

<u>Signën Clinical Discoveries Limited</u>	
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Title: SOP- Trial Management- Monitoring	
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Background

Signën Clinical Discoveries LTD (SCD) Standard Operating Procedures (SOPs) are designed to ensure that clinical research, and its supporting activities, is conducted to the principles of Good Clinical Practice (GCP)(1) and Good Data Management Practices (GDMP) (2). GCP is an international ethical and scientific quality standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of trials that involve the participation of human subjects. Compliance with GCP provides assurance that the data and reported results are credible and accurate, and that the rights, wellbeing and safety of participants are protected.

GCP states that all clinical trial information shall be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

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 1.38”

Section 5.18 of ICH GCP states in detail the minimum requirements 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/amendment(s), with GCP, and with the applicable regulatory requirements. Monitoring is 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 and assure

the reliability and integrity of a trial's quality control systems and are a way of measuring performance against recognised standards (Quality Assurance or QA).

Purpose

The purpose of this Standard Operating Procedure (SOP) is to describe the monitoring procedures for clinical trials

Scope

Monitoring Activities and Study Monitor Qualifications

Procedure

1 Qualification of monitors

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

The monitor should be familiar with the Investigational Medicinal Product (IMP), the protocol, information sheet and consent form, as well as the SCD SOPs, GCP and applicable regulatory requirements.

Before assigning any monitor to new monitoring task a short course refreshment should be applied

2 Types of monitoring

2.1 Coordinating Centre day-to-day monitoring

Day-to-day monitoring should be carried out by those responsible for running the study. This would normally include:

- Data collected are consistent with protocol
- CRFs are being completed by authorised staff
- No key data is missing
- Data appears to be valid

2.2 Central Monitoring

Centralised procedures can be used to confirm patient eligibility (usually through the collection of pathology reports to substantiate a diagnosis), to corroborate the existence of the patient (for example, through ONS flagging or collection of a an imaging investigation) and to determine the outcome (for example, ONS flagging for survival end-points or central assessment of the results of an investigation, such as a X-ray or scan).

In large, multi-centre studies, central monitoring of data using statistical techniques is particularly useful for identification of unusual patterns of data, and can be used to detect sites or individuals where there may be deviation from the protocol. This may

be due to a misunderstanding, but could indicate falsification of data. In either case, further investigation is required; a site visit, and additional training and support may be needed.

Although omissions (e.g. failure to report a serious adverse event) or data entry errors cannot be detected directly, it may be possible to compare data from the different sites to identify sites that warrant investigation.

Examples of central statistical monitoring techniques include:

1. Missing or invalid data

Range checks can be used to identify unlikely or implausible values, such as extreme values for weight, or diastolic greater than systolic blood pressure. For studies using electronic data capture methods, these checks can usefully be built into the data collection form; any such automatic safeguards should be validated to ensure that they function correctly.

2. Calendar checks

Examining the day of the week that patients were randomised can be revealing (e.g. randomisation on Sunday in a study of patients attending outpatient clinic). It is also helpful to compare the order of study forms (particularly if they have an ordered numbering system) with the dates they were completed.

3. Unusual data patterns

Data from one site can be compared with data for the trial as a whole to identify patterns such as digit preference, rounding, or unusual frequency distribution (e.g. mean, variance, skewness). Such checks can be applied both to a single variable (e.g. systolic blood pressure) and to the joint distribution of several variables (e.g. systolic blood pressure and weight).

4. Rates of reporting

The frequency of reported adverse events and of missing data can be compared between centres.

5. Repeated measures

Where the same variable is measured on multiple occasions for each participant during the study, it is possible to check that the variability and within individual changes of such repeated measurements is broadly consistent with the pattern seen for the trial as a whole.

6. Comparison with external sources

Checks with birth and death registries or with disease-specific registries (e.g. cancer registry) can be used to identify that particular patients exist and that particular events have (or have not) occurred.

In applying all these check it is important to recognise that some variability is to be expected. Data that are too good should raise suspicion in the same way as data that are unusually poor.

2.3 On-site monitoring

On-site monitoring visits may be used in a variety of different ways:

- to educate staff about the trial; review understanding of the protocol and trial procedures;
- to verify that the staff at the site have access to the necessary documents to conduct the trial;
- to ensure that the required pharmacy and laboratory resources are adequate;
- to check adherence to the protocol and GCP by reviewing such things as signed consent forms and patient eligibility, and
- to verify selected data items and/or serious adverse events recorded on the CRFs compared with data in the clinical records to identify errors of omission as well as inaccuracies.

Arrangements for site visiting may vary from routine visits to all sites, visits to a random selection of sites or visits targeted at less experienced sites or those for which the central monitoring procedures suggest possible problems.

3 Extent of monitoring

Monitoring should be proportionate to the objective, purpose, design, size, complexity, blinding, endpoints and risks associated with the clinical trial. It is the Chief Investigator's (CI) responsibility to determine the appropriate level and nature of monitoring required for their clinical trial.

3.1 Risk Assessment

Attachment 1 contains an example risk assessment form that can be used to determine the appropriate level of monitoring for your study.

In general, for most studies there will be a need for on-site monitoring, however, in some academic clinical trials, the CI in conjunction with the Sponsor, may decide that central monitoring alongside relevant training and meetings with extensive written guidance can assure appropriate conduct of the trial.

A low-risk study (ie score of 1-8) could entail some coordinating centre day-to-day monitoring and possibly central monitoring.

A medium-risk study (ie score of 9-16) could entail coordinating centre day-to-day monitoring, central monitoring as well as some on-site monitoring if issues arise at a site, or at a pre-determined level (eg 10%).

A high-risk study (ie score of 17-25) would definitely entail all the above types of monitoring.

4 Monitor's responsibilities

Monitors, in accordance with the requirements decided by the CI and Sponsor, 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 of the monitor's responsibilities as noted in section 5.18.4 of ICH GCP can be found in Appendix 2.

5 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

6 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.

6.1 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.

6.2 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). DMCs should 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.

6.3 Trial Steering Committee (TSC)

The role of a 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.

References

1. Medicines for Human Use (Clinical Trials) Regulations 2004, Schedule 1, Part 2 (<http://www.uk-legislation.hmso.gov.uk/si/si2004/20041031.htm>)
2. Good Clinical Data Management Practices, Society for Clinical Data Management, July 2008,US
3. CT-Toolkit (2004) Monitoring Procedures, http://www.cttoolkit.ac.uk/db/documents/Trial_MP.pdf
4. ICH GCP (1996), Section 1.8, 5.18 and 5.5.2
5. DAMOCLES Study Group (2005) A proposed charter for clinical trial data monitoring committees: helping them to do their job well. Lancet 365: 711-722

Attachments

1. **Monitoring Assessment tool**

Investigator Name	
Project Title	

Hazard	Impact	Likelihood	Risk Score
Trial design, randomisation system and outcome measures			0
Participating sites			0
Study population			0
Medicinal product			0
Trial supplies			0
Data management systems			0
Potential for adverse drug reactions			0
Oversight mechanisms			0
Mean Average			0

Impact		Likelihood	
1	Low	1	Remote
2	Moderate	2	Unlikely
3	Significant	3	Possible
4	Major	4	Likely
5	Catastrophic	5	Certain

Impact x Likelihood = Risk Score.

Risk Score ÷ Number of hazards = Mean Average.

Score	
Low risk (ie 1 – 8)	
Medium risk (ie 9-16)	
High risk (ie 17-25)	

CI Signature	Name (Print)	Date
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Hazard	To consider when applying score
Trial design, randomisation system and outcome measures	<ul style="list-style-type: none"> • Double-blind? • Placebo? • Rand between 2 IMP?
Participating sites	<ul style="list-style-type: none"> • Number of sites • International?
Study population	<ul style="list-style-type: none"> • Vulnerable? • Healthy volunteers? • Palliative?
Medicinal product	<ul style="list-style-type: none"> • Licensed? • First in man? • Used within SmPC?
Trial supplies	<ul style="list-style-type: none"> • UK Pharmaceutical company? • International supplier?
Data management systems	<ul style="list-style-type: none"> • Excel spreadsheet? • Paper-based? • Online database (eg Inform)?
Potential for adverse drug reactions	<ul style="list-style-type: none"> • Known safety profile? • Used outside SmPC? • Possible teratogenic? • Cytotoxic?
Oversight mechanisms	<ul style="list-style-type: none"> • TMG? • DMC? • TSC?

2 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 the 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 disposition of unused investigational product(s) at the trial sites complies with applicable regulatory requirement(s) and is in accordance with the sponsor.
- d. Verifying that the investigator follows the approved protocol and all approved amendment(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 trial 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 trial staff are adequately informed about the trial.
- h. Verifying that the investigator and 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.