South Eastern Health and Social Care Trust

Standard Operating Procedure (SOP)
Research and Development Office

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Author:	Alison Murphy, Research Manager Endorsed by Paul Carlin
Approved by:	Dr David Hill
Signed:	
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1.0	Oct 2007	Katrina Hughes	N/A
2.0	Aug 2011	Alison Murphy	Updated to reflect new SOP format. Included guidance on trial site 'good housekeeping' and central monitoring. Revised information on on-site monitoring to reflect provision by CRSC

Table of Contents

1. INTRODUCTION

Monitoring is defined in The International Conference on Harmonisation of Good Clinical Practice (ICH GCP) guidelines as:

"The act of overseeing the progress of a clinical trial, and of ensuring that it is conducted, recorded, and reported in accordance with the protocol, SOPs, GCP, and the applicable regulatory requirement(s)", ICH GCP, section 1.8"

Section 25.18 of ICH GCP states in detail the minimum requirement for monitoring of clinical trials.

The purpose of monitoring is to verify that:

- Rights and well-being of the human subjects are protected.
- The reported trial data are accurate, complete and verifiable from source documents
- The conduct of the trial is in compliance with the currently approved protocol/amendments(s), with GCP, and with the applicable regulatory requirements.

Monitoring has an integral role in the Quality Control (QC) of a clinical trial and is designed to verify the quality of the study. Audits are designed to assess the reliability and integrity of a trial's quality control systems and are a way of measuring performance against recognised standards and therefore ensure a Quality Assurance (QA) mechanism.

2. OBJECTIVE

The objective of this Standard Operating Procedure (SOP) is to describe the monitoring procedures for clinical trials sponsored by South Eastern Health and Social Care Trust.

3. SCOPE

This Standard Operating Procedure applies to clinical trials sponsored by South Eastern Health and Social Care Trust.

4. PROCESS

There are various forms of monitoring that can be undertaken in a trial. Monitoring should be proportionate to the objective, purpose, design, size and complexity, blinding, endpoints and risks associated with the clinical trial. It is the Sponsor's responsibility to determine the appropriate level and nature of monitoring required for their clinical trial.

4.1 Oversight committees

The funding body or sponsor may specify particular oversight arrangements. But even if they do not, some form of oversight is strongly recommended for all trials, although the

appropriate structures will vary according to the size, complexity and risks associated with the trial.

4.1.1 Trial Management Group (TMG)

Every trial should have a TMG, although in simpler studies this may comprise only one individual: the CI. For larger studies, this normally includes individuals who are responsible for the day to day management of the trial (e.g. the CI, trial coordinator, statistician, research nurse, data manager). The group's role is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The terms of reference for these groups should be held with the CI.

4.1.2 Data Monitoring Committee (DMC)

A DMC should be considered for all trials, although one may not be always necessary (e.g. non first in man phase I/II studies). A DMC may be set up for all phase III clinical trials. Its role is to review the accruing trial data at intervals to monitor the progress of the trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial (ICH GCP 5.5.2) and to assess whether there are any safety issues that should be brought to participants' attention.

The DMC should be the only body that has access to unblinded data.

DMCs might consider using the DAMOCLES Charter proposed in the Lancet 2005 as a model for the organisation of the IDMC.

4.1.3 Trial Steering Committee (TSC)

The role of the TSC is to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. It should agree the trial's protocol and any protocol amendments and provide advice to the investigators on all aspects of the trial.

The TSC may have members who are independent of the investigators, in particular an independent chairperson.

Generally within the South Eastern Health and Social Care Trust these are in place for larger high-risk studies.

4.2 Trial Site 'Good Housekeeping'

Day to day monitoring should be carried out by those responsible for the running of the trial. These activities may include, but are not restricted to, ensuring adherence to protocol, ensuring CRF's completed by authorised persons, ensuring no key data is missing and the data is valid, and reviewing recruitment rates and withdrawals.

4.3 Central Monitoring

Central monitoring involves the use of statistical techniques. These activities may include, but are not restricted to, range checks, calendar checks, review of unusual data patterns, rates of reporting between sites and repeated measures.

4.4 On-site Monitoring

In general, there is a need for on-site monitoring to help gain independent assurance that research is being conducted to the appropriate regulatory and professional standards, facilitate the development of GCP compliant research teams and where appropriate verify the accuracy and completeness of reported clinical trials data. The level of on-site monitoring should be proportionate to the objective, purpose, design, size and complexity, blinding, endpoints and risks associated with the clinical trial. It is the Sponsor's responsibility to determine the appropriate level and nature of on-site monitoring required for a clinical trial.

On-site monitoring of clinical trials sponsored by the South Eastern Trust will be performed by the Clinical Research Support Centre (CRSC), unless other monitoring arrangements are in place, for example if a trial is supported by a Clinical Trials Unit (CTU) or has a dedicated Trial Manager.

Monitoring will generally be requested by the Research Office before a trial begins, during recruitment and at the completion of a trial.

4.4.1 Qualification of monitors

Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. The monitor should keep training records, including relevant qualifications.

The monitor should be familiar with the Investigational Medicinal Product (IMP), the protocol, information sheet and consent for, as well as the South Eastern Health and Social Care Trust SOP's, GCP and applicable regulatory requirements.

4.4.2 Monitor's responsibilities

Monitors should ensure that the trial is conducted and documented properly by carrying out as a minimum the following activities:

- Data collected is consistent with adherence to the protocol
- Case Report Forms (CRFs) are being completed by authorised personnel as designated by the delegation log
- No key data is missing
- Data appears to be valid (ie within range and consistent)
- Check adherence to protocol and GCP
- Verify selected items recorded on CRFs match data in participants' health records
- Confirm that the participant has provided written consent

Full details are provided in appendix 1.

4.4.3 Monitoring Procedures

As on-site monitoring is generally performed by the CRSC their SOPs for conducting monitoring visits should be followed by their monitors.

In the event of other on-site monitoring arrangements, the six procedures attached to this SOP (Appendix 2) provide an outline of the information required by the Trust to ensure compliance with statutory requirements.

4.4.4 Monitoring report

Following the monitoring visit, the monitor should provide to the CI and the Sponsor a report which should include:

- Date, site, name of monitor
- Name of CI/Principal Investigator or other site personnel in attendance
- Summary of documents the monitor has reviewed, along with a statement of findings, deviations, deficiencies, conclusions, actions taken or recommended

5. REGULATIONS, GUIDELINES, REFERENCES, SOP LINKS ETC

http://www.ct-toolkit.ac.uk/route_maps/stations.sfm?current_station_id=319&view_type_map)

DAMOCLES Study Group (2005) A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet 365: 711-722

ICH GCP (1996), Section 1.8, 5.18 and 5.5.2

6. APPENDICES

6.1 Appendix 1: Monitor's responsibilities under ICH GCP (full details)

6.2 Appendix 2: Procedures for On-site Monitoring

6.1 Monitor's responsibilities under ICH GCP (full details)

The monitor(s) in accordance with the sponsor's requirements should ensure that the trial is conducted and documented properly by carrying out the following activities when relevant and necessary to the trial and the trial site:

a. Acting as main line of communication between the sponsor and the investigator.
b. Verifying that the investigator has adequate qualifications and resources and remain adequate throughout the trial period, that facilities, including laboratories, equipment, and staff, are adequate to safely and properly conduct the trial and remain adequate throughout the trial period.
c. Verifying, for the investigational product(s):
    I. That storage times and conditions are acceptable, and that supplies are sufficient throughout the trial.
    II. That the investigational product(s) are supplied only to subjects who are eligible to receive it and at the protocol specified dose(s).
    III. That subjects are provided with necessary instruction on properly using, handling, storing, and returning the investigational product(s).
    IV. That the receipt, use, and return of the investigational product(s) at the trial sites are controlled and documented adequately.
    V. That the disposing of unused investigational product(s) at the trial sites complies with applicable regulatory requirements) and is in accordance with the sponsor.
d. Verifying that the investigator follows the approved protocol and all approved amendments(s), if any.
e. Verifying that written informed consent was obtained before each subject's participation in the trial.
f. Ensuring that the investigator receives the current Investigator's Brochure, all documents, and all trail supplies needed to conduct the trial properly and to comply with the applicable regulatory requirement(s).
g. Ensuring that the investigator and the investigator's trail staff adequately informed about the trial.
h. Verifying that the investigator's trial staff are performing the specified trial functions, in accordance with the protocol and any other written agreement between the sponsor and the investigator/institution, and have not delegated these functions to unauthorized individuals.
i. Verifying that the investigator is enrolling only eligible subjects.
j. Reporting the subject recruitment rate
k. Verifying that source documents and other trial records are accurate, complete, kept up-to-date and maintained.
l. Verifying that the investigator provides all the required reports, notifications, applications, and submissions, and that these documents are accurate, complete, timely, legible, dated, and identify the trial.
m. Checking the accuracy and completeness of the CRF entries, source documents and other trial-related records against each other. The monitor specifically should verify that:
    I. The data required by the protocol are reported accurately on the CRFs and are consistent with the source documents.
    II. Any dose and/or therapy modifications are well documented for each of the trial subjects.

III. Adverse events, concomitant medications and intercurrent illnesses are reported in accordance with the protocol on the CRFs.
IV. Visits that the subjects fail to make, tests that are not conducted, and examinations that are not performed are clearly reported as such on the CRFs.
V. All withdrawals and dropouts of enrolled subjects from the trial are reported and explained on the CRFs.

n. Informing the investigator of any CRF entry error, omission, or illegibility. The monitor should ensure that appropriate corrections, additions, or deletions are made, dated, explained (if necessary), and initialled by the investigator or by a member of the investigator's trial staff who is authorised to initial CRF changes for the investigator. This authorisation should be documented.
o. Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, Research ethics Committees, the sponsor, and the applicable requirement(s).
p. Determining whether the investigator is maintaining the essential documents pertinent to the stage of the project .
q. Communicating deviations from the protocol, SOPs, GCP, and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.

6.2 Procedures for On-site Monitoring

Procedure 1 Check the On-Site Trial Master File

Check 100% Exist	**Yes**	**No**	**Not Checked (N/C) or Not Applicable (N/A)**	**Comments (include dates of relevant documents)**
Investigator Brochure plus updates				
A copy of the approved study protocol is present and signed (dated prior to implementation)				
Previous protocol versions present, signed and dated				
Copies of any protocol amendments				
Sample case report form				
Copies of the present patient information sheet and consent form approved by the Ethics Committee				
Copies of previous patient information sheet and consent form approved by the Ethics Committee				
Any other written information that the patient receives				
“Out of hours” contact information as provided by patients				
Example of letter to GP informing of patients trial participation				
Advertisement for subject recruitment				
Financial agreements				
Insurance statement (where required)				
The study Sponsorship Agreement and any other contracts relating to the research				
Copy of Ethics Committee Application				
Any correspondence with the Ethics Committee following application				
Any correspondence with the Ethics Committee following				

approval, such as approvals of protocol changes				
The Ethics Committee approval letter				
The Ethics Committee Composition				
Site Specific Assessment documentation (where required)				
Copy of Research Governance application				
The Research Governance approval letter				
Submission to and clinical trial authorisation from the Medicines and Health Care products Regulatory Agency identifying versions of documentation and annual “birth date” for the study				
Clinical Trial Agreement				
Curriculum Vitae present for all personnel (Signed and dated)				
Laboratory documentation including ranges and lab accreditation				
Sample of label(s) attached to the IMP container (GMP complaint)				
Instructions for handling the IMP				
Shipping records				
Certificate of Analysis				
Medication receipts				
Decoding procedures				
Patient randomisation codes and emergency code-breaks				
Monitoring Log and reports				
All original signed consents, filed in recruitment order				
Serious Adverse Event reporting procedure				
Copies of any serious adverse event reports made under the Medicines for Human Use (Clinical Trials) Regulations 2004				
Records of expedited SUSAR reports to MHRA, ethics and				

other appropriate bodies				
Copies of any adverse incident reports made under the normal reporting procedure used by the Trust / PCT				
Notification by Sponsor to Investigators of safety information				
Copies of yearly/interim study update reports submitted to the Ethics Committee and Research & Development				
Completed Subject Participation Log including those considered for the trial and not entered				
Drug Accountability Forms				
Signature Log				
Record of retained body fluids/tissue samples				
Delegation log of roles and responsibilities identifying all study personnel				
Records of telephone conversations/notes of study meetings				
Other correspondence				
Copies of research related publications				

Procedure 2 Check Other Source Data Including Health Records

Check 100% Exist	**Yes**	**No**	**Not Checked (N/C) or Not Applicable (N/A)**	**Comments (include dates of relevant documents)**
Are consent forms present for all those listed on the participant log?				
Are the correct patient information sheets and consent forms in use, as approved by the Ethics Committee?				
Is consent given prior to study procedures?				
Are all consent forms signed and dated by participant, researcher, witness, as appropriate?				
Have all procedures prescribed by the Ethics Committee been followed? Is there evidence of adherence to any special procedures in use for minors and incapacitated patients (if required)?				
Do participants meet the protocol Inclusion and Exclusion criteria?				
Do Case Report Forms and other study documents such as data collection sheets contain any entry error, omission or illegibility?				
Has the Investigator or person designated by the Investigator made appropriate corrections, additions, or deletions that are dated and initialled by the Investigator or person designated by the Investigator?				
Are deviations from the protocol or non-compliance with legislation and guidance documented and resolved?				
Have any unreported Serious				

Adverse Events that have been discovered during routine monitoring been documented, and reported to the Sponsor?				
Check 100% of Records	**Yes**	**No**	**Not Checked (N/C) or Not Applicable (N/A)**	**Comments (include dates of relevant documents)**
Have any unreported Adverse Events that have been discovered during routine monitoring been documented and reported to the Sponsor?				
Is informed consent recorded in writing in the health records?				
Is it stated in the patient health records that the patient has received a copy of the patient information sheet and signed consent form?				
Is a copy of signed consent for each patient recruited present in patient health records?				
Are study activities recorded in health records?				
Is there present in the patient health records a letter (to GP) informing of patients trial participation?				
Are reported Serious Adverse Events verifiable against patient records?				
Is withdrawal from the study documented (where applicable)?				
Is a label attached to the outside cover of the health records stating that the patient is taking part in a clinical trial?				
Are Primary outcome data consistent with source data?				

Procedure 3 Check Investigational Medicinal Products

Check 100% Exist	**Yes**	**No**	**Not Checked (N/C) or Not Applicable (N/A)**	**Comments (include dates of relevant documents)**
Are supplies being stored appropriately?				
Is a temperature log being maintained?				
Are drug accountability forms present and completed appropriately?				
Does patient administration match site accountability records?				
Has unused medication been returned?				
Is the amount of returned medication consistent with drug accountability records?				
Has unused medication expired?				
Are further supplies of the IMP required at Site?				

Procedure 4 Check Data Protection and Information Security

Check 100%	**Yes**	**No**	**Not Checked (N/C) or Not Applicable (N/A)**	**Comments (include dates of relevant documents)**
Do all researchers know where to find their Trust's data protection and information security policies and related information?				
Are all study participants' identifiable data collected during the study stored securely, whether on paper or computer?				
Is paper documentation stored in lockable cabinets, in a lockable room?				
Are study documentation such as questionnaires and other data collection instruments designed in such a way that they do not carry patient identifiable data?				
Are computer files containing identifiable data stored on a remote server? If not, why not?				
Are files password protected?				
Do data files for analysis use study id so individuals cannot be identified from them?				
Are computer files from which research participants can be identified stored on mobile devices?				

Procedure 5 Check Workplace Policies, Procedures and Contracts

Check 100%	**Yes**	**No**	**Not Checked (N/C) or Not Applicable (N/A)**	**Comments (include dates of relevant documents)**
Have the Investigator and all site staff working on the trial received training in Good Clinical Practice (GCP)?				
Is there evidence that all personnel have been trained in the protocol?				
Are all researchers aware of local policies and procedures regarding health and safety, adverse incident reporting etc.? (pay particular attention to staff from other institutions working on an honorary contract.)				
Is there evidence of • Local standard operating procedures? • Compliance with local standard operating procedures?				
Do all members of the research team who are not employees of this particular Alliance trust have honorary contracts of employment?				

Procedure 6 Check Equipment

Check 100%	**Yes**	**No**	**Not Checked (N/C) or Not Applicable (N/A)**	**Comments (include dates of relevant documents)**
Is all equipment used in the conduct of the study calibrated according to local Trust Policy?				
Do all fridges or freezers used in the conduct of the study have a thermometer in place to record temperature?				
Is a temperature log being maintained on a regular basis for all fridges or freezers used in the conduct of the study?				