SOP18b: Standard Operating Procedure for Preparing for External Audit and Inspection

Authorship Team: Jemma Hughes, Tina Morgan, for Joint SOP Group on Trial Processes (viz Leanne Quinn, Ian Russell, Anne Seagrove, Bridget Wells).

Authorised for implementation by WWORTH (JMG Ian Russell in chair)

Signature

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2 Glossary

The full Glossary is in Swansea University H drive/Documents/526-WWORTH/Development Group/Glossary.

3 Introduction

Standard Operating Procedures (SOPs) are succinct formal documents designed to achieve consistency in specified trial functions by specifying standard practice in performing those functions (GCP 1.55 & 5.1.1 – EMeA, 2002). While SOPs should cite relevant legislation & regulations, and key references & evidence, they need not expound theory.

WWORTH SOPs should accord with all relevant regulations, including the European Union Clinical Trial Directive, ICH Good Clinical Practice (GCP) and the current NHS Research Governance Framework. They will seek to distinguish between regulations for CTIMPs and for other research.

This document forms part of the set of standard operating procedures of the West Wales Organisation for Rigorous Trials in Health - WWORTH. It identifies the roles, responsibilities and actions of the individuals involved in preparing for and hosting audits and inspections by outside bodies.

An inspection may be located at the site of the trial, at the sponsor, trial unit or other establishments deemed appropriate by the Regulatory Authority (ICH GCP 1.29). An inspection is a formal process that has legal implications if non-compliance with the regulations is found. A regulatory inspection is very often “notified”; however there are exceptions if the Competent Authority (CA) has concerns for patient safety or grounds to suspect that improper practices are occurring at a site (see WWORTH SOP19a Pharmacovigilance & 19b Urgent Safety Measures). Under these circumstances, a “triggered” inspection will take place whereby inspectors have the legal right of entry to inspect premises at any time without notification. It is therefore imperative that all trial related documentation is maintained and continually updated in readiness for an inspection (see WWORTH SOP03 Master Site File).

An audit is a more informal and planned process and is typically conducted by the sponsor. Throughout the audit general information exchange between the auditor and the person(s)/institution being audited is acceptable and essentially is used as an evaluation tool. Any results obtained from an audit should be used to train staff and improve upon the quality of research conducted. Very often an internal audit is undertaken prior to an external inspection (see WWORTH SOP18a Quality Management).
4 Purpose

Both audits and inspections take place to examine ‘systems’ and look for good control of processes and opportunities for process improvement. This SOP will cover the processes necessary to prepare, host and participate in an MHRA inspection (see WWORTH SOP15 MHRA Approval).

The same principles should be applied in preparation for internal departmental audits, Sponsor’s or other regulatory inspection and Site inspections. This might involve audits of informed consent forms, adherence to the protocol (including subject eligibility criteria) and adverse event reporting.

5 Roles and responsibilities

It is a legal responsibility for the sponsor to ensure trials are regulatory compliant (see WWORTH SOP31 Sponsorship and Adoption).

The CI is ultimate responsibility for ensuring that the obligations of the inspection or audit are fulfilled. Tasks required to achieve this will usually be delegated to the trial manager (TM) and trial data manager (TDM); or to the WWORTH manager for an inspection or audit of the trial unit. For site inspections this responsibility may be delegated to the site PI or other local trial staff.

The PI is responsible for ensuring that all documents, personnel, office space and facilities required at a site are available.

The WWORTH Manager is responsible for coordinating the response to a general inspection of WWORTH, liaising with staff on all WWORTH trials to be audited, and delegating tasks where appropriate. He or she is also responsible, in association with the relevant TMs, for ensuring that TMFs for all WWORTH trials are complete and comply with regulatory requirements at all times.

The TM is responsible for assigning preparation tasks, arranging the attendance of trial personnel required for the inspection, and appointing a hosting facilitator, if delegated by the CI and for ensuring that suitable office accommodation and any facilities (e.g. printing or photocopying) are provided if required by the inspector(s).

The TDM is responsible for ensuring that all documents in the TMF are available in the format required by the inspector(s).

All WWORTH and trial staff are responsible for cooperating with staff preparing for audit, providing expertise (e.g. IT staff) and assisting where
appropriate.

6 Procedure

(a) Pre-Inspection

6.1 GCP Compliance Report

As part of the assessment process as to whether an Organisation will be chosen for Inspection, a yearly GCP Compliance report is completed and returned to the MHRA. The Compliance report details the numbers of clinical trials sponsored or hosted and request details of the number of patients recruited split according to trial type such as Phase 1.

6.2 What Inspectors are looking for

An inspector will be looking for a number of things during the inspection process including:

- Ensuring that the rights, safety and wellbeing of subjects are maintained.
- Ensuring regulatory compliance.
- Assessing staff competency and training, the organisation’s facilities and trial procedures undertaken.
- All trial related documentation.
- Verifying the integrity of the data captured.

The document ‘Common findings from inspections conducted by the MHRA’ is included as Appendix 1.

6.3 Personnel required during an Inspection

The following personnel, where appropriate, should be available to answer questions, and attend the opening and closing meeting before the inspector leaves the site.

- An appropriate representative of the sponsor
- Chief Investigators (CI) and any collaborating PI(s) for that site
- Trial Co-ordinators /Trial team personnel
6.4 General Preparation for Inspection

Prior to an inspection taking place it is important to organise/identify:

- An organisational dossier, for submission prior to the Inspection, which details the Organisational structure

- A room for the inspection to be conducted in.

- A further room close to the room where the inspection will take place, in order to house all trial documents that will need to be reviewed.

- Photocopying facilities.

- Facilities for printing out electronic files if requested.

- The name of the inspector and the scope of the inspection and all dates agreed in advance. It is essential that sufficient notice should be given to those expected to attend the inspection, with dates for availability of all involved, agreed well in advance. The hosting facilitator (who may be the WWORTH manager or a trial-specific or site-specific appointee) should negotiate a timetable of events and all roles and responsibilities agreed with the inspector(s).

- Inspection training/mock interviews for staff to prepare for an inspection and this should be documented in the staff training records.

- Refreshments for the inspection team

6.5 Preparation of Trial Documentation

Prior to the inspection, it is important that the Organisational dossier (if Systems Based Inspection) is prepared, and all trial documentation for the trials to be inspected is up to date, reviewed and staff are familiar with their location and content. Many inspecting bodies will require all this documentation in paper format: if so, documents held electronically should be printed out in advance of the inspection.
The documentation that will need to be inspected includes:

6.5.1 **For a central trial inspection**

*Trial Master File (TMF)*: This is kept in the trial office, and must include all the essential documentation related to the trial. Any information or documents missing must be recorded on a file note and an explanation given. The TMF will be used as a focus for the Inspection.

6.5.2 **For site inspections:**

This will include any system relating to the life cycle of a trial from trial registration through to close out and archiving, including contractual details of any third party archiving facilities used. Many departments/sites may be involved in all these aspects from Medical Records to Pharmacy so it will be necessary for WWORTH to involve relevant PIs for all sites inspected.

6.6 **Documentation contents:**

- **TMF (CTU & Sites)**: This must include all the essential documentation related to the trial. Any information or documents missing must be recorded on a file note and an explanation given (ref SOP3).

- **Case Report Forms (CRF) (CTU & Sites)**: These must be completed and have been monitored by a designated WWORTH or trial member prior to the inspection. Any e-CRFs should be printed out or downloaded to CD. Any queries should be addressed and resolved.

- **Patient hospital notes/subject notes/source documentation (primarily clinical site inspection)**: All documentation used as source records must be available on the day of inspection. Patient hospital notes should include up to date annotations, General Practitioner (GP) letters, laboratory results, X-ray results etc. related to participation in the clinical trial. It may be useful to ensure patient notes are booked out for a few days prior to, during and few days after the inspection to ensure adequate review time and availability. If there are legitimate reasons why a patient’s hospital notes cannot be available, this must be explained if possible in advance of the inspection.

- **Pharmacy/drug accountability records (primarily clinical site inspection)**: All records pertaining to drug accountability must be accurate, complete and available for inspection. All signature logs must be maintained and any involved staff available for
questioning. Pharmacy SOPs for drug accountability must be up to date and available (see WWORTHSOP04 Trial Supplies Labelling).

- **Patient Information Sheets and Informed Consent Forms (CTU & Sites):** The inspector may ask for verbal clarification of the informed consent procedure for the individual clinical trial including requesting to see evidence of how eligibility was clearly assessed. Further, the Inspector will expect to see copies of the consent form and patient information sheet in the patient medical notes as well as in the trial site file. All email correspondence relating to the management of the patient in trial must also be printed and kept in the correspondence section of notes.

  The Investigator and study personnel involved in the informed consent process may be required to jointly discuss this with the inspector or they may be asked separately. The approved subject information sheet and all the informed consent forms must be available for review. These should all be monitored prior to an inspection.

- **Staff Training Records/CVs (CTU & Sites):** A file of all staff training records must be available and up to date. A copy of the CVs of all past and present trial personnel must be available, signed and dated in black ink. All central WWORTHS staff must have an understanding and overview of GCP and the staff that has direct involvement in trial authorisation must have undergone GCP training. All site and central trial staff involved in the conduct of the trial and who have a direct impact on the patient must have undergone GCP training. Laboratory staff and staff involved in performing diagnostic tests must have an overview and understanding of GCP (see WWORTHSOP02 Training).

- **WWORTHSOPs (CTU and sites):** A file of all SOPs/MOPs/Guides/Work instructions/policies and procedure etc. used within WWORTH (for a site inspection, those used within the trial) must be available. This may include archived SOPs. Ensure all staff are familiar with their content and that relevant training has been provided and documented in the staff training records (see WWORTHSOP01a on SOPs and WWORTHSOP02 Training).
(b) During Inspection

6.7 Practical arrangements

6.7.1 Meeting the Inspector or inspecting team
It must be agreed who will meet and greet the inspector. Ensure that they are met by the agreed time and in the agreed location.

Identification from the inspector must be obtained.

The inspector must be accompanied at all times to any relevant departments during the inspection. Ensure all relevant departments are prepared and ready for an inspector.

6.7.2 During the Inspection
An outline of the inspection process will be provided and the expected duration. (This will normally be agreed prior to the Inspection and there is normally a degree of flexibility for change in the programme). It may be necessary to have early starts and late finishes during an inspection. This must be arranged and agreed with the inspector and study team prior to the inspection.

During an inspection, information must not be volunteered. If you do not know the answer to a question agree that you will clarify the answer at a later date. Do not attempt to answer questions for which you are not clear of the answers. You may consult colleagues during this process but any information exchange should take place in a separate room from the inspector. A record of all questions asked must be kept and answers provided.

A review of any requested documentation should take place prior to it being given to the inspector (refSOP17; SOP22a). A list must be kept of any documentation requested and documents provided must be photocopied and marked "confidential". Under no circumstances should original documents be given to an inspector.

A round up at the end of each day is important to ensure that the inspection objectives are being met and that any information that has been requested has been provided.

(c) End Of Inspection

6.7.3 End of the inspection
At the end of the inspection a meeting will take place where the inspector
will provide verbal feedback of the findings. This will then be followed with a detailed written inspection report. If there are any serious inspection findings the WWORTH team or Host R&D Management team will consult all participating CI/PiPs prior to a response being sent to the Competent Authority.

The sponsor must ensure that an accurate and rapid response to any inspection findings is provided to the CA along with any supporting material. Please note that in some cases the sponsor may delegate duties to individual members of the study team to undertake. The responsibilities remain ultimately with the appointed sponsor.

Dissemination of Inspection findings should be used to evaluate research practices, and assist in staff training. Improving upon the quality of research conducted by implementing solutions to remedy the findings should be a priority after an inspection.

6.1 Classification of Findings

Critical:

a) Where evidence exists that significant and unjustified departure(s) from applicable legislative requirements has occurred with evidence that

i. the safety or well-being of trial subjects either have been or have significant potential to be jeopardised, and/or

ii. the clinical trial data are unreliable and/or

iii. there are a number of Major non-compliances (defined in (c) and (d)) across areas of responsibility, indicating a systematic quality assurance failure, and/or

b) Where inappropriate, insufficient or untimely corrective action has taken place regarding previously reported Major non-compliances (defined in (c) and (d)).

Major:

c) A non-critical finding where evidence exists that a significant and unjustified departure from applicable legislative requirements has occurred that may not have developed into a critical issue, but may have the potential to do so unless addressed, and/or

d) Where evidence exists that a number of departures from applicable legislative requirements and/or established GCP guidelines have
occurred within a single area of responsibility, indicating a systematic quality assurance failure.

Other:

e) Where evidence exists that a departure from applicable legislative requirements and/or established GCP guidelines and/or procedural requirement and/or good clinical practice has occurred, but it is neither Critical nor Major.

7 Training plan

All WWORTH staff involved with trials must undertake the appropriate generic and trial-specific training to ensure that they meet with the specific employers’ mandatory training requirements and the specific requirements of the trial. For example, for SU staff, all new employees must attend induction, fire and safety training (as well as role-specific training courses, e.g. laboratory safety). For new staff, additional training requirements should be identified alongside the specific role requirements and the WWORTH Unit Manager should make provision for the new staff member to attend the necessary courses as soon after appointment as is practicably possible.

It is the responsibility of the WWORTH Unit Manager (alongside the CI or TM) to identify all the SOPs that are relevant to a specific trial and in which the new member of staff should be trained. The WWORTH UM or the SOP author will provide group training for trial staff and/or one-to-one training, as required for new staff in relation to the specific SOPs identified. Training records should be filed both by the main employer and the staff member, in accordance with the specific employer requirements. Trial specific training should be filed in TMF or TSF as appropriate and every individual involved in a trial should have an individual training record (see WWORTH SOP2 Training).

Where the tasks specified in the individual SOPs are delegated to WWORTH staff, CIs/PIs or TMs, these delegated staff must ensure that they have attended a training course on GCP and keep up-to-date through attending refresher courses.

It is the responsibility of the CI/PI to ensure that all staff allocated duties on the study delegation log template of responsibilities are suitably trained in the activities linked to those duties (see WWORTH SOP16 Site Setup, Appendix 9 and Appendix 10).

Each trial should maintain a central training log and ensure that WWORTH has access to that log, not least to integrate the logs of staff who work on more than one trial. Similarly trials should ensure that each site maintains a local
training log, not least to integrate the logs of staff who work for more than one sponsor.

Training in principle will take place during WWORTH SOP meetings to approve the SOP. The SOP will become effective after the training in principle.

Training in practice will be effective once a team member has completed the SOP’s tasks. The staff member will sign the “training in practice log” (see WWORTH SOP02 Training). New staff members will receive one-on-one training from either the author of this SOP or a suitable person from WWORTH (e.g. Manager, QAO) on use of this SOP.

8 References

1. ICH Harmonised Tripartite guideline for Good Clinical Practice (1996)


9 Related SOPs

WWORTH SOP01a on SOPs
WWORTH SOP02 Training
WWORTH SOP03 Master Site Files
WWORTH SOP04 Trial Supplies Labelling
WWORTH SOP05 Informed Consent
WWORTH SOP15 MHRA Approval
WWORTH SOP17 Monitoring
WWORTH SOP18a Quality Management
WWORTH SOP19a Pharmacovigilance_19bUSMs
WWORTH SOP22a Data Collection Management
WWORTH SOP31 Sponsorship and Adoption
WWORTH SOP32 Detecting and Managing Misconduct, Serious Breaches and Deviations from GCP/Protocol

10 Appendices

Appendix 1: Common findings from inspections conducted by the MHRA
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This is based on a presentation given by the MHRA to the NHS R&D Forum Research Governance Working Group in Nov 2005 and from the experience of five non-commercial organisations that have been inspected.

MHRA experience of non-commercial organisations

- Organisations are very open to recommendations & proactive in response to inspection findings
- Organisations are willing to develop systems through extensive networks
- Findings are often in-line with those identified by internal audit/R&D function
- Findings are very similar to those in commercial organisations

NHS organisation-wide

- Potentially inadequate systems to ensure researchers do not commence research before all approvals are in place
- Unclear sponsorship arrangements for DDX studies rolled over to CTA studies
- Inadequate pharmacovigilance systems and/or inadequate use of systems in place
- Lack of written agreements between departments documenting role in IMP trials

Contract management

- Omissions, errors and discrepancies in contracts
- Responsibilities of collaborating parties not clearly defined
- Unclear ownership of documents and data
- Lack of consistency between protocol and contract
- Many activities delegated to Chief Investigator without agreements or robust systems in place

Quality systems

- Lack of essential SOPs
- Uncontrolled documents used in place of SOPs
- SOPs / Protocol do not reflect current practice or current legislation
- Insufficient time between issuing and implementing SOPs, leading to training issues
- Meetings and decisions not documented
- In-process checks not documented
- Internal audit programmes built around Research Governance Framework only and do not take account of Clinical Trials Regulations
Investigational Medicinal Product

- Missing or unsigned documentation (e.g. shipping records, accountability, dosing records)
- Inadequate provisions for storage of IMPs i.e. not kept separate to usual clinical supplies
- Emergency codes not supplied concurrent with supplies or prior to study start
- Insufficient records for the chain of custody (from purchase to destruction) for marketed products used in clinical trials
- Ethical approval
- Lack of approval for study advertising
- Study conduct at sites outside of those in the application

Informed consent

- No records of consent being taken
- Missing elements
- Inconsistencies with protocol
- Forms not updated with amendments, poor version control
- Incorrect form used
- Unclear process

Pharmacovigilance

- Lack of involvement of Principal or Chief Investigator
- Lack of awareness of legislative requirements (7 and 15 day reports)
- Failure to distinguish AEs and ADRs
- Failure to identify ‘Serious events’
- Failure to consider event expectedness, and hence to identify events which require IMMEDIATE reporting
- Failure to monitor pregnancy to outcome
- Failure to monitor increased severity or frequency through trend analysis

Research staff

- Lack of evidence of GCP training amongst PIs and research staff
- Inadequate arrangements for cover in absence of PIs
- Poor document control and management
- Delegation logs incomplete. Delegated responsibilities not clear.
- Lack of documentary evidence of PIs involvement in trial e.g. informed consent procedure
- Unclear indemnity arrangements for honorary contract holders
- Records retention and management
- Issues relating to record management outside the control of the Central Records Department.
- Facilities and offices used to temporarily store Medical Records of trial subjects, and trial-related documents, e.g. consent forms and CRFs, not sufficiently secure
- Tracing system may be inadequate for all records required to reconstruct clinical trial historically
- Inadequate retention period in radiology
- Inadequate retention of evidence of validation for alternative media used to store records
- Inadequate retention of QA and QC data in laboratories
- Inadequate retention of raw source data with implementation of electronic archiving
- Information Management & Technology
- Lack of organisation-wide disaster recovery plan
- Lack of procedures and documentation to provide assurance that computer systems are demonstrably fit for purpose
- Some locally developed systems not sufficiently secure

Data Integrity
- Methods of analysis are inadequately documented (or have not been considered)
- Systems and procedures for data management (including assurance for the validity of the data) are absent, inadequate or failing
- Miscellaneous findings
- Lack of documentation of validation of computer systems
- Lack of GCP training or evidence of training
- Study documentation not in secure place with restricted access
- Poor document control – involvement of Principal Investigator variable and not documented
- Poor document control – inadequate retention periods for documentation
- Unidentified or unexpected laboratory samples analysed for a range of tests - this may be outside the protocol and therefore without consent

A review of existing policies and systems (including organisation-wide policies not specific to research) against these findings will identify areas of work. These should be prioritised using a risk-based approach.

**Recommendation 10: Review your system against the common findings from inspections conducted by the MHRA**
- Test your systems for compliance.
- Document and prepare an action plan for any system development.