

<u>Signën Clinical Discoveries Limited</u>	
Affiliate Location: Jeddah, Saudi Arabia Date: 25 February 2009	
Title: SOP- Trial Management- Protocol Development	
Authorized Signature:	Date: 25 February 2009
Third Party Approval:	Date: 25 February 2009

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.

A protocol is a document that describes the objective(s), design, methodology, statistical considerations and organisation of a study (3). A protocol should also include the background and rationale for a study.

According to the principles of GCP, a clinical study should be scientifically sound, and described in a clear, detailed protocol. The principles of GCP also state that a study should be conducted in compliance with the protocol that has received prior independent ethics committee (IEC) approval/favourable opinion.

Purpose

This SOP describes the process for generating a clinical study protocol.

Scope

This SOP applies to all personnel who are involved in the development, production and review of clinical study protocols for studies undertaken by SCD

Procedure

1. Selecting the protocol development team

The protocol development team shall include persons responsible for setting the objectives of the study, and for the design, methodology and organization of the study. The statistical considerations of the study shall be the responsibility of a statistician. At least one member of the team shall be responsible for quality control/quality assurance of the protocol. The size of the team will vary according to the nature, complexity and size of the clinical study and the expertise of the team members. The team will comprise the Chief Investigator and personnel representing other disciplines as appropriate (including but not limited to trial manager, statistician, health economist, qualitative researcher), A representative of the sponsor and other external personnel may be involved, as appropriate.

2. Protocol authorship

The protocol development team shall select an author who will be responsible for the writing and production of the protocol. The author shall collate relevant study information from the protocol development team members and present such information in an agreed format.

3. Content of the protocol

Once the research idea has been established, the protocol development team shall develop a draft protocol synopsis for review and approval. The synopsis may contain some or all of the following information: brief rationale for the study; primary and secondary endpoints participant population and proposed recruitment numbers, and treatment schedule. The application to the funder will usually serve as the protocol synopsis. The protocol development team shall then use the approved synopsis as the basis for a full clinical study protocol. The protocol shall contain at least the following information:

- Study number (where required, eg. EudraCT number and/or ISRCTN or similar)[8]
- Study background
- Study objective(s)
- Design and methodology (study size, treatment schedules, primary and secondary endpoints, etc)
- Organization (recruitment, site initiation, follow-up, etc)
- Publication policy
- For trials of Investigational Medicinal Products, a definition of end of study, arrangements for adherence to GCP, plans for trial supplies and pharmacovigilance arrangements shall be included [4, 5].

The protocol development team may refer to the International Conference on Harmonisation Guideline for Good Clinical Practice (ICH GCP Guideline) [3], see Appendix 1 of this SOP, and the relevant section of the Medical Research Council/

Department of Health(MRC/DH) Joint Project [4, 6] for content of the protocol. The content of the protocol will vary according to the nature, complexity and size of the clinical study.

The protocol development team shall agree the content of the protocol through face-to-face meetings, conference calls and/or email communications.

4. Format and storage of the protocol

The protocol shall be created electronically in Microsoft Word or similar software package using an agreed format. The protocol shall be stored on the assigned project-specific drive and backed-up on a regular basis.

5. Document control

The author assigned by the protocol development team shall be responsible for document control, i.e. shall always be considered to have the latest version of the protocol document. The assigned author shall be responsible for implementing any changes to the document that may be required during the development process.

6. Protocol review

The protocol shall be circulated for review by email, fax or post by the assigned author, or other agreed member of the protocol development team. The protocol shall be reviewed by personnel with medical and statistical knowledge. Further review of the protocol may be carried out by other members of the protocol development team, as appropriate. Sponsor review may also be conducted.

Review may be conducted electronically or using paper copy. The assigned author will be responsible for collating review comments and resolving any conflicting comments with the reviewers. The assigned author shall incorporate the consolidated comments and the protocol shall be circulated for further review as necessary. When a consensus has been reached the protocol will be finalised and signed-off.

7. Protocol sign-off

The protocol shall be signed off by the principal investigator, other personnel with medical knowledge if necessary, and personnel with statistical knowledge. Sponsor sign-off may also be required. The author will be responsible for ensuring the final version of the protocol is filed as part of the Trial Master File [7].

8. Submission to ethical committee/regulatory body

For studies requiring a favourable opinion from an ethics committee and/or a Clinical Trial Authorisation (CTA), the protocol development team shall assign responsibility for submission of the protocol to an ethical committee/regulatory body as part of an application for a favourable ethical opinion or CTA [8], [9].

9. Protocol amendments

A protocol amendment is a written description of a change(s) to, or formal clarification of, a protocol [3]. Any amendments to the clinical trial protocol following sign-off shall be incorporated into the protocol by the assigned author, or other

agreed member of the protocol development team. The protocol shall then be reviewed as described above.

The UK Department of Health Research Governance Framework for Health and Social Care [10] states that the principal investigator (or chief investigator for multicentre trials) of the trial is responsible for ensuring that substantive changes to the protocol are submitted for ethical review (by the Main Research Ethics Committee) and for the sponsor's agreement.

For studies requiring a Clinical Trial Authorisation (CTA), amendments to the protocol will be notified to the competent authority (Medicines and Healthcare Regulatory Agency in the UK) according to CRC SOP TM-002-** [8] and CRC SOP TM-008-** [9].

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. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Guideline for Good Clinical Practice E6(R1), Current Step 4 version (dated 10 June 1996) <http://www.ich.org/LOB/media/MEDIA482.pdf>
4. MRC/DH joint project . (http://www.ct-toolkit.ac.uk/route_maps.cfm)
5. CRC SOP TM-003-** Sponsor Safety and Pharmacovigilance Responsibilities
6. http://www.ct-toolkit.ac.uk/_db/_documents/Protocol.pdf
7. CRC Work Instruction TM-001-01-** Trial Master File
8. CRC SOP TM-002-** Request for Clinical Trial Authorisation to the Competent Authority
9. CRC SOP TM-008-** Obtaining the favourable opinion of an Ethics Committee for Health Related Research Ethics Submission
10. Department of Health. Research Governance Framework for Health and Social Care. Second edition, 2005
http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/@dh/@en/documents/digitalasset/dh_4122427.pdf

Appendix

International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Harmonised Tripartite Guideline. Guideline For Good Clinical Practice E6(R1). Current Step 4 version, dated 10 June 1996.

CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

- General Information
- Background Information
- Trial Objectives and Purpose

- Trial Design
- Selection and Withdrawal of Subjects
- Treatment of Subjects
- Assessment of Efficacy
- Assessment of Safety
- Statistics
- Direct Access to Source Data/Document
- Quality Control and Quality Assurance
- Ethics
- Data Handling and Record Keeping
- Financing and Insurance
- Publication Policy
- Supplements