final monitoring visit (study close out visit).

14. At the final monitoring visit, in addition to the activities for monitoring visits described above, the R&D Coordinator ensures that the PI understands their responsibilities[2] with respect to
    14.1. filing end of study declaration to the Research Ethics Committee and MHRA.
    14.2. submitting a final report to the Research Ethics Committee, MHRA and Research Department
    14.3. study archiving arrangements
    14.4. drug accountability (destruction where applicable)

Serious breaches of GCP or patient safety

15. If any Monitoring Visit identifies any serious breaches of GCP or the trial protocol, the R&D Coordinator(s) alerts the Research Manager, CRO Director, Director of R&D, Medical Director and appropriate members of Trust management as applicable.
    15.1. The Director of R&D or delegate informs the PI of the serious breach and suspends further recruitment until further notice if appropriate.
    15.2. The Research Department takes the appropriate actions as described in the Protocol Non-Compliance and Management of Serious Breaches SOP C125 informing the MHRA and Research Ethics Committee as applicable.

B. Studies using a CTU/CRO for full project management

Monitoring procedures

1. The PI or delegate informs the CRO or CTU as soon as the first patient is recruited into the study.
2. The CRO or CTU undertakes monitoring activities and pharmacovigilance activities as delegated to them.
3. The CRO or CTU keeps the Sponsor informed as appropriate.

Serious breaches of GCP or patient safety

4. If any Monitoring Visit identifies any serious breaches of GCP or the trial protocol, the CRO or CTU notifies the R&D Coordinator who alerts the Research Manager, CRO Director, Director of R&D, Medical Director and appropriate members of Trust management as applicable.
    4.1. The Director of R&D or delegate informs the PI of the serious breach and suspends further recruitment until further notice if appropriate.
    4.2. The Research Department takes the appropriate actions as described in the Protocol Non-Compliance and Management of Serious Breaches SOP C125 informing the MHRA and Research Ethics Committee as applicable. Where this responsibility is delegated to the CTU/CRO in the collaboration agreement the CTU/CRO takes the appropriate action as described in their own relevant SOPs, keeping the Sponsor informed as appropriate.

[2] Refer to investigator study close out responsibilities guidance, Appendix 2

Appendix 1. Associated Documents

	Document	Research Department network drive	Website	Database	Created by
1	Monitoring visit letter template	S:\General\!_Working Drafts\Research Governance\Monitoring documents	No	No	PC
2	Monitoring visit log	S:\General\!_Working Drafts\Research Governance\Monitoring documents	No	No	PC
3	Audit & Monitoring Schedule	S:\General\!_Working Drafts\Research Governance\Monitoring documents	No	No	EW/AL
4	Investigator site file template	S:\General\Research Governance\Project Authorisation\Templates\Site file index	No	No	TL
5	Investigator study close out responsibilities	S:\General\!_Working Drafts\Research Governance\Monitoring documents\close out	No	No	PC
6	MHRA Guidance for the notification of serious breaches of GCP or the trial protocol	NA	NA	NA	MHRA

Appendix 2. Investigator study close out responsibilities guidance

Study close out

Investigator responsibilities

Study close out should occur as soon as possible after the last patient has completed all scheduled visits associated with the study (also known as Last Patient Last Visit, LPLV). At study close out the site Principal Investigator (PI) should ensure that all study obligations have been met and post study obligations are understood. Principal Investigator responsibilities are detailed below.

#	**Responsibility**	**Action required**
1	Confirm that all study procedures have been completed	Data collected, and study drug and supplies are returned to the responsible party or prepared for destruction.
2	Ensure all Investigational medicinal product (IMP) has been accounted for and that arrangements have been made for destruction	Responsibility for the IMP at site rests with the PI. The PI may have delegated responsibility to the Pharmacy Clinical Trial Manager. This should be clearly documented in the Investigator site file. The PI should ensure that they have discussed IMP accountability, destruction and archiving of pharmacy-related study documentation with the Pharmacy Clinical Trial Manager. If IMP records are to be retained elsewhere location and access should be documented in the Investigator Site File and on the archiving list.
3	Ensure the Investigator site file is well organised and complete	Ensure that the study documents are filed according to the Sponsor template and an index is completed and filed at the front of the file. Documents should be filed in chronological order with the latest document at the front. For clarity multiple copies of the same document should be destroyed. Each document should be filed once in the appropriate section. If a second copy is deemed appropriate a file note explaining location of the original document may avoid confusion. The site file should be complete; all efforts should be made to obtain all documents.

		A file note should be added where a document is missing and filed in the section where the document should be filed. The site file should be easy to follow by people other than the research team e.g. auditors and inspectors. Any historical decisions made with regard to conduct of the study which are not easily understood from the study documentation should be file noted appropriately .e.g. errors made by the PI or REC on document version control Superseded documents should be marked as such and filed in a superseded documents section
4	Ensure that the Investigator site files and CRFs are accessible for external audit or inspection	The documents in the Investigator site file demonstrate compliance with ICH GCP and will be scrutinised during an audit or inspection to confirm this compliance. The PI must ensure that all documents are archived in a way that ensures they are readily available upon request.
5	Ensure that the investigator site file and Case Report Forms are archived in appropriate place	The archive should contain all essential documents as required in Section 8 "Essential documents for the conduct of a clinical trial " of the E6 ICH guidelines on Good Clinical Practice, All essential documents should be boxed and labelled with trial name, reference number, trial site name (and number if applicable), the name of the CI and lead centre and the date they were archived. The room must be fireproof, waterproof and secure, with access only by authorised personnel
6	A record of what is archived and where should be retained and be accessible on request by the principal investigator and/or a named archivist	The PI retains responsibility for the study documentation and should ensure that an accurate record of exactly what is archived. This record should be retained with the archived documents. A copy should be retained by the PI. The Research Department should be provided with this list of archived document and informed of who the archivist is and where the archived files are located. If archived documents are reviewed at a later date, who, what and when they were accessed should be recorded.

7	Records are to be retained for a minimum of 15 years	The sponsor i.e. Research Department should be contacted after 15 years for confirmation that documents may be destroyed
8	Ensure the Research Ethics Committee (REC) have been informed of study completion	The CI with support from the Research Department or delegated CTU/CRO as required, will submit the "Declaration of the End of a Clinical Trial form" to the REC on receipt of confirmation that the LPLV at all sites has been reached. A copy of the form will be sent to the Research Department and all PIs. The PI is responsible for filing this in the Investigator site file.
9	Ensure the Regulatory Authority (MHRA) have been informed of study completion	The Research Department or delegated CTU/CRO will submit the "Declaration of the End of a Clinical Trial form" to the MHRA on receipt of confirmation from the CI that the LPLV has been reached at all sites. It is the CI's responsibility to inform the Research Department of this milestone, requesting that the declaration is sent to the MHRA and providing any information required. A copy of the form will be sent to the CI and PIs. The PI is responsible for filing this in the Investigator site file.
10	Prepare and submit a report summarising study conduct to the REC and MHRA within 12 months of the end of the clinical trial	The CI has a responsibility to submit a summary of the final report on the research to the REC and MHRA within 12 months of the end of the project; where necessary the Research Department will provide support for submission. The summary of the final report may be enclosed with the end of study declaration, or sent to the REC and MHRA subsequently. There is no standard format for final reports. As a minimum, the REC and MHRA should receive information on whether the project achieved its objectives, the main findings and arrangements for publication or dissemination of the research, including any feedback to participants.
11	Complete a Final Study Report	On completion the final study report should be archived with all study documentation The CI should inform the Research Department of any publication that results from a research project.