STUDY SITE STANDARD OPERATING PROCEDURES

Clinical Trials Centre
Faculty of Medicine
The University of Hong Kong

STUDY SITE
STANDARD OPERATING PROCEDURES

Clinical Trial Centre

Faculty of Medicine
The University of Hong Kong

2/F, Block B, Nurses' Quarters, Queen Mary Hospital, 102 Pokfulam Road, Hong Kong
Telephone (852) 2855 4667 Fax: (852) 2974 1248
Website: http://www.hku hk/ctc

Published in Hong Kong by:
The Clinical Trials Centre
The Faculty of Medicine
The University of Hong Kong
Hong Kong SAR
PR China

ISBN 962-85405-2-1

Design and Layout: Polly Yu Production Ltd

Printed and bound in Hong Kong

For ordering details, please contact the publisher at
e-mail: ctcentre@hkucc.hku.hk

Being the first edition, the authors would gladly appreciate any constructive comments relating to the particular contents of this book, in order that any future editions can be updated accordingly.

James Thorburn B.Sc. Clinical Trials Education Co-ordinator, CTC.
Selene Tam Ph.D., B.H.Sc. R.N. Project Manager, CTC
Yolanda Yan B.Sc.N., R.N. Research Nurse, CTC
Johan Karlberg Ph.D., M.D. Director, CTC

CONTENTS

CLINICAL PROCEDURES

APPENDICES

INTRODUCTION

Over the years there have been a number of distinct changes in the way in which clinical research or more specifically, clinical trials on new investigational products are conducted. In particular, is the introduction of the ICH GCP Good Clinical Practice (ICH-GCP) guidelines in 1996; the international ethical and scientific standard for designing, conducting, recording and reporting clinical trials.

For international recognition, all aspects of clinical research should comply with the ICH GCP guidelines therefore, with the introduction of such guidelines, virtually all aspects of new investigational product trials are now performed in accordance to standard operation procedures (SOPs). For example, protocol development, finance, contracts, budget management, study site monitoring, data management, medical statistics, medical writing, central laboratory investigations and quality assurance such as audits. In all these areas, either the Sponsor, or a Contract Research Organisation (CRO) has developed SOPs for their full range of in-house, trial related activities.

However, to date there is to our knowledge no complete manual of study site SOPs for personnel such as Clinicians or Research Nurses involved in clinical trials, that ensures maximum compliance with the ICH GCP principles. Since the Clinical Trials Centre at The University of Hong Kong is responsible for clinical trial assurance at our own study sites, we therefore felt compelled to develop a full set of study site SOPs, that would be not only assist in ensuring compliance with GCP, but would also be useful source of information to anyone involved in clinical trials.

These study site SOPs have been compiled by a team of clinical research professionals with varying backgrounds in order to provide assistance to investigative site personnel involved in clinical trials whether they are an Investigator, Clinical Research Co-ordinator or Research Nurse. The study site SOPs are an essential tool that will ensure not only consistent attainment of high standards of all relevant staff involved in clinical trials, but they will also provide assurance that the requirements of the ICH GCP guidelines are met.

In addition to being a useful source of essential information for study site personnel, these study site SOPs form part of the curriculum of a twenty-hour specialised module of the Master of Medical Sciences degree in Clinical Research Methodology. The specialised module, entitled Good Clinical Practice (GCP) and Study Site Management, is offered by the University of Hong Kong as a short 20-hour course as well as to our clinical staff and other research support personnel involved in clinical research at the University.

The SOPs presented in this book only provide a framework for the establishment of a study sites own SOPs. The Investigator should therefore review all the SOPs individually and make any necessary adjustments to ensure compatibility with their own study site personnel, institutional and local regulatory requirements.

Effective Date: _____

Issue Date: _____

SOP No: P1

PREPARATION OF A CLINICAL TRIAL PROTOCOL AND AMENDMENTS

APPROVED BY:

_____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: P1

PREPARATION OF A CLINICAL TRIAL PROTOCOL AND AMENDMENTS

I. Purpose

This SOP is designed to assist the Investigator in the preparation and submission of a clinical trial protocol and amendments.

II. Other Related Procedures

SOP P3: Review and Validation of Clinical Trial Protocol
SOP P4: Review of Protocol Amendments
SOP P7: Contracts and Budgets
SOP P13: Independent Ethics Committee or Institutional Review Board

III. Procedures

A clinical trial protocol is a document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually gives the background and rationale for the trial, but these could be provided by other protocol referenced documents.

1. *General Information (Title Page)*

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

The protocol's face sheet is the primary source of identifying information for the Protocol. Each protocol submitted must therefore have a title page or face sheet that contains the following items:

	Yes	No*
a. Protocol title, protocol identifying number, and date. Any amendment (s) should also bear the amendment number(s) and date(s).	❑	❑
b. Name and address of the Sponsor and Monitor (if other than the Sponsor).	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
c. Name and title of the person(s) authorised to sign the protocol and the protocol amendment(s) for the Sponsor.	❑	❑
d. Name, title, address, and telephone number(s) of the Sponsor's medical expert (or dentist when appropriate) for the trial.	❑	❑
e. Name and title of the Investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).	❑	❑
f. Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than Investigator).	❑	❑
g. Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.	❑	❑
2. *Background Information*		
a. Name and description of the investigational product(s).	❑	❑
b. A summary of findings from non clinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.	❑	❑
c. Summary of the known and potential risks and benefits, if any, to human subjects.	❑	❑
d. Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).	❑	❑
e. A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).	❑	❑
f. Description of the population to be studied.	❑	❑
g. References to literature and data that are relevant to the trial, and that provide background for the trial.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
3. *Trial Objectives and Purpose*		
a. A detailed description of the objectives and the purpose of the trial.	❑	❑
4. *Trial Design*		
The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:		
a. A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.	❑	❑
b. A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.	❑	❑
c. A description of the measures taken to minimise/avoid bias, including:		
i. randomisation	❑	❑
ii. blinding	❑	❑
d. A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).	❑	❑
e. The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.	❑	❑
f. A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.	❑	❑
g. Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.	❑	❑
h. Maintenance of trial treatment randomisation codes and procedures for breaking codes.	❑	❑
i. The identification of any data to be recorded directly on the CRFs (i. e. no prior written or electronic record of data), and to be considered to be source data.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
4. *Selection and Withdrawal of Subjects*		
a. Subject inclusion criteria.	❑	❑
b. Subject exclusion criteria.	❑	❑
c. Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:		
i. When and how to withdraw subjects from the trial/ investigational product treatment.	❑	❑
ii. The type and timing of the data to be collected for withdrawn subjects.	❑	❑
iii. Whether and how subjects are to be replaced.	❑	❑
iv. The follow-up for subjects withdrawn from investigational product treatment/trial treatment.	❑	❑
5. *Treatment of Subjects*		
a. The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.	❑	❑
b. Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.	❑	❑
c. Procedures for monitoring subject compliance.	❑	❑
6. *Assessment of Efficacy*		
a. Specification of the efficacy parameters.	❑	❑
b. Methods and timing for assessing, recording, and analysing of efficacy parameters.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
7. *Assessment of Safety*		
a. Specification of safety parameters.	❑	❑
b. The methods and timing for assessing, recording and analysing safety parameters.	❑	❑
c. Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.	❑	❑
d. The type and duration of the follow-up of subjects after adverse events.	❑	❑
8. *Statistics*		
a. A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).	❑	❑
b. The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.	❑	❑
c. The level of significance to be used.	❑	❑
d. Criteria for the termination of the trial.	❑	❑
e. Procedure for accounting for missing, unused, and spurious data.	❑	❑
f. Procedures for reporting any deviation(s) from the original statistical plan. Any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate.	❑	❑
g. The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
9. ***Direct Access to Source Data/Documents***		
a. The Sponsor should ensure that it is specified in the protocol or other written agreement that the Investigator(s)/institution(s) will permit trial-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data/documents.	❑	❑
10. ***Quality Control and Quality Assurance***	❑	❑
11. ***Ethics***		
a. Description of ethical considerations relating to the trial.	❑	❑
12. ***Data Handling and Record Keeping***		
a. Publication policy, if not addressed in a separate agreement.	❑	❑
13. ***Financing and Insurance***		
a. Financing and insurance if not addressed in a separate agreement.	❑	❑
14. ***Publication Policy***		
a. Publication policy, if not addressed in a separate agreement.	❑	❑
15. ***Supplements***	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Section	*Comments*

Effective Date: _____

Issue Date _____

SOP No: P2

PRE-STUDY VISIT

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS.

No	*Section No*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1		3.	
2.		4.	

SOP No: P2

PRE-STUDY VISIT

I. Purpose

The purpose of this procedure is to describe the actions that need to be taken by the study site staff during a Pre-Study visit by the Sponsor.

II. Other Related Procedures

SOP P3: Review and Validation of Clinical Trial Protocol
SOP P4: Review of Protocol Amendments
SOP P5: Review of Investigator's Brochure
SOP A2: Format for Investigators CV

III. Procedures

		Yes	No*
a)	Prior to the release of any information to the Investigator, the Investigator will be required to sign a Confidentiality Statement provided by the Sponsor.	❑	❑
b)	Discuss with the Monitor brief details of the study and ensure that any written notes made at the time are retained and then subsequently filed in the Investigators study file.	❑	❑
c)	Discuss with the Monitor the recruitment rates and relevant recruitment strategies that will be utilised during the study.	❑	❑
d)	If there are any devices or items of equipment that are to be used by patients or subjects in the study, request the Monitor to explain and demonstrate the item and its functions.	❑	❑
e)	Ensure that details of the date of the next available IRB/IEC meeting or a list of alternative dates is available, as this information will be required by the Monitor.	❑	❑
f)	The Investigator/Clinical research Coordinator (CRC) will need to provide the Monitor with a signed and up to date copy of the Investigator's and CRC's CV.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

		Yes	No*
g)	The Monitor will ensure the Investigator has a current version of the study protocol along with any amendments, if appropriate.	❑	❑
h)	The Investigator and CRC should briefly review with the Monitor the contents of the Investigator's Brochure, and should make notes of any points that need further clarification, explanation or expansion by the Monitor.	❑	❑
i)	Provide the Monitor with an out of hours telephone contact number and/or fax number or email address for the Investigator or the CRC in order to allow the Monitor to be able to contact the Investigator out of clinical hours, if required.	❑	❑
j)	Accompany the Monitor on a visit of the Investigator's premises in order that he/she can inspect and assess the resources available at the Investigator's site.	❑	❑
k)	After the Pre-study visit, the Investigator/CRC should complete the checklist shown on page 4 of this SOP.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Appendix A

PRE-STUDY VISIT SUMMARY FORM

Date of Visit:

_____

Duration:

_____

Sponsor Contact Details

ATTACH BUSINESS CARD

Protocol Name: _____

Protocol No: _____ Date of Protocol: _____

	Yes	No	
Is it the final version of the protocol?	❑	❑	Draft No. _____

		Yes	No
1.	Is the study protocol acceptable?	❑	❑
2.	Are the benefits of the study greater than the risks for the study subjects?	❑	❑
3.	Are the following terms and conditions acceptable?	❑	❑
	a) insurance and indemnity	❑	❑
	b) compensation	❑	❑
	c) publication policy	❑	❑
	d) schedule of payments	❑	❑

_____ _____

Signature Date

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: P3

REVIEW AND VALIDATION OF CLINICAL TRIAL PROTOCOL

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: P3

REVIEW AND VALIDATION OF CLINICAL TRIAL PROTOCOL

I. Purpose

This SOP is designed to assist department staff in the checking of a protocol prepared by an external Sponsor, and is designed to enable adequate review of salient points. It may also be used as a guide for the preparation or review of site-generated protocols, or assisting an external Sponsor in writing a protocol.

II. Other Related Procedures

SOP P4: Review of Protocol Amendments
SOP P7: Contracts and Budgets
SOP P13: Independent Ethics Committee or Institutional Review Board

III. Procedures

A clinical trial protocol is a document that describes the objective(s), design, methodology, statistical considerations, and organisation of a trial. The protocol usually gives the background and rationale for the trial, but these could be provided in other protocol referenced documents.

	Yes	No*
1. *General Information*		
a) Check the title of the protocol and identify the protocol number and date.	❑	❑
b) Ensure that the name and address of the Sponsor and Monitor appears somewhere on the protocol. It is usually on the title page or in the appendix.	❑	❑
c) Identify the name and title of the person(s) who are authorised to sign the protocol and the protocol amendments.	❑	❑
d) Check that the name, title, address and telephone number(s) of the Sponsor's medical expert (or dentist when appropriate) for the trial is documented on the protocol.	❑	❑
e) Check that the protocol also includes the name and title of the Investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
f) In addition to the above, ensure that the name, title, address and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical decisions (if other than Investigator) is clearly stated.	❑	❑
g) If clinical laboratories are used, ensure that the name and address of the laboratory and any other medical and/or technical department(s) and/or institutions involved in the trial are identified.	❑	❑

2. *Background Information*

a) Identify the name and description of the investigational product(s) from the protocol.	❑	❑
b) Read the summary of the findings from non-clinical studies that are potentially clinically significant and that are relevant to the trial.	❑	❑
c) Check the summary of the known and potential risks and benefits, if any, to human subjects.	❑	❑
d) Look at the description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).	❑	❑
e) Check to see if there is a statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).	❑	❑
f) Identify the description of the population to be studied.	❑	❑
g) Briefly review the references to literature and data that are relevant to the trial, and that provide background for the trial.	❑	❑
In checking the protocol, remember that the ideal clinical situation is not always the ideal clinical trial situation, and most study protocols are a compromise between the two.	❑	❑

3. *Trial Objectives and Purpose*

a) Check that the protocol contains a detailed description of the objectives and the purposes of the trial.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

		Yes	No*
4.	***Trial Design***		
	The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design, and therefore, a description of the trial design, should include:		
	a) A specific statement of the primary endpoints, if any, to be measured during the trial.	❑	❑
	b) A description of the type/design of trial to be conducted (e.g. double-blind, placebo controlled, parallel design) and a schematic diagram of the trial design, procedures and stages.	❑	❑
	c) A description of the measures taken to minimise/avoid bias, e.g. Randomisation and Blinding.	❑	❑
	d) A description of the trial treatment(s) and the dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labeling of the investigational product(s).	❑	❑
	e) The expected duration of subject participation, and a description of the sequence and duration of all trial periods, include follow-up, if any.	❑	❑
	f) A description of the "stopping rules" or "discontinuation criteria" for individual subjects, part of trial and entire trial.	❑	❑
	g) Accountability procedures for the investigational product(s), includingthe placebo(s) and comparator(s), if any.	❑	❑
	h) Maintenance of trial treatment randomisation codes and procedures for breaking codes.	❑	❑
	i) The identification of any data to be recorded directly on the CRFs (i. e. no prior written or electronic record of data), and to be considered to be source data.	❑	❑
5.	***Selection and Withdrawal of Subjects***		
	a) Identify the subject inclusion criteria for the study.	❑	❑
	b) Identify the subject exclusion criteria for the study.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
c) Check the subject withdrawal criteria (i.e. terminating investigational product treatment) and procedures specifying.	❑	❑
d) Know when and how to withdraw subjects from the trial/ investigational product treatment.	❑	❑
e) Determine the type and timing of the data to be collected for withdrawn subjects.	❑	❑
f) Note the follow-up for subjects withdrawn from investigational product treatment/trial treatment.	❑	❑

6. ***Treatment of Subjects***

The treatments to be administered including the names of all the products, the dose, the dosing schedule, the route/mode of administration and the treatment periods including the follow-up period for subjects for each investigational product treatment/trial group/arm of the trial should be clearly stated throughout the protocol.

a) Identify the medications/treatments permitted (including rescue medication) and not permitted before and/or during the trial.	❑	❑
b) Check the procedures for monitoring subject compliance.	❑	❑

7. ***Assessment of Efficacy***

a) Check the specification of the efficacy parameters.	❑	❑
b) Understand the methods and timing for assessing, recording, and analysing the efficacy parameters.	❑	❑

8. ***Assessment of Safety***

a) Check the specification of the safety parameters.	❑	❑
b) Understand the methods and timing for assessing, recording and analysing safety parameters.	❑	❑
c) Identify the procedures for eliciting reports of and for recording and reporting adverse events and inter-current illnesses.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
d) Ensure that the type and duration of the follow-up of subjects after serious adverse events is known.	❑	❑
9. *Statistics*		
a) A description of the statistical methods to be employed, including timing of any planned interim analysis.	❑	❑
b) Identify the number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.	❑	❑
c) Check the level of significance to be used.	❑	❑
d) Identify the particular criteria for the termination of the trial.	❑	❑
e) Note the procedure for accounting for missing, unused and spurious data.	❑	❑
10. *Direct Access to Source Data/Documents*		
a) The Sponsor should ensure that it is specified in the protocol or other written agreement that the Investigator /institutions will permit trial-related monitoring, audits IEC/IRB review, and regulatory inspections, providing direct access to source data/documents. Check this is the case.	❑	❑
11. *Quality Control and Quality Assurance*		
a) *Ethics:*		
Look for a description of the ethical considerations relating to the trial. For a detailed checklist see SOP P10.	❑	❑
b) *Finance and Insurance:*		
Check to see if the protocol mentions any issues relating to finance and insurance. If not, this will normally be addressed in a separate agreement with the Investigator. For a detailed checklist see SOP P7.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
c) *Publication Policy:*		
Sponsors sometimes make reference to a specific set of guidelines concerning the publication of trial data by Investigators. If this is not documented in the protocol it should be addresses in a separate agreement. For a detailed checklist see SOP P3.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: P4

REVIEW OF PROTOCOL AMENDMENTS

APPROVED BY: _____

Investigator

_____

Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: P4

REVIEW OF PROTOCOL AMENDMENTS

I. Purpose

To describe the procedure for reviewing any proposed changes to a protocol that may be introduced during the study.

II. Other Related Procedures

SOP P3: Review and Validation of Clinical Trial Protocol
SOP P13: Independent Ethics Committee or Institutional Review Board

III. Procedures

	Yes	No*
a) On determining the need for, or advantage that would be obtained from, the introduction of an amendment to the protocol, all relevant parties should be consulted before the amendment is implemented.	❑	❑
b) The IEC/IRB must be informed of the amendment(s). Except where necessary to eliminate an immediate hazard, or when the change involves only logistical or administrative aspects of the trial, the amendment should not be implemented without documented approval from the IEC/IRB.	❑	❑
c) Where there is an external Sponsor, no amendment(s) to the protocol may be implemented without the expressed agreement of the Sponsor.	❑	❑
d) On receiving an amendment from an external Sponsor, the Investigator must review it in conjunction with the protocol. If the Investigator agrees with the amendment, it should be signed.	❑	❑
e) The Investigator must ensure that all staff involved in the study are informed of the amendment(s) in a timely fashion. As soon as the amendment is available, it should be implemented.	❑	❑
g) Sponsors have different methods of producing amendments sometimes it will be an additional page, sometimes the whole protocol will be rewritten as an amended version, especially if the amendment causes changes throughout the protocol.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
h) If the amendment is supplied as a loose-leaf page, it is recommended that a hand-written comment be made at the appropriate part of the original protocol, to indicate the existence of the amendment(s)	❑	❑
i) If the protocol is rewritten as a new version, one old version should be filed and endorsed to make it apparent to a prospective reader that it has been superseded, and on what date The remaining protocols should be returned to the Sponsor or destroyed in order to prevent confusion	❑	❑

* If the answer is NO to any of the above specify reason(s) on the last page of this SOP

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: P5

REVIEW OF INVESTIGATOR's BROCHURE

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: P5

REVIEW OF INVESTIGATOR's BROCHURE

I. Purpose

To describe procedures associated with the review of the Investigator's Brochure.

II. Other Related Procedures

SOP P2: Pre-study Visit
SOP P13: Independent Ethics Committeeor or Institutional Review Board

III. Procedure

The Investigator's Brochure (IB) is a compilation of the clinical and non clinical data on the investigational product(s) that is relevant to the study of the investigational product(s) in human subjects.

	Yes	No*
1. ***General Considerations***		
a) Check that the **title page** of the Investigator's Brochure includes the Sponsor's name, the identity of each investigational product(s) and the release date. There should also be an edition number and a reference to the number and date of the edition that it supersedes.	❑	❑
b) A Sponsor usually likes to include a **confidentiality statement** instructing the Investigator/recipients to treat the IB as a confidential document. Confirm that this is the case.	❑	❑
2. ***Contents of the Investigator's Brochure***		
a) All IBS should have a **table of contents** outlining the relevant sections of the documentation enclosed. Check to see that the IB contains a table of contents.	❑	❑
b) A **brief summary** highlighting the significant, physical chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic and clinical information available that is relevant to the stage of clinical development of the new investigational product should be included in the IB. Identify that the IB has this information contained in it.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
c) An **introduction section** that contains the chemical name (and generic and trade name(s) when approved) of the investigational products, the active ingredients, the investigational product(s) pharmacological class and it's expected position within this class, should be clearly documented. In addition, the rationales for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic or diagnostic indications, should also be included. Determine that this is the case.	❑	❑
d) A **description of the investigational product(s) substances,** including its chemical and or structural formula should also be included in the IB. Check also that the IB contains a brief summary of the product(s) relevant physical, chemical and pharmaceutical properties.	❑	❑
e) Identify whether the IB contains the **results of all-relevant non-clinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies.** These should be clearly documented and provided in summary form.	❑	❑
f) Review the **summary of the non-clinical pharmacology** aspects of the investigational product(s) and, where appropriate, the significant metabolites studied in animals.	❑	❑
g) A **summary of the pharmacokinetics and biological transformation and disposition of the investigational product(s)** in all species studied should be given. Identify that this is included in the IB.	❑	❑
h) The **toxicological effects** found in relevant studies conducted in different animals' species should also have been reviewed.	❑	❑
i) Identify and review the information contained in the **discussion of the known effects of the investigational product(s) in humans.** The information provided in the IB should include information on the pharmacokinetics, metabolism, pharmacodynamics, dose response, safety,efficacy and other pharmacologic activity of the product(s).	❑	❑
j) **Information on the pharmacokinetics of the investigational product(s)** should be presented in the IB, including (if available) information relating to the bioavailability of the investigational product(s), population sub-groups, interactions, other relevant pharmacokinetics data. Check that this information is available.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
k) Read the information relating to the **safety and efficacy of the investigational product(s)** and the tabular summaries of all adverse drug reactions for all of the clinical trials. Note also the important differences in **adverse drug reaction** patterns/incidences across indications or subgroups.	❑	❑
l) Information relating to the **marketing of the investigational product(s)** and whether the product has been approved is normally included in the IB. Look for any significant information from the marketed use of the product and its formulations, dosages, routes of administration and adverse product reactions. In addition, identify the information about which countries the investigational product did **not** receive approval or registration or was withdrawn from marketing or registration.	❑	❑
m) Read thoroughly the **final section** that provides the investigator with a complete overview and discussion of the non-clinical and clinical data. This section also usually contains a summary of the information on different aspects of the investigational product(s). This section provides the Investigator with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials. In addition, where appropriate, the published reports on related products are also included. The information contained in this final section of the IB is important, as it could help the Investigator to anticipate potential adverse drug reactions or other problems in clinical trials.	❑	❑

3. *Other Information*

a) All Investigators must know where the IB is kept.	❑	❑
b) If any new information arises during the trial, the Monitor should supply the Investigator with an update or a revised version of the IB. The Investigator should follow the procedure described in (c) below to ensure that all Investigators and the CRC are familiar with the updated IB.	❑	❑
c) In order for an Investigator to become more familiar with the IB, the Investigator could prepare a short talk on each section of the brochure and present this to the members of the study team.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: P6

REVIEW OF CASE REPORT FORM

APPROVED BY: _____

Investigator

_____

Signature/Date

REVISIONS:

No.	*Section No.*	*Page No*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1		3.	
2.		4.	

SOP No. P6

REVIEW OF CASE REPORT FORM

I. Purpose

To describe the procedure for reviewing and validating Case Report Forms (CRFs) before the start of the trial.

II. Other Related Procedures

SOP T4: Case Report Form Completion

III. Procedures

The CRF is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

	Yes	No*
a) During the first meeting(s) with the Monitor, or other representative of the Sponsor setting up the study, identify whether the study site will be involved in checking draft CRFs.	❑	❑
b) Ensure that the review of the draft CRF occurs as soon as possible after receiving it, as there can be a tight schedule in the weeks leading up to the start of the trial and postponements, because CRFs are not ready, can be significant.	❑	❑
c) Wherever possible, ensure that at least one member of the research team checks the CRFs. If an Investigator has been closely involved in designing and writing the protocol, it is better that he/she does not check the CRFs.	❑	❑
d) If possible compare the CRFs with others from similar trials in order to highlight any deficiencies.	❑	❑
e) Ensure that either the Investigator or the CRC completes a test of the CRF in a true-to-life situation, using real source documents when filling in the forms.	❑	❑
f) The CRC should complete the CRF checklist (see example on page 3).	❑	❑
g) Inform the Sponsor in writing of any comments, as soon as possible.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

CASE REPORT FORM CHECKLIST

		Yes	No
1.	Is there some kind of trial identification present on the CRF?	❑	❑
2.	Is there a space for a patient identification code or the patient's initials? (Note: The patient's full name should **not** appear on the CRF)	❑	❑
3.	Is there sufficient space and detail for all of the following information?		
	(a) Demographic data on each patient?	❑	❑
	(b) Diagnosis of the patient?	❑	❑
	(c) Inclusion and exclusion criteria?	❑	❑
	(d) Administration of the study medication?	❑	❑
	(e) Recording of concomitant medications?	❑	❑
	(f) Recording of efficacy parameters?	❑	❑
	(g) Recording of adverse events?	❑	❑
	(h) Reasons for withdrawal?	❑	❑
4.	Is there a form for reporting Serious Adverse Events?	❑	❑
5.	Are the instructions for completing the CRFs clear?	❑	❑
6.	Are the forms well laid out?	❑	❑
7.	Is the order of the questions logical?	❑	❑
8.	Do you find the forms too detailed?	❑	❑
9.	Do the forms lack detail?	❑	❑
10.	Do you ever need to complete the same data twice?	❑	❑
11.	Do you have difficulty understanding any of the questions, e.g. knowing whether to tick 'Yes' or 'No'?	❑	❑
12.	Are there any abbreviations or terms, which you do not immediately understand?	❑	❑
13.	Is it always clear what needs to be completed and when?	❑	❑
14.	Do you need to refer to the protocol or Investigator's Brochure to complete the form?	❑	❑
15.	For written responses – is there enough space to write your answer?	❑	❑

Section	*Comments*

Effective Date _____

Issue Date. _____

SOP No: P7

CONTRACTS AND BUDGETS

APPROVED BY _____

Investigator

_____

Signature/Date

REVISIONS·

No	*Section No*	*Page No*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP

Date	*Signed*	*Date*	*Signed*
1		3	
2		4	

SOP No: P7

CONTRACTS AND BUDGETS

I. Purpose

II. Other Related Procedures

None

III. Procedures

1. *Study Contract*

a) *Basic Principles of Study Contract Development*

A contract is a written, dated and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

There is always a contract for phase I, II and III and perhaps phase IV studies. Usually the Sponsor/Contract Research Organisation (CRO) provides a contract, which protects the interests of the Sponsor/CRO, but not necessarily the Investigator, study site staff, department/unit or institution. Also, some contracts provided by international pharmaceutical companies or CRO's refer to the relevant legal aspects or requirements of the Sponsor's home country e.g. USA and UK, rather than the one where the study is to be conducted.

For comprehensive legal indemnity it is necessary to modify a contract provided by the Sponsor/CRO. For large institutions or Academic Centres and Site Management Organisations there is a common core group of personnel dealing with study contracts and budgets. In such cases the institutions own contract is merged with the one provided by the Sponsor or CRO. After review and acceptance of the merged contracts by legal experts a so-called 'Master Contract' will have been developed. The Master Contract can not only be used for the specific study but, also as a template for any further future study contracts between the two parties.

b) *Basic Principles of Preparing the Study Site Contract*

The main elements to be included in this review process, should in the first instance be reviewed by a local legal expert and these are are listed as follows:

	Yes	No
• Law to govern the study	❑	❑
• Publication Right	❑	❑
• Indemnification	❑	❑
• Medical Care Expenses	❑	❑
• Early termination of study	❑	❑
• Budget	❑	❑
• Responsibilities of Principal Investigator	❑	❑
• Use of Name (Sponsor and Institution)	❑	❑

2. *Budget*

a) *Basic Principles of Budget Development*

The ICH-GCP Guideline states, "*the financial aspects of the trial should be documented in an agreement between the Sponsor and the Investigator/Institution* (ICH –GCP E6 Guideline 5. 9).

This means that the Sponsor/CRO should reimburse the Investigator and or the institution for any study induced costs. Patients costs that would occur without the conduct of the study are normally not paid for by the Sponsor. Any examination or procedure requested by the Sponsor/CRO should not in any way be borne by the patient.

It is usually not common practice to pay the patients for study participation; however, sometimes a reasonable reimbursement is made for travel expenses and perhaps loss of income.

A preliminary budget is usually provided by the Sponsor/CRO, but the total amount may not be sufficient for all trial induced costs such as study site team working hours, laboratory tests/specialist examination procedures, study document handling and communications. It is therefore advisable that the study site makes an estimate of the budget.

For each visit, one should preferably estimate the time for each activity by the Investigator as well as the CRC. The estimate is normally based on the study flow chart as found in the study protocol, and example of which is given below. The costs for laboratory and specific examinations and procedures should also be included.

	V1 Screening Visit	V2-V7 Treatment Visit	V8 End of Treatment Visit	V9 End of Study Visit
Informed Consent	X			
Medical History	X			
Previous Medication	X			
Physical Examination	X	X	X	X
Vital Signs	X	X	X	X
Clinical Signs and Symptoms	X	X	X	X
Safety Laboratory	X	X	X	X
Adverse Event	X	X	X	X
Concomitant Medication	X	X	X	X
Investigational Product	issue		collection	collection
Treatment Compliance	X	X	X	X
Patient's Study Card	X			

b) *Basic Principles of Budget Estimation*

The time needed for the Investigator and CRC for one single study subject is calculated and multiplied by the hourly rate of each member of staff involved. The cost of laboratory and specific examinations is also added. Finally, the patient based costs estimate is multiplied by the number of patients recruited (see checklist below).

- The one off costs that are associated with a trial include GCP training, Investigator Meeting, Monitor Meeting, and Study site Initiation and Closure (see checklist below).

- The Institution in question is commonly adding an administration fee to the direct fee ranging from 20% to 100% depending on the geographic location and the reputation of the institution conducting the study.

- The usual payment intervals being:

  - ❑ 25% when contract is signed.
  - ❑ 25% when 50 % study patients have been recruited.
  - ❑ 25% 100 % of study patients have been recruited.
  - ❑ 25% Study site closure.

c) *Sample Budget Checklist*

One off costs

- ❑ GCP Training
- ❑ Investigator Meeting
- ❑ Monitors Meeting
- ❑ Study Site Initiation
- ❑ Study Site Closure
- ❑ Communications
- ❑ Others

Per patient cost (over all visits) are based on the trial specific flow chart.

- ❑ Informed Consent
- ❑ Medical History
- ❑ Previous Medication
- ❑ Physical Examination
- ❑ Vital Signs
- ❑ Clinical Signs and Symptoms
- ❑ Safety Laboratory Tests
- ❑ Adverse Events
- ❑ Concomitant Medication
- ❑ Investigational Product
- ❑ Treatment Compliance
- ❑ Patient's Study Card
- ❑ Data Queries
- ❑ Others

Total cost per patient

- ❑ Multiply by the number of patients

Total cost

- ❑ Total Direct Cost
- ❑ Total Indirect Cost
- ❑ Total Cost

Effective Date: _____

Issue Date: _____

SOP No: P8

STUDY ORGANISATION AND PLANNING

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: P8

STUDY ORGANISATION AND PLANNING

I. Purpose

To provide an overview for the organisation and planning of each clinical trial performed in the research group.

II. Other Related Procedures

All SOPs

III. Procedures

Study Organisation represents a study related activity or a set of activities that is contracted by the Sponsor.

1. *Staffing*

a) Nominate the individuals responsible for the trial as early as possible and preferably no later than when it seems likely the trial will proceed to IEC/IRB application.

b) Ensure that names and roles of individuals involved in the trial have been agreed and their back-up personnel are also identified, no later than the start of the trial.

c) Identify which staff are involved in the trial need GCP training and whether they are adequately qualified to perform their duty.

d) The CRC should complete the Involved Personnel Contact Form (refer to Appendix A).

2. *Locality*

a) Assess space for interviewing and examination of study subjects, storage of study related materials, and equipment.

b) At the beginning of the trial, thought should be given to the archiving requirements.

3. *Interaction with Other Departments*

a) Liaise with the other Departments involved, for example Laboratory, Pharmacy, and Data Management/Statistical groups.

b) Identify who to contact and their back-up personnel if not available (refer to Appendix A).

4. *Study Drugs*

a) Determine who is responsible for the handling of study drugs. Will it be the Pharmacy, the Investigator, the Sponsor or the CRO?

b) Identify the responsible person, his/her contact details and the back-up personnel, for the handling of study drugs (refer to Appendix A, Section h).

c) Make arrangements for the receipt and storage of study drugs in accordance with the requirements of the Sponsor if applicable.

d) At the beginning of the trial, discuss and agree with the Sponsor if any special requirements are needed for the post-trial therapy.

5. *Ethics Committee*

a) Identify who to contact, contact details and his/her back up personnel (refer to Appendix A) for IEC/IRB.

b) Ensure that the ethical aspects of the study have been taken care of in accordance with the local IEC/IRB requirements and that the written approval from the IEC/IRB has been obtained before the enrolment of the first subject.

c) If independent data monitoring is also to be performed during the trial, identify the personnel responsible for the collection of the data, and to who reports should be sent to (refer to Appendix A).

6. *General Study-related Information*

a) For Sponsor study trials, identify who to contact, contact details and his/her back-up personnel (refer to Appendix A).

b) Discuss and agree with the Sponsor the overall numbers of subjects and the number at each study site.

c) Check that the procedure for randomisation and stratification have been established.

d) Before enrolment of the first subject, ensure all involved staff are familiar with the protocol and if applicable the IB and in particular the procedure for reporting adverse events.

e) Ensure a study initiation meeting has taken place and its details recorded and filed.

f) Schedule study meetings within the study site to discuss study progress and maintain interest in the study.

g) Liaise and discuss with other Departments involved with the trial to ensure that any concerns are dealt with efficiently, such as the Pharmacy, Laboratories, Data Management/ Statistical Groups.

Appendix A

INVOLVED PERSONNEL CONTACT FORM

(a) Investigator

Name: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Qualifications: _____

Previous trial experience: _____

Short, updated CV, including GCP training compiled: ❑ Yes ❑ No

Employment terms: _____

Formal attachment: _____

Other (please specify): _____

Designated person to contact if unavailable: _____

(b) Co-Investigator

Name: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Qualifications: _____

Previous trial experience: _____

Short, updated CV, including GCP training compiled: ❑ Yes ❑ No

Employment terms: _____

Formal attachment: _____

Other (please specify): _____

Designated person to contact if unavailable: _____

(c) Clinical Research Co-ordinator (CRC)

Name: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Qualifications: _____

Previous trial experience: _____

Short, updated CV, including GCP training compiled: ❑ Yes ❑ No

Employment terms: _____

Formal attachment: _____

Other (please specify): _____

Designated person to contact if unavailable: _____

(d) Study Nurse, if different from the CRC

Name: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Qualifications: _____

Previous trial experience: _____

Short, updated CV, including GCP training compiled: ❑ Yes ❑ No

Employment terms: _____

Formal attachment: _____

Other (please specify): _____

Designated person to contact if unavailable: _____

(e) Other Involved Study Staff

Name: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Qualifications: _____

Previous trial experience: _____

Short, updated CV, including GCP training compiled: ❑ Yes ❑ No

Employment terms: _____

Formal attachment: _____

Other (please specify): _____

Designated person to contact if unavailable: _____

Name: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Qualifications: _____

Previous trial experience: _____

Short, updated CV, including GCP training compiled: ❑ Yes ❑ No

Employment terms: _____

Formal attachment: _____

Other (please specify): _____

Designated person to contact if unavailable: _____

(f) Personnel to be contacted Regarding Study Site Space

Description space: _____

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Designated person to contact if unavailable: _____

Please refer below for details

Back-up Personnel

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

(g) Personnel to be Contacted Regarding Equipment

Type of equipment: _____

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Designated person to contact if unavailable: _____

Please refer below for details

Back-up Personnel

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

(h) Personnel to be contacted Regarding the Handling of Study Drugs

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Designated person to contact if unavailable: _____

Please refer below for details

Back-up Personnel

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

(i) Personnel to be Contacted Regarding the Ethics Committee

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Designated person to contact if unavailable: _____

Please refer below for details

Back-up Personnel

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

(j) Independent Data Monitoring

	Local Contact	Overseas Contact
Name of contact:	_____	_____
Position:	_____	_____
Speciality:	_____	_____
Direct phone no:	_____	_____
Secretary phone no:	_____	_____
Home phone no:	_____	_____
Mobile/Pager no:	_____	_____
Fax no:	_____	_____
E-mail address:	_____	_____
Designated person to contact if unavailable:	_____	_____

Please refer below for details

Back-up Personnel

Name:	_____	_____
Position:	_____	_____
Speciality:	_____	_____
Direct phone no:	_____	_____
Secretary phone no:	_____	_____
Home phone no:	_____	_____
Mobile/Pager no:	_____	_____
Fax no:	_____	_____
E-mail address:	_____	_____

(k) Sponsor Details

	Local Contact	Overseas Contact
Name of contact:	_____	_____
Position:	_____	_____
Speciality:	_____	_____
Direct phone no:	_____	_____
Secretary phone no.	_____	_____
Home phone no:	_____	_____
Mobile/Pager no:	_____	_____
Fax no:	_____	_____
E-mail address.	_____	_____
Designated person to contact if unavailable:	_____	_____

Please refer below for details

Back-up Personnel

Name:	_____	_____
Position	_____	_____
Speciality:	_____	_____
Direct phone no:	_____	_____
Secretary phone no:	_____	_____
Home phone no:	_____	_____
Mobile/Pager no	_____	_____
Fax no	_____	_____
E-mail address:	_____	_____

(l) Monitor Details

Name of contact: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Designated person to contact if unavailable: _____

Please refer below for details

Back-up Personnel

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

(m) Contract Research Organisation Details

Name of contact: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Designated person to contact if unavailable: _____

Please refer below for details

Back-up Personnel

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

(n) Contact Details for the Issue of Randomisation Numbers

Name of contact: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Designated person to contact if unavailable: _____

Please refer below for details

Back-up Personnel

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

(o) Statistician

Name of contact: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Designated person to contact if unavailable: _____

Please refer below for details

Back-up Personnel

Name: _____

Position: _____

Speciality: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

(p) Data Management

Name: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Qualifications: _____

Previous trial experience: _____

Employment terms: _____

University attachment: _____

HA attachment: _____

Other (please specify): _____

Designated person to contact if unavailable: _____

(q) Medical Writer

Name: _____

Direct phone no: _____

Secretary phone no: _____

Home phone no: _____

Mobile/Pager no: _____

Fax no: _____

E-mail address: _____

Qualifications: _____

Previous trial experience: _____

Employment terms: _____

University attachment: _____

HA attachment: _____

Other (please specify): _____

Designated person to contact if unavailable: _____

Effective Date: _____

Issue Date: _____

SOP No: P9

STUDY SITE TEAM: DEFINITION OF RESPONSIBILITIES

APPROVED BY: _____

Investigator

_____

Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No. P9

STUDY SITE TEAM: DEFINITION OF RESPONSIBILITIES

I. Purpose

To assist in the division and allocation of responsibilities within the study team and to ensure smooth running of the trial. To provide the Sponsor with an overview of the division of responsibilities of the study site personnel.

II. Other Related Procedures

All SOPs

III. Procedures

Each clinical trial must have one Investigator, who has overall responsibility for the welfare of the trial subjects, conduct of the study, administration of drugs, ensuring that local management needs are met, ensuring that IEC/IRB requirements are met, and his/her study staff has knowledge of GCP. The Investigator, may however, if required, allocate day to day responsibility of the trial to a Co-Investigator and/or a Clinical Research Coordinator (CRC).

During the pre-study phase, the Investigator, Co-Investigator, CRC, and other study site staff must discuss and define the study procedures.

Responsibilities that can be delegated will depend on the suitability of the individuals to perform the tasks.

The CRC should, with the Investigator and/or Co-Investigator, discuss and agree the allocation of tasks with other study staff members, and the allocation of the tasks should be documented accordingly, see Appendix A.

If an external Sponsor exists, the Investigator or the CRC should advise the Sponsor of the planned division of tasks, contact names, roles of other individuals involved with the trial in other departments and any changes of staff.

The Investigator or the CRC should appraise the need for additional staff, and discuss any additional needs with the Study Monitor.

Appendix A

CHECKLIST OF STUDY TEAM RESPONSIBILITIES

Study Team Responsibilities	*Study Site*	*Sponsor/CRO*	*Pharmacy*	*Laboratory*
Submit Ethics Committee Application				
Study Organisation and Planning				
Preparation of Study Site Files				
Study Finance/Budget/Contract				
Recruitment of Subjects				
Take Informed Consent				
Sign Prescriptions				
Record and Report Adverse Events				
Storage of Study Medication				
Dispense Study Medication to Patients				
Receipt of un-used Medication				
Sign-off Case Report Forms (CRFs)				
Make Corrections/Alterations to CRFs				
Conduct Clinical Examinations				
Evaluate Laboratory Reports				
Venepuncture				
Shipment of blood/biological samples				
Analyses of blood/biological samples				
Receipt of Completed CRFs				
Data Queries and Resolution				
Archiving of Study Data				
Develop Clinical Standard Operating Procedures				
Independent Data Monitoring				
Data Analysis				

N.B. Shaded areas indicate the responsibilities for the different staff involved in clinical trials.

Appendix B

OVERVIEW OF STUDY RELATED RESPONSIBILITIES

	Study Site *Principal Investigator*	*Study Site* *Co Investigator*	*Study Site* *CRC/ Study Nurse*	*Sponsor/ CRO*	*Other Study Staff*	*Pharmacy*	*Labs*
Submit Ethics Committee Application							
Study Organisation and Planning							
Preparation of Study Site Files							
Study Finance/Budget/Contract							
Recruitment of Subjects							
Take Informed Consent							
Sign Prescriptions							
Record and Reporting of Adverse Events							
Storage of Study Medication							
Dispense Study Medication to Patients							
Receipt of un-used Medication							
Sign-off Case Report Forms (CRFs)							
Make Corrections/Alterations to CRFs							
Conduct Clinical Examinations							
Evaluate Laboratory Reports							
Venepuncture							
Shipment of blood/biological samples							
Analyses of blood/biological samples							
Receipt of Completed CRFs							
Data Queries and Resolution							
Archiving of Study Data							
Compilation of Clinical Procedure SOPs							
Independent Data Monitoring							
Data Analysis							

N.B. Shaded areas indicate the responsibilities for the different staff involved in clinical trials.

Effective Date: _____

Issue Date: _____

SOP No: P10

RECRUITMENT OF SUBJECTS

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: P10

RECRUITMENT OF SUBJECTS

I. Purpose

To describe the procedure for recruiting subjects into a study, and entry of subjects on the intention to enroll list.

II. Other Related Procedures

SOP P2: Pre-study Visit
SOP P3: Review and Validation of Clinical Trial Protocol
SOP T5: Obtaining written Informed Consent

III. Procedures

1. *Planning*

a) Identify who is responsible for the recruitment of trial subjects.

b) Identify the hospital/department/centre/private practice where the pool of potential candidates who meet the inclusion criteria stated in the protocol are located.

c) Discuss the study, responsibilities and procedures involved in recruiting subjects for the study, with the staff at the recruitment site.

d) Determine the recruitment procedures or strategies to be employed, e.g. sending out letters, calling the potential candidates, advertising for subjects using information posters or television and radio.

e) Identify ways to motivate potential candidates. Consider for example, explaining the benefits of the study to the patient, the advantages of having additional medical tests and examinations performed on a regular basis, and the possibility of reimbursement of travel expenses.

f) Enter every potential candidate on an "intention to enroll" list for the study. Subjects should be entered on this list regardless of how likely they are to give their consent.

For items a-f above, complete the form shown in Appendix A.

2. ***Enrollment***

a) Schedule an appointment with the subject and inform the Investigators of the date of the visit.

b) Check again whether the potential subject fulfill the inclusion/exclusion criteria before enrollment. Some studies require that the results of specific tests such as a liver biopsy, blood tests or ultrasound are available. If not, these tests may need to be scheduled and/ or performed before enrollment.

c) Ensure that subject has signed the Informed Consent Form.

d) Enter the subject details on the subject identification list.

3. ***Recruitment Progress Monitoring***

a) Plot a recruitment rate graph showing a comparison of the actual and expected recruitment rate, see Appendix B for an example.

b) Assess the recruitment rate regularly to ensure that an effective recruitment procedure is being used, and make any necessary changes to the procedure whenever necessary.

c) For planning purposes, compile a flow chart that shows the schedule of expected visits for each subject enrolled in the study see Appendix C.

Appendix A

1. **Person responsible for the recruitment process;**

   Name: _____

   Title: _____ Tel No: _____

2. **Where will the potential study subjects identified be recruited?**

   _____

3. **Department(s) that have been identified and the name of the person to contact for liaison**

   Title: _____ Contact Person: _____

   Location: _____ Tel No: _____

   Department: _____ Contact Person: _____

   Location: _____ Tel No: _____

4. **The planned strategies of recruitment procedures:**

   _____

   _____

   _____

5. **Ways identified to motivate potential subjects:**

   _____

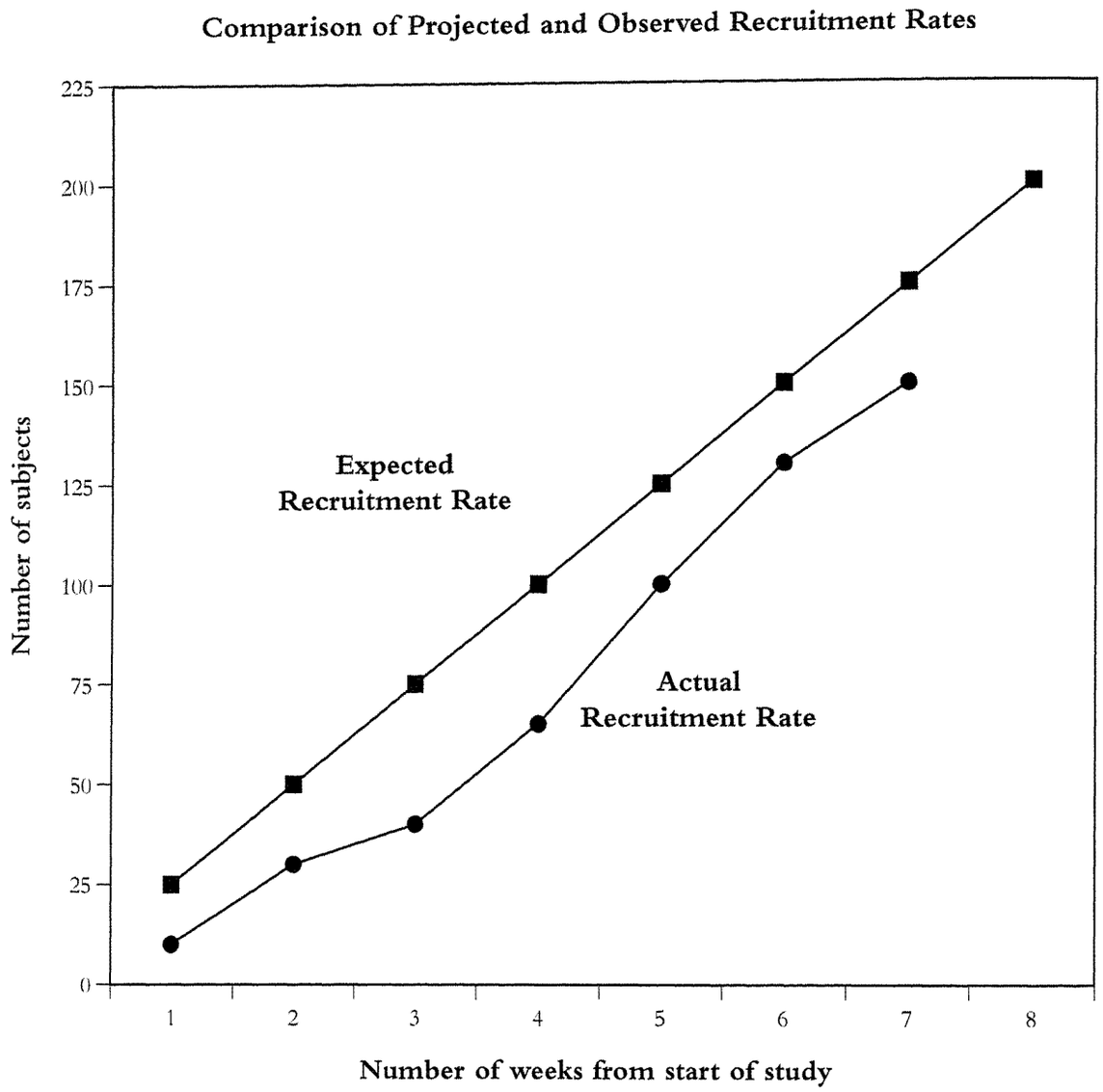
   _____

   _____

Appendix B

RECRUITMENT RATE GRAPH

In the example given below, 200 subjects were projected to be recruited in 8 weeks.



Appendix C

RECRUITMENT VISIT RECORD

Month	*June*						
Week No.	*26*						
Date	*21*	*22*	*23*	*24*	*25*	*26*	*27*
Subject S1	Visit 3						
Subject S2	Visit 3						
Subject S3		Visit 2					
Subject S4							
Subject S5							
Subject S6							
Subject S7							
Subject S8							
Subject S9							

Effective Date: _____

Issue Date: _____

SOP No: P11

PRE-STUDY PLANNING OF INVESTIGATIONAL PRODUCTS AND DEVICES

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: P11

PRE-STUDY PLANNING OF INVESTIGATIONAL PRODUCTS AND DEVICES

I. Purpose

To describe the pre-study procedures relating to the receipt, storage dispensing and accountability of investigational products and devices used in clinical trials.

II. Other Related Procedures

SOP T2: Blinding: Codes and Code Breaking
SOP T3: Investigational Products Accounting and Dispensing

III. Procedures

Investigational drugs are experimental by definition. For this reason, all aspects of drug manufacture, distribution, storage, handling and dispensing and excess recovery are subject to GCP guidelines. The Investigator at the individual study site is ultimately responsible for all study drug management. However, this responsibility may be delegated to a Pharmacist or CRC.

	Yes	No*
1. *General*		
a) The Investigator and the CRC are responsible for ensuring that adequate communication exists between the Sponsor and the individual responsible for the management of the investigational products.	❑	❑
b) Review fully the study protocol and discuss with the Sponsor the following issues relating to the investigational products and devices:		
• Description	❑	❑
• Packaging	❑	❑
• Labelling plans of the study drug(s)	❑	❑
• Space required to store the drug(s)	❑	❑
c) Establish with the Sponsor the procedure(s) that should be followed for requesting further supplies of the study medication.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
d) Agree with the Sponsor the methods and/or forms to be used for documenting the movement of trial medication with all the involved parties.	❑	❑
e) Discuss and agree with the Sponsor the documentation required for procedures to check subject compliance with a study drug(s) e.g. checking that the diary cards are consistent with returns and/or measuring plasma or urine levels of the drug.	❑	❑
f) Agree on the documentation for the presentation format (e.g. blister packs, inhaler device or liquid) of the study drug(s) before the entry of the first patient into the study.	❑	❑
2. *Delivery and Storage of Study Medication(s)*		
a) Document the receipt of each delivery of study drug(s) at the study site and/or pharmacy and notify the Sponsor in writing of the receipt in accordance with their requirements.	❑	❑
b) Document the conditions of storage as requested by the Sponsor, e.g. the daily temperature of the refrigerator which stores the study drug (s).	❑	❑
c) Ensure that sufficient space will be made available to store the drug(s) until arrangements have been made by the Sponsor that the unused drugs can be retrieved or destroyed.	❑	❑
d) Establish the procedures to be followed for the return or destruction of the trial drugs at the end of the study. If the medication is to be destroyed without being returned to the Sponsor, this action should be documented clearly before the beginning of the study.	❑	❑
3. *Preparation for Dispensing*		
a) Document in the Investigators study file who has direct access to the study medication during the study.	❑	❑
b) If the drugs are to be dispensed by the Investigator and not a Pharmacist, identify a secure area with restricted access and conditions appropriate for the storage of study medication.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
4. *Supply of Medication on a Named-Subject Basis*		
a) Discuss with the Sponsor whether a named patient supply of the study medication will be available at the end of the study.	❑	❑
b) Agree with the Sponsor the procedure(s) for requisitioning the study medication for the named subjects/patients.	❑	❑

5. *Accountability*

Discuss and agree with the Monitor the procedures to be employed for ensuring proper and adequate accountability of the investigational product (s) or devices.

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: P12

PRE-STUDY PLANNING FOR LABORATORY INVESTIGATIONS

APPROVED BY: _____

Investigator

_____

Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: P12

PRE-STUDY PLANNING FOR LABORATORY INVESTIGATIONS

I. Purpose

To describe the procedures for the planning of laboratory facilities for a clinical trial.

II. Other Related Procedures

SOP P3: Review and Validation of Clinical Trial Protocol
SOP P4: Review of Protocol Amendments
SOP P6: Review of Case Report Form
SOP P7: Contracts and Budgets
SOP P8: Study Organisation and Planning
SOP P9: Study Team: Definition of Responsibilities
SOP P14: Investigator Meeting and GCP Training
SOP P15: Pre-Study Checklist

III. Procedures

	Yes	No*
a) Use the checklist shown in Appendix A of this SOP, to determine the basic laboratory requirements and any procedures that are required for the study.	❑	❑
b) As early as possible, commence discussions with the Sponsor concerning the laboratories to be used for the analysis of samples.	❑	❑
c) Agree in principle, at least before submission of the protocol to the IEC/IRB, the laboratory facilities that will be used.	❑	❑
d) Establish who will be responsible for the supply of necessary materials such as needles, syringes and containers etc.	❑	❑
e) Check that any instructions concerning the handling of samples has been established.	❑	❑
f) Check that the procedure for the transportation of samples has been established.	❑	❑
g) Ensure that any possible difficulties that might arise in adhering to any of the procedures is documented clearly and that such details are communicated to the Sponsor.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
h) Identify the individual who will be responsible to liaise with the Sponsor, both on the local laboratory site and with any external laboratories. Such liaison should extend to facilitating the appropriation of relevant documentation.	❑	❑
j) Ensure that appropriate laboratory reference ranges and documents pertaining to Quality Assurance procedures are in place at the laboratories.	❑	❑
k) Ensure that all reports, or duplicates of reports, are maintained in an appropriate way to meet with local management requirements and those, where reasonable, of any Sponsor. Above all, confidentiality of subjects to whom reports relate must be ensured.	❑	❑
l) Determine if the subject's family doctor, where appropriate, and any other doctors involved in the care of the individual should be notified of any findings from the laboratory reports.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Appendix A

PLANNING FOR LABORATORY INVESTIGATIONS

Sponsor Name _____

Protocol Name _____

Protocol Number _____ Date of Protocol _____

Type of Sample	*Analysis Required*	*Central Laboratory*	*Laboratory Name*	*Contact Name Telephone No & email address*	*Special Handling Instructions*	*Who will supply materials?*
Whole Blood						
Seperated Serum						
Separated Plasma						
Stool						
Urine						
CSF						
Other						

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: P13

INDEPENDENT ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD

APPROVED BY: _____

Investigator

_____

Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: P13

INDEPENDENT ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD

I. Purpose

To describe your duties concerning ethical approval of the clinical study by an Independent Ethics Committee (IEC) or Institutional Review Board (IRB).

II. Other Related Procedures

SOP P4: Review of Protocol Amendments
SOP T5: Obtaining Written Informed Consent
SOP T6: Adverse Event and Serious Adverse Event Reporting

III. Procedures

The IEC/IRB is an independent body- a review board or a committee, institutional, regional, national or supranational, constituted of medical professionals and non-medical members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial. The IEC/IRB should provide public assurance of protection by reviewing and approving or providing favourable opinion on the trial protocol, the suitability of the Investigator (s), facilities and the methods and materials to be used in obtaining and documenting informed consent should also be review by the IEC/IRB.

1. *Preparation before IEC/IRB Submission*

(a) At the earliest opportunity, the Investigator should have checked when the IEC/IRB holds its meetings. If it does not meet very often this can delay the start of the trial. The Investigator should also check the normal response time for processing such applications.

(b) The Investigator may designate a member of staff to prepare the submission. However, he/she must take responsibility for reading it and signing it off.

(c) If more than one Centre is using the same IEC/IRB, the Investigator should identify whether each study Centre should independently obtain IEC/IRB approval, or whether one central IEC/IRB approves the trial for all Centres.

2. *EC Submission*

Ensure all the following documents are submitted to the IEC/IRB for review and they all are listed in the submission letter (Appendix A). Each document should have an version number or date if applicable.

(a) IEC/IRB Application Form for Review of Clinical Trials Protocol.
(b) The study protocol and any protocol amendment(s).
(c) Subject/patient informed consent form and information sheet with translation if required.
(d) Subject/patient recruitment procedures including any advertisement(s).
(e) Investigator's Brochure and any additional safety information.
(f) Signed and dated Investigator's CV.
(g) Any other related documents requested by the IEC/IRB e.g. insurance, indemnity, structured interview forms or questionnaires.

3. *EC Response Letter*

Check that the EC reply letter contains the following information:

(a) The identification of the study e.g. protocol number and title.
(b) The name and version number (if any) of all the document(s) reviewed by the committee.
(c) The date of review by the IEC/IRB.
(d) Information about the study-related decisions/opinions.
(e) Procedures for appealing against the decision or opinions of the IEC/IRB (if any).
(f) The title and name, occupation and institutional affiliation of each member of the IEC/IRB who gave approval.
(g) Statement of IEC/IRB compliance with any local regulation or international guideline such as ICH GCP Guidelines (if appropriate).

To ensure that the above information is included in the approval letter, a standardised IEC/IRB Review and Approval Form could be prepared for the IEC/IRB to fill and sign up the approval (Appendix B).

4. *Further Communications with the IEC/IRB*

Report promptly to the IEC/IRB any of the following occurrences:

(a) Significant changes or deviations of the study protocol.
(b) All Adverse Events that are both serious and unexpected.
(c) New information that may effect adversely the safety of the subjects or the conduct of the trial. During the trial, maintain contact with the IEC/IRB and submit periodic reports to the IEC/IRB at least once a year as a minimum. Information required to be included in the periodic report is shown in Appendix C.
(d) When the study has ended or has been terminated for whatever reason(s). Submit a final report to the IEC/IRB at the end of the study. Information to be included in the final report is shown in Appendix D.

Appendix A

SAMPLE OF SUBMISSION LETTER TO IEC/IRB

(Date of submission)

(Name of the IEC/IRB)
(Address of the IEC/IRB)

Dear Chairperson and Members,

Re: Application for Approval

Protocol: (Protocol Number)
(Protocol Name)

I forward herewith the above-named protocol and essential trial documents according to the ICH GCP Guidelines for approval by your committee.

I look forward to receiving any comments that you may have in relation to the above.

Also enclosed is an Ethics Committee Review and Approval Form for your convenience. Please fill in and sign accordingly if you approve the above protocol and the enclosed essential trial documents.

Thank you for your attention.

Yours sincerely,

_____

(Name of Principal Investigator)

Enclosed:
1. IEC/IRB Application Form for Review of Clinical Trial Protocol
2. Protocol (version 2 December 1999)
3. Protocol Amendments (International-I version 21 Jan 2000)
4. Investigator's Brochure (7th edition, February 1999)
5. Patient Information and Informed Consent Form- English (dated December 1999)
6. Patient Information and Informed Consent Form- Chinese (dated 2 December 1999)
7. Advertisement- English and Chinese (dated November 1999)
8. Insurance Policy
9. Current Investigator's Curriculum Vitae
10. IEC/IRB Review and Approval Form

Appendix B

ETHICS COMMITTEE REVIEW AND APPROVAL FORM

Protocol Number: _____

Protocol Title: _____

Date of Protocol: _____

Name and Address of Investigator: _____

_____

Name of Ethics Committee: _____

Documents have been reviewed and approved:

1. Protocol (number of protocol) (version 2 December 1999)
2. Protocol Amendments (dated 21 January 2000)
3. Investigator's Brochure (7th edition, February 1999)
4. Patient Information and Informed Consent Form- English (dated 3 December 1999)
5. Patient Information and Informed Consent Form- Chinese (dated 3 December 1999)
6. Advertisement- English and Chinese (dated 3 November 1999)
7. Insurance Policy
8. Current Investigator's Curriculum Vitae

Committee Members who reviewed and approved the above trial documents:

Title/Name	Designation	Department/Institution	Male/Female	Involve-ment in the protocol review

This is to certify that the Ethics Committee is organised and operated according to ICH GCP Guidelines and the applicable laws and regulations (if appropriate).

Signature of Chairperson of the Ethics Committee: _____

Name of Chairperson of the Ethics Committee: _____

Date of Approval (DD/MM/YY): _____

Appendix C

PERIODIC PROGRESS REPORT

Protocol Number: _____

Protocol Name: _____

Progress Report	Review period – previous IEC/IRB approval date: dd___ mm___ yy___ expiry date: dd___ mm___ yy___
Any changes among the participating investigators	IfYES, specify
Any changes in the study protocol during the review period	IfYES, specify and • Attach a copy of the original IRB protocol Indicate all proposed changes • Attach a copy of Patient/Subject Information Sheet (English and Chinese) Indicate all proposed changes • Attach a copy of Patient/Subject Consent Form (English and Chinese) Indicate all proposed changes
Any complaints about the research	IfYES, specify
Any severe adverse events during the review period	IfYES, specify
Any recent findings reported or obtained thus far, especially information about risks associated with the research	IfYES, specify

Study progress	Total number of subjects entered into study: Total number of subjects still to be entered into study: Total number of subjects completed study: Total number of subjects dropped out from study: Reasons for drop-out:
Declaration	The information supplied above is to the best of my/our knowledge and belief accurate. Signature of Investigator(s) Date _____ _____ _____ _____ _____ _____ _____ _____

Appendix D

FINAL REPORT

Protocol Number: _____

Protocol Name: _____

Any complaints about the research	IfYES, specify
Any adverse event during the study period – mild, moderate or severe events	IfYES, specify
Study subjects	Total number of subjects entered into study: Total number of subjects completed study: Total number of subjects dropped out from study: Reasons for drop-out:
Publicity of research results	Have there been any publications/reports from the study? IfYES, specify. Plans of additional publications/report. IfYES, specify.
Main results of study	
Declaration	The information supplied above is to the best of my/our knowledge and belief accurate. Signature of Investigator(s) Date _____ _____ _____ _____ _____ _____ _____ _____

Effective Date: _____

Issue Date: _____

SOP No: P14

INVESTIGATOR MEETINGS AND GCP TRAINING

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: P14

INVESTIGATORS' MEETING AND GCP TRAINING

I. Purpose

To describe the purpose and need for Investigator meetings in clinical trials and the need for adequate and formal GCP training for all staff involved in clinical research.

II. Other Related Procedures

SOP P9: Study Team: Definition of Responsibilities

III. Procedures

Investigators' Meeting

Investigators' meeting is usually organised by the Sponsor to train investigative staff about a particular study protocol and other study specific procedures. In some circumstances, an Investigators' meeting may not be required, but if one is required, it is usually because the study is a large multi-centre study or is particularly complex in nature.

Meeting Agenda

If an Investigators' meeting is determined to be the best way to train investigative staff about the study, a meeting agenda will usually be prepared by the Sponsor or the CRO assigned by the Sponsor. The Investigators' meeting will usually consist of a series of short presentations by staff from the Sponsor Company and/or CRO staff and will focus on most, if not all, of the following topics:

(a) Profile and Clinical Pharmacology of the Investigative Product.
(b) Efficacy and safety data from previous studies.
(c) Statistical Analysis Plan.
(d) Diagnosis and treatment of disease with the Investigative Product
(e) Study Protocol.
(f) Protocol Amendments.
(g) Laboratory Requirements.
(h) Case Report Forms and completion of CRFs.
(i) Study Logistics.
(j) Regulatory Issues.
(k) Study Site Planning.
(l) Monitoring.
(m) Adverse Events Reporting.
(n) Close-out Visit.
(o) Contractual Relation between Investigator and Sponsor.
(p) Publication Policy.

The Investigators' meeting is an ideal opportunity at which to raise any questions you may have regarding the study. Before attending the Investigators' meeting, ensure that you have read the study protocol and are reasonably familiar with its content.

If there are some aspects of the protocol, that require further clarification, you should not hesitate to prepare questions in advance of the meeting. In addition, if there are other members of staff involved in the study, who are unable to attend the Investigators' meeting, but who have some questions relating to the study that you are unable to answer before the meeting, make a note of their question(s) so that you can raise the question at the meeting and provide them with an answer later.

Note:

It is important to revise the information provided at the Investigators' meeting before the commencement of the study, to ensure that the information is consolidated and not forgotten.

Good Clinical Practice (GCP) Training

The importance of training in Good Clinical Practice (GCP) cannot be over emphasised. GCP details the quality processes required in the conduct of clinical trials.

In many countries world wide, GCP is a legal requirement and if these rules are not followed the Departments of Health who make decisions about licensing of a new product will reject the clinical trial data submitted as it may be unreliable. This might also damage the research credibility of the Investigator and the study centre.

It is vital therefore that all Investigators who undertake clinical trials have a good understanding of the ICH GCP guidelines, in particular those contained in section E6 of the guideline. Investigators participating in clinical trials should also be aware of the statements contained in section 4.1.4 and 4.2.4 of the E6 ICH GCP in which it is stated,

Section 4.1.4

"The Investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements".

Section 4.2.4

"The Investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions".

Effective Date: _____

Issue Date: _____

SOP No: P15

PRE-STUDY CHECKLIST

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: P15

PRE-STUDY CHECKLIST

I. Purpose

To outline, using a checklist, the critical pre-study requirements and procedures to be followed in clinical trials.

II. Other Related Procedures

All Pre Study SOPs (P1–P14 inclusive)

III. Procedures

Before embarking on clinical trials, Investigators should be fully aware of the requirements made of them. Trials must be taken seriously; they should be performed with utmost care and attention and the study site must be properly organised to deal with all aspects of the trials and, in particular, the mass of documentation that is generated. This SOP will help you to be sure that you have identified the most critical elements and procedures that are required for a good quality clinical trial.

(a) Before proceeding further, ensure that all the pre-study SOPs have been followed.

(b) Complete the final checklist shown on the next page of this SOP and where required, provide additional information on the attached comment sheet.

(c) After completing the checklist on the following page, and confirmed that you have followed the various pre-study SOPs, proceed to the SOPs in the next section entitled 'Trial Operation'.

PRE-STUDY CHECKLIST

		Done	Not Applicable
(a)	Date and Signed CV.	❑	❑
(b)	Read the study protocol, and sign it if you agree with it.	❑	❑
(c)	Familiarise yourself with the investigational drugs/devices by reading the Investigator's Brochure.	❑	❑
(d)	Review the CRFs and practice completing them in order to identify any likely problems.	❑	❑
(e)	Compile a financial agreement and study budget with the Sponsor.	❑	❑
(f)	Confirm your position about indemnity and compensation for the trial subject/patients.	❑	❑
(g)	Submit the protocol to IEC/IRB for approval.	❑	❑
(h)	Organise a meeting with all members of your clinical trial team.	❑	❑
(i)	Appoint a CRC if required.	❑	❑
(j)	Discuss and determine the particular responsibilities of the staff in the clinical trial team.	❑	❑
(k)	Estimate the number of subjects/patients that can be recruited using retrospective data.	❑	❑
(l)	Familiarise yourself with GCP requirements.	❑	❑
(m)	Formulate a recruitment strategy and arrange special clinics if necessary.	❑	❑
(n)	Check that facilities that are required are available and functional.	❑	❑
(o)	Locate a suitable place to store the trial documentation.	❑	❑
(p)	Check that all materials and documents for the trial have been received and securely stored.	❑	❑
(q)	Prepare the study files.	❑	❑
(r)	Discuss with the Sponsor requirements requiring archiving of study materials at the end of the study.	❑	❑

* *Provide additional information if required on the comments sheet on the next page.*

Signature of Investigator: ..... Date: .....

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: T1

SITE INITIATION VISIT

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: T1

SITE INITIATION VISIT

I. Purpose

To describe the procedures for site staff to follow, prior to and during the Sponsor's site initiation visit.

II. Other Related Procedures

SOP P2: Pre-study Visit
SOP P3: Review and Validation of Clinical Trial Protocol
SOP P4: Review of Protocol Amendments
SOP P5: Review of Investigator's Brochure
SOP P6: Review of Case Report Form
SOP P7: Contracts and Budgets
SOP P8: Study Organisation and Planning
SOP P9: Study Team: Definition of Responsibilities
SOP P10: Recruitment of Subjects
SOP P11: Pre-Study Planning of Investigational products and Devices
SOP P12: Pre-Study Planning for Laboratory Investigations
SOP P13: Independent Ethics Committee or Institutional Review Board
SOP P14: Investigator Meeting and GCP Training
SOP P15: Pre-Study Checklist

III. Procedures

The site initiation visit involves a detailed discussion of the type of subject/patient to be recruited, the completion of the CRF and administrative procedures to be followed. In addition, some evaluation of the Investigator's understanding of the protocol, his/her obligations during the study and the likely recruitment rate will also be discussed and agreed. Other matters, such as verification of data obtained in the study may also be discussed.

	Yes	No*
1. *Preparation for the Site Initiation Visit*		
a) Agree with the Monitor the scheduled date, time and location of the study initiation visit.	❑	❑
b) Ensure that the Investigator/CRC and any other relevant staff involved with the study have been advised of the meeting and are able to attend.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
c) Before the meeting complete the checklist contained in Appendix A of this SOP in order to establish that the Investigator's file contains all the required regulatory documents.	❑	❑

2. ***During the Site Initiation Visit***

a) Establish the monitoring visit schedule with the Monitor.	❑	❑
b) Ensure that the names and contact numbers of the relevant medical and study personnel of the Sponsor or CRO are available and documented clearly.	❑	❑
c) Check that the procedures and plans for storage, dispensing and return of study medication have been agreed and finalised with the Sponsor and Pharmacy.	❑	❑
d) Ensure that all relevant study site personnel fill out the Site Personnel/ Signature Log, which should be provided by the Monitor.	❑	❑
e) Review the documents used in the shipment of the investigational products to the study site.	❑	❑
f) Check that the quantity of CRFs that have been requested or shipped to the study site are sufficient for the number of subjects/patients that are likely to be recruited into the study.	❑	❑
g) Check that other related supplies are available, or are to be shipped to the study site at a later date, and that they are available in sufficient quantities.	❑	❑
h) Check that laboratory facilities and arrangements for the dispatch of samples to the laboratory are organised and that any specialised equipment that may be required will be available throughout the period of the trial, e.g. centrifuge, freezer, etc.	❑	❑
i) Ensure that you are familiar with the procedure for entering data in the CRF, as well as making changes and corrections.	❑	❑
i) Make sure that you understand the requirements that source documents and raw data will need to be available during monitoring visits to enable the Monitor to perform source data verification at each monitoring visit.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
k Review the arrangements that you have made for organising and maintaining your study files.	❑	❑
l) Unless already discussed, ascertain that the procedures relating to the archiving of study records at the end of the study is agreeable to the Sponsor.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Appendix A

CHECKLIST OF CONTENTS IN SITE INVESTIGATOR's FILE

		Yes	No*
1.	Investigator's Brochure (IB) and any updates.	❑	❑
2.	Signed Protocol and amendments, if any, and sample CRF.	❑	❑
3.	Information given to trial subject. Informed consent form (including all applicable translations) and any other written information including any revisions.	❑	❑
4.	Advertisement for subject recruitment including any revisions (if used).	❑	❑
5.	Financial aspects of the trial (unless stored elsewhere).	❑	❑
6.	Insurance Statement (where required).	❑	❑
7.	Signed Agreement between involved parties, e.g. Investigator/Institution and Sponsor, Investigator/Institution and CRO, Sponsor and CRO, Investigator/ Institution and authority(ies) (where required).	❑	❑
8.	Dated, documented approval/favourable opinion of IEC/IRB of the following including any updates:		
	• Protocol	❑	❑
	• CRF (if applicable)	❑	❑
	• Any other written information to be provided to the subjects	❑	❑
	• Advertisement for subject recruitment (if used)	❑	❑
	• Subject compensation (if any)	❑	❑
	• Any other documents given approval/favourable opinion	❑	❑
9.	IEC/IRB composition.	❑	❑
10.	Regulatory authority(ies) authorisation/approval/notification of protocol (where required).	❑	❑
11.	CV and/or other relevant documents evidencing qualifications of Investigator (s) and Co-Investigators.	❑	❑
12.	Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/ or test(s) included in the protocol and any updates.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

		Yes	No*
13.	Medical/laboratory/technical/procedures/tests certification or accreditation or established quality control and/or external quality control assessment or other validation and updates (where required).	❑	❑
14.	Instructions for handling of investigational product(s) and trials related materials (if not included in protocol or Investigator's Brochure).	❑	❑
15.	Shipping records for investigational product(s) and trial related materials.	❑	❑
16.	Decoding procedures for blinded trials.	❑	❑
17.	Trial initiation monitoring report.	❑	❑
18.	Relevant correspondence, letters, notes and notes of telephone calls.	❑	❑
19.	Signed informed consent forms.	❑	❑
20.	Source documents.	❑	❑
21.	Notification by Investigator to Sponsor of Serious Adverse Events and related reports.	❑	❑
22.	Notification by Sponsor and/or Investigator of unexpected adverse drug reactions and other safety information.	❑	❑
23.	Notification by Sponsor to Investigator of safety information.	❑	❑
24.	Copies of signed, dated and completed CRFs.	❑	❑
25.	Interim or annual reports to IEC/IRB and authority(ies).	❑	❑
26.	Subject screening Log.	❑	❑
27.	Subject identification code list.	❑	❑
28.	Subject enrolment log.	❑	❑
29.	Investigational product accountability at the study site.	❑	❑
30.	Signature sheet.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

		Yes	No*
31.	Record of retained body fluids/tissue samples (if any).	❑	❑
32.	Investigational product accountability at site.	❑	❑
33.	Documentation of investigational product destruction (if destroyed at site).	❑	❑
34.	Completed subject identification list.	❑	❑
35.	Final report by Investigator to IEC/IRB where required, and where applicable, to the regulatory authority(ies).	❑	❑
36.	Clinical study report.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Section	*Comments*

Effective Date _____

Issue Date _____

SOP No: T2

BLINDING: CODES AND CODE BREAKING

APPROVED BY _____

Investigator

_____

Signature/Date

REVISIONS

No	*Section No*	*Page No*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP

Date	*Signed*	*Date*	*Signed*
1		3	
2		4	

SOP No. T2

BLINDING: CODES AND CODE BREAKING

I. Purpose

To describe the procedure in blinded trials for dealing with the codes and when and how the codes may be broken.

II. Other Related Procedures

SOP P3: Review and Validation of Clinical Trial Protocol
SOP P11: Pre-Study Planning of Investigational Products and Devices
SOP T3: Investigational Products and Accounting and Dispensing

III. Procedures

Blinding is a procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding is where the subjects are unaware of the treatment assigned, and double blinding is where the subject(s), Investigator(s), Monitor, and in some cases, data analyst(s) are unaware of the treatment assignments.

1. *Prior to the Study*

The Sponsor of the clinical trial will normally plan and organise the procedures for blinding, randomisation, coding and possible code breaking. However, because procedures for breaking codes vary from study to study, the protocol and procedure must be reviewed in detail, and a procedure established before the first patient begins treatment.

Ensure that a 24 hour contact number for the Sponsor is available. Obtain the names and telephone numbers of the necessary persons to contact, and keep the details in an accessible place which is known to all department staff.

2. *During the Study*

The codes may be contained in individual sealed envelopes stored at the study site to be opened by the Investigator or a Pharmacist, or the code may only be available via the Sponsor.

All staff involved in a clinical study must know the method for obtaining the code.

3. *Breaking the Code*

When the code is broken for an individual subject, this must be clearly documented in the subject(s) CRF with the reasons for breaking the code. In addition, the code envelope that was opened should be signed and dated by the Investigator and also annotated with the reason and retained for the sponsor.

4. *Reasons for Breaking the Code*

The code should generally only be broken in the case of an serious adverse event or emergency, where it is necessary for the Investigator to know which treatment the patient is receiving, before the condition can be treated. Unless it is an emergency, or if there is any doubt as to whether a code should be broken, contact the Sponsor or their representatives prior to breaking the code.

Effective Date: _____

Issue Date: _____

SOP No: T3

INVESTIGATIONAL PRODUCTS ACCOUNTING AND DISPENSING

APPROVED BY: _____

Investigator

_____

Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: T3

INVESTIGATIONAL PRODUCTS ACCOUNTING AND DISPENSING

I. Purpose

To describe the procedures and responsibilities for the receipt and storage of investigational products (study drugs) and trial devices at the study site, and the documentation of their location from the time of receipt to final removal (or destruction).

II. Other Related Procedures

SOP P9: Study Team: Definition of Responsibilities
SOP P11: Pre-Study Planning of Investigational Products and Devices
SOP T2: Blinding: Codes and Code Breaking
SOP SC1: Study Closure Visit

III. Procedures

Investigational product(s) are a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use

The Sponsor has numerous responsibilities associated with the supplying and handling of Investigational products to Investigators/Institutions. In addition to the Sponsor's responsibilities, the Investigator also has to assume responsibility for investigational product(s) supplied to him by the Sponsor in connection with a particular trial or study. Where allowed or required the Investigator may assign some or all of the Investigator's duties for investigational product(s) accountability at the trial site to an appropriate Pharmacist or another appropriate individual who is under the supervision of the Investigator. In this case, an agreement should be made between the individual who is responsible for the management of the investigational products and the Sponsor.

The individual designated for the management of investigational products is responsible for the following:

- Receipt
- Storage
- Dispensing
- Retrieval of unused investigational products from the subjects
- Return of unused investigational products to the Sponsor

	Yes	No*
1. *Responsibilities*		
a) Ensure that the individual responsible for management of the investigational products knows, and has easy access to relevant information about the trial and the drug, e.g. copies of the protocol and Investigator's Brochure.	❑	❑
b) Check that the individual responsible for the management of the investigational product(s) knows the written procedures as agreed by the Sponsor.	❑	❑
c) Ensure that sufficient and timely supplies of the investigational product are available during the study.	❑	❑
2. *Accountability*		
a) Ensure that the investigational products accountability procedures are met to the satisfaction of the Sponsor.	❑	❑
b) Complete the investigational products accountability document on an ongoing basis: on arrival of the supplies, each time drugs are dispensed, on return from the subjects and when the drugs are sent back to Sponsor and/or destroyed.	❑	❑
3. *Dispensing*		
a) Ensure that subjects are supplied with the appropriate study drugs, at the appropriate times and in compliance with the protocol.	❑	❑
b) Note the batch or serial numbers, expiry dates and the doses of the medication when they are dispensed to the study subjects.	❑	❑
c) Because of the nature of the drugs, local regulations or to ensure blinding, sometimes restrictions will be set on who may give investigational products to subjects. Document the identified person in this case.	❑	❑
d) Ensure that the subject understands when and how to take the medication, and where necessary how to record the relevant details.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
e) Identify and document any individual who may alter the subject's trial medication if the protocol allows dosage adjustment or other flexibility of regime.	❑	❑

4. *Subject Compliance*

a) When conducting follow-up visits the Investigator or CRC is responsible for assessing the subject's compliance with a trial medication e.g. ensuring returned tablets are consistent with records on diary cards.	❑	❑
b) Document any problems encountered with a subject's compliance.	❑	❑

5. *Return of Trial Medication by the Subject*

a) Document the procedure for dealing with unused study drug(s) returned by subject, e.g. will they be returned to directly to Pharmacy or to the Investigator or the CRC? Will tablets be counted, inhalers weighed etc? Where will they be stored?	❑	❑
b) When all the subjects have completed the study, and the required documents have been completed, ensure that the individual responsible for the management of the medication, or the Investigator has signed and dated the documents for its accuracy and completeness.	❑	❑

6. *Return of Trial Medication by the Sponsor*

a) Ensure that all investigational products are returned to the Sponsor at the end of the study.	❑	❑

7. *Supply of Medication on a Named-Patient/Subject Basis at the End of a Study*

a) Discuss with the Sponsor whether a named-patient/subject supply of the study medication will be available at the end of the study, for a named patient/subject basis before the enrollment of the first subject.	❑	❑
b) Agree with the Sponsor about the procedure(s) for requisitioning the investigational product if it is available on a named-patient basis.	❑	❑
c) Establish if there will be any interactions between the study drug and any post trial drugs that may be prescribed or considered.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
d) Establish who will be responsible for the post-trial care of the named patient/subject if it is not the Investigator.	❑	❑
e) Document the procedure for monitoring subjects if they are to receive any trial medication after the completion of the study, on a named-patient supply of the study drug. This should include a frequency of follow up visits acceptable to the Sponsor.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: T4

CASE REPORT FORM COMPLETION

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: T4

CASE REPORT FORM COMPLETION

I. Purpose

To describe the procedure for completing, signing and correcting Case Report Forms (CRFs).

II. Other Related Procedures

SOP P6: Review of Case Report Form
SOP P9: Study Team: Definition of Responsibilities
SOP T6: Adverse Event and Serious Adverse Event Reporting
SOP SC2: Archiving of Study Data

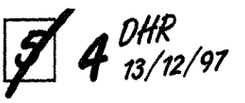
III. Procedures

The CRF is a printed, optical, or electronic document designed to record all of the protocol required information to be reported to the Sponsor on each trial subject. The Investigator holds the responsibilities for ensuring the accuracy, completeness, legibility, and timeliness of the data reported to the Sponsor in the CRFs.

	Yes	No*
a) Check that the data reported on the CRFs, derived from source documents, is consistent with the source documents. If not, the discrepancies should be explained.	❑	❑
b) Only the Investigator, Co-Investigators, CRC and any other study personnel named in the Study File may complete CRFs.	❑	❑
c) Use a **black** ballpoint pen to complete the CRFs.	❑	❑
d) Insert a suitable separator between the CRFs when they are printed on NCR (no carbon required) paper.	❑	❑
e) If you cannot complete part of the form, write down 'unknown', 'uncertain', 'missing' or 'test not done', as appropriate, or similar unambiguous words. Avoid using the ambiguous phrase, 'not available'.	❑	❑
f) Ensure that the Investigator signs and dates all completed CRFs to indicate that he/she believes that they are complete and correct. Note: Some Sponsors require a signature on each page of the CRF and some only need a signature and date on the final page.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
g) Ensure all data entries in the CRF are clearly written in order to avoid the generation of data queries.	❑	❑
h) When corrections to entries in the CRF need to be done, cross out the incorrect entry with a single line — the incorrect entry should still be readable. **On no account use liquid correcting fluid.** Initial and date the correction, and give an explanation of why it was changed (if necessary).	❑	❑



i) Agree with the Monitor the procedures to be used when it is necessary to make corrections after copies of the CRFs have been taken from the study site, and follow the procedures in all cases.	❑	❑
j) The Investigator should comment on and document any significance noted on the CRFs for any laboratory values outside the laboratory's reference range, or some other range agreed with the Sponsor, to avoid the generation of data queries.	❑	❑
k) Unless otherwise agreed, ensure that the laboratory values entered on the CRFs are without conversion from the printed reports, even if in a multi-centre study the units of measurement differ from centre to centre. Discuss this with the Sponsor.	❑	❑
l) For reasons of confidentiality, the subject's full name should never appear on the CRFs. However, the Investigator must keep a record of all subjects in the study that identifies the subject's full name and their subject code number. This must be also be archived by the Investigator after completion of the trial (**see SOP SC2: Archiving of Study Data).**	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: T5

OBTAINING WRITTEN INFORMED CONSENT

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No. T5

OBTAINING WRITTEN INFORMED CONSENT

I. Purpose

This SOP describes the procedure for obtaining personal written informed consent from a study subject. This involves ensuring that they understand what they are signing by means of a verbal explanation and a written subject information sheet. This SOP describes the two phases.

II. Other Related Procedures

SOP: P3: Review and Validation of Clinical Trial Protocol
SOP: P4: Review of Protocol Amendments

III. Procedures

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

	Yes	No*
1. *General*		
a) Check that the content of the informed consent document contains the necessary statements and critical elements as outlined by the checklist in Appendix A of this SOP. If anything is missing consult Appendix B of this SOP.	❑	❑
b) Ensure that the written informed consent form, and any other written information provided to a subject or the subject's legal representative has the written approval/favourable opinion of the local IEC/IRB.	❑	❑
c) Check that the informed consent form, and any other written information that is given to patients/subject(s) includes any new details which may be relevant to the subject's willingness to participate or continue their participation in the study. **Note: Any revised versions of the subject/patient information sheet and informed consent form must be approved by the Ethics Committee/IRB in advance of its use.**	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
d) Ensure that any information given to patients/subject(s) or the patients/ subject's legal representative, whether it is written or oral, is expressed in a language that the subject can comprehend and understand.	❑	❑
e) For long trials, consider whether informed consent needs to be repeated at intervals during the trial.	❑	❑

2. ***Taking Informed Consent***

a) Prior to asking the subject to give consent, give a brief description of the study to each subject, using non-technical language and a language understandable to him or her.	❑	❑
b) Provide the subject and the subject's legal representative sufficient time and opportunity to inquire about details of the trial, and to decide whether or not they wish to participate.	❑	❑
c) Never excessively influence a subject to participate or to continue to participate in a trial.	❑	❑
d) When explaining the information about a study to a subject, discuss the full contents of the patient information sheet and consent form.	❑	❑
e) The person taking signed informed consent should sign and date the form and print their name in block letters, under their signature.	❑	❑

3. ***Documentation of Informed Consent***

When the informed consent is signed by the subject ensure that:

a) The informed consent documentation, clearly identifies the person who performed the informed consent.	❑	❑
b) That the subject or the subject's legal representative signs the informed consent.	❑	❑
c) That an impartial witness, if required, also signs the informed consent document (see Section 4a).	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
d) Give a copy of the signed and dated written informed consent and any other written information given to the subject or the subjects legal representative, and keep one copy in the Investigator's file.	❑	❑

4. *Vulnerable Subjects*

a) If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness is required during the entire informed consent discussion.	❑	❑
b) When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.	❑	❑
c) In paediatric studies, the Investigator is required to obtain written permission from the parents and when applicable, assent from the child before the study except when specifically exempt by the IEC/IRB. Assent should be obtained from children who are competent to understand, and the purpose, risks and benefits of a study should be explained to the subjects. Assent must be an active affirmation by the research subject and should usually be obtained from any child with an intellectual age of 7 years or more. The protection provides the opportunity for a child 7 years or older to refuse participation in studies or procedures done for research purposes.		
For research that involves:		
No greater than minimal risk Obtain assent of the child and permission of at least one parent.	❑	❑
Greater than minimal risk and prospect of direct benefit		
• Assent of the child and permission of at least one parent	❑	❑
• Anticipated benefit justifies the risk, and	❑	❑
• Anticipated benefit is at least as favourable as that of alternative approaches	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
Greater than minimal risk and no prospect of direct benefit		
• Assent of the child and permission of both parents	❑	❑
• Only a minor increase over minimal risk	❑	❑
• Likely to yield generalisable knowledge about the child's disorder	❑	❑
Any other research		
• Assent of the child and permission of both parents	❑	❑
• IEC/IRB finds that the research presents a reasonable opportunity to further the understanding, prevention or alleviation of a serious problem affecting the health or welfare of children, and	❑	❑
• It is approved after consultation with a panel of experts in pertinent disciplines and following publication and public comment.	❑	❑

5. ***Emergency Situations***

a) Research in patients requiring emergency care may be conducted and informed consent/permission/assent altered or waived when all of the following conditions are met:

• The clinical condition is potentially life-threatening or permanently disabling and the only known therapy is investigational or non-validated;	❑	❑
• Informed consent/permission/assent cannot be obtained at the time the investigational treatment needs to be started; and	❑	❑
• There is no accepted therapy that is clearly superior to the experimental therapy.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Appendix A

CHECKLIST FOR PATIENT INFORMATION SHEET

		Yes	No
1.	A statement to say that the clinical trial involves research.	❑	❑
2.	The purpose of the trial.	❑	❑
3.	The trial treatment(s) and the probability for random assignment to each treatment.	❑	❑
4.	The trial procedures to be followed, including all invasive procedures.	❑	❑
5.	The subject's responsibilities.	❑	❑
6.	Those aspects of the trial that are experimental.	❑	❑
7.	The reasonably foreseeable risks or inconveniences to the subject and when applicable, to an embryo, foetus, or nursing infant.	❑	❑
8.	The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.	❑	❑
9.	The alternative treatment(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.	❑	❑
10.	The compensation and/or treatment available to the subject in the event of trial-related injury.	❑	❑
11.	The anticipated prorated payment, if any, to the subject for participating in the trial.	❑	❑
12.	The anticipated expenses, if any, to the subjects for participating in the trial.	❑	❑
13.	That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.	❑	❑

		Yes	No
14.	That the Monitor(s), the Auditor(s), the IEC/IRB, and the Regulatory Authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorising such access.	❑	❑
15.	That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.	❑	❑
16.	That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.	❑	❑
17.	The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of a trial-related injury.	❑	❑
18.	The foreseeable circumstances and/or reasons under which the subject's participation the trial may be terminated.	❑	❑
19.	The expected duration of the subject's participation in the trial.	❑	❑
20.	The approximate number of subjects involved in the trial.	❑	❑

APPENDIX B

GUIDELINES FOR RESEARCHERS SUBJECT/PATIENT INFORMATION SHEET AND CONSENT FORM

The guidance, which follows, applies primarily to studies that must comply with the ICH Good Clinical Practice guidelines. However, the principles and much of the content will be of use to researchers writing information sheets in their particular fields, for research involving patients, patient volunteers and healthy volunteers.

Potential recruits to your research study must be given sufficient information to allow them to decide whether or not they want to take part. An Information Sheet should contain information under the headings given below where appropriate, and in the order specified. It should be written in simple, non-technical terms and be easily understood by a lay person. Use short words, sentences and paragraphs.

Use the headed paper of the hospital/institution where the research is being carried out. Plain un-headed paper is not acceptable.

1. STUDY TITLE

Is the title self-explanatory to a lay person? If not, a simplified title should be included.

2. INVITATION PARAGRAPH

This should explain that the subject/patient is being asked to take part in a research study. The following is a typical example:

"You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your family doctor if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part."

3. WHAT IS THE PURPOSE OF THE STUDY?

The background and aim of the study should be given here. Also mention the duration of the study.

4. WHY HAVE I BEEN CHOSEN?

You should explain how the subject/patient was chosen and how many other patients will be studied.

5. DO I HAVE TO TAKE PART?

You should explain that taking part in the research is entirely voluntary. You could use the following paragraph:

"It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. This will not affect the standard of care you receive."

6. WHAT WILL HAPPEN TO ME IF I TAKE PART?

You should say how long the subject/patient will be involved in the research, how long the research will last (if this is different), how often they will need to visit a clinic (if this is appropriate) and how long these visits will be. You should explain if the patient will need to visit their family doctor (or clinic) more often than for his/her usual treatment and if travel expenses are available. What exactly will happen e.g. blood tests, x-rays, interviews etc.? Whenever possible you should draw a simple flowchart or a plan indicates what will happen at each visit. What are the patient's responsibilities? Set down clearly what you expect of them.

You should set out simply the research methods you intend to use; the following simple definitions may help:

- ***Randomised trial:***

  "Sometimes because we do not know which way of treating patients is best, we need to make comparisons. People will be put into groups and then compared. The groups are selected by a computer which has no information about the individual, i.e. by chance. Patients in each group then have a different treatment and these are compared".

  You should tell the subject/patient what chance they have of getting the study drug/treatment e.g. a one in four chance.

- ***Blind trial:***

  "In a blind trial you will not know which treatment group you are in. If the trial is a double blind trial, neither you nor your doctor will know in which treatment group you are (although, if your doctor needs to find out he/she can do so)".

- ***Crossover trial:***

  "In a crossover trial the groups each have the different treatments in turn. There may be a break between treatments so that the first drugs are cleared from your body before you start the new treatment"

- ***Placebo:***

  "A placebo is a dummy treatment such as a pill which looks like the real thing but is not. It contains no active ingredient".

7. WHAT DO I HAVE TO DO?

Are there any lifestyle restrictions? You should tell the subject/patient if there are any dietary restrictions. Can the subject/patient drive/drink/take part in sport? Can the subject/patient continue to take their regular medication? Should the patient refrain from giving blood? What happens if the subject/patient becomes pregnant?

Explain (if appropriate) that the subject/patient should take the medication regularly.

8. WHAT IS THE DRUG OR PROCEDURE THAT IS BEING TESTED?

You should include a short description of the drug or device and give the stage of development.

You should also state the dosage of the drug and method of administration. Patients entered into drug trials should be given a card (similar to a credit card) with details of the trial they are in. They should be asked to carry it at all times.

9. WHAT ARE THE ALTERNATIVES FOR DIAGNOSIS OR TREATMENT?

For therapeutic research the patient should be told what other treatments are available.

10. WHAT ARE THE SIDE EFFECTS OF TAKING PART?

For any new drug or procedure you should explain to the patients the possible side effects. If they suffer these or any other symptoms they should report them next time you meet. You should also give them a contact name and number to phone if they become in any way concerned.

The known side effects should be listed in terms the patient will clearly understand (e.g. "damage to the heart" rather than "cardiotoxicity"; "abnormal liver tests" rather than "raised liver enzymes"). For any relatively new drug it should be explained that there may be unknown side effects.

11. WHAT ARE THE DISADVANTAGES AND RISKS OF TAKING PART?

For studies where there could be harm to an unborn child if the patient were pregnant during the study, the following (or similar) should be said:

"It is possible that if the treatment is given to a pregnant woman it will harm the unborn child. Pregnant women must not therefore take part in this study, neither should women who plan to become pregnant during the study. Women who are at risk of pregnancy may be asked to have pregnancy test before taking part to

exclude the possibility of pregnancy. Women who could become pregnant must use an effective contraceptive during the course of this study. Any woman who finds that she has become pregnant while taking part in the study should immediately tell her research doctor."

Use the pregnancy statement carefully. In certain circumstance (e.g. terminal illness) it would be inappropriate and insensitive to bring up pregnancy.

There should also be an appropriate warning and advice for men if the treatment could damage sperm which might therefore lead to a risk of a damaged foetus.

If future insurance status could be affected by taking part this should be stated. If the patients have private medical insurance you should ask them to check with the company before agreeing to take part in the trial. They will need to do this to ensure that their participation will not affect their medical insurance.

You should state what happens if you find a condition of which the patients was previously unaware. Is it treatable? What are you going to do with this information? What might be uncovered (e.g. high blood pressure, HIV + status)?

12. WHAT ARE THE BENEFITS OF TAKING PART?

Where there is no intended clinical benefit to the patient from taking part in the trial this should be stated clearly.

It is important not to exaggerate the possible benefits to the particular patient during the course of the study, e.g. by saying they will be given extra attention. This could be seen as coercive. It would be reasonable to say something like:

"We hope that both/all the treatments will help you. However, this cannot be guaranteed. This information we get from this study may help us to treat future patients with [name of condition] better."

13. WHAT IF NEW INFORMATION BECOMES AVAILABLE?

If additional information becomes available during the course of the research you will need to tell the patient about this. You could use the following:

"Sometimes during the course of a research project, new information becomes available about the treatment/drug that is being studied. If this happens, your research doctor will tell you about it and discuss with you whether you want to continue in the study. If you decide to withdraw your research doctor will make arrangements for your care to continue. If you decide to continue in the study you will be asked to sign an updated consent form."

"Also, on receiving new information your research doctor might consider it to be in your best interests to withdraw you from the study. He/She will explain the reasons and arrange for your care to continue."

14. WHAT HAPPENS WHEN THE RESEARCH STUDY STOPS?

If the treatment will not be available after the research finishes this should be explained to the patient. You should also explain to them what treatment will be available instead. Occasionally the company sponsoring the research may halt the study. If this is the case the reasons should be explained to the patient.

15. WHAT IF SOMETHING GOES WRONG?

You should inform patients how complaints will be handled and what redress may be available. Is there a procedure in place? You will need to distinguish between complaints from patients as to their treatment by members of staff (doctors, nurses etc.) and something serious which occurs during or following their participation in the trial i.e. a reportable serious adverse event.

"If you are harmed by taking part in this research project, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain about any aspect of the way you have been approached or treated during the course of this study, the normal health service complaints mechanisms may be available to you."

16. THE ANTICIPATED PRORATED PAYMENT, IF ANY, TO THE SUBJECT FOR PARTICIPATING IN THE STUDY

17. THE ANTICIPATED EXPENSES, IF ANY, TO THE SUBJECT FOR PARTICIPATING IN THE TRIAL

18. WILL MY TAKING PART IN THIS STUDY BE KEPT CONFIDENTIAL?

You will need to obtain the patient's permission to allow restricted access to their medical records and to the information collected about them in the course of the study. You should explain that all information collected about them will be kept strictly confidential. A suggested form of words for company sponsored research is:

"If you consent to take part in the research any of your medical records may be inspected by the company sponsoring (and/or the company organising) the research for purposes of analysing the results. They may also be looked at by people from the company and from regulatory authorities to check that the study is being carried out correctly. Your name, however, will not be disclosed outside the hospital or your family doctor's surgery".

Or for other research,

"All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it."

You should explain that for studies not being conducted by a GP, the patient's own GP will be notified of their participation in the trial. This should include other medical practitioners not involved in the research who may be treating the patient. You should seek the patient's agreement to this. In some instances agreement from the patient that their GP can be informed is a precondition of entering the trial.

19. WHAT WILL HAPPEN TO THE RESULTS OF THE RESEARCH STUDY?

You should be able to tell the patients what will happen to the results of the research. When are the results likely to be published? Where can they obtain a copy of the published results? Will they be told which arm of the study they were in? You might add that they will not be identified in any report/publication.

20. WHO IS ORGANISING AND FUNDING THE RESEARCH?

The answer should include the organisation or company sponsoring or funding the research (e.g. Medical Research Council, pharmaceutical company, charity, academic institution).

The patient/subject should be told whether the doctor conducting the research is being paid for including and looking after the patient in the study. This refers to payment other than that to cover necessary expenses such as laboratory tests arranged locally by the researcher, or the costs of a research nurse. You could say:

"The sponsors of this study will pay [name of hospital department/research fund] for including you in this study" or "Your doctor will be paid for including you in this study."

21. WHO HAS REVIEWED THE STUDY?

You may wish to give the name of the Institutional Review Board or Research Ethics Committee(s) which reviewed the study (you do not however have to list the members of the Committee).

22. CONTACT FOR FURTHER INFORMATION

You should give the subject/patient a contact point for further information. This can be your name or that of another doctor/nurse involved in the study.

Remember to thank your patient/subject for taking part in this study!

The patient/subject information sheet should be dated and given a version number.

The patient/subject information sheet should state that the subject/patient will be given a copy of the information sheet and a signed consent form to keep.

SAMPLE OF SUBJECT/PATIENT CONSENT FORM

[Form to be on headed paper]

Centre Number: _____

Study Number: _____

Patient Identification Number for this trial: _____

Title of Project: _____

Name of Doctor/Investigator: _____

Please initial box

1. I confirm that I have read and understood the information sheet dated __/__/__ (version _____) for the above study and have had the opportunity to ask questions. ❑
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ❑
3. I understand that sections of any of my medical notes may be looked at by responsible individuals from [company name] or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. ❑
4. I agree to take part in the above study. ❑

Name of patient or Legal Guardian (or Impartial Witness)	*Date*	*Signature*
Name of person taking consent (if different from Doctor/Investigator)	*Date*	*Signature*
Doctor/Investigator	*Date*	*Signature*

Copies to:
- Subject/Patient
- Researcher
- Hospital/Clinic Records

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: T6

ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

APPROVED BY: _____

Investigator

_____

Signature/Date

REVISIONS:

No.	*Section No.*	*Page No*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: T6

ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

I. Purpose

To describe the procedures for eliciting, recording and reporting adverse events and serious adverse events.

II. Other Related Procedures

SOP P13: Independent Ethics Committee or Institutional Review Board
SOP T4: Case Report Form Completion

III. Procedures

Adverse Events (AE)
An AE is any untoward medical occurrence in a subject/patient administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign including an abnormal laboratory finding, symptom, or disease or accident temporarily associated with the use of a medicinal (investigational) product, whether or not related to the product.

Serious Adverse Events (SAE)
A SAE is **any** untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening
- Requires inpatient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

	Yes	No*
1. *General Information*		
a) Ensure that all staff in contact with subjects are responsible for noting adverse events that are reported by the subject and make known to appropriate staff e.g. medical or nursing staff.	❑	❑
b) Ensure that all adverse events are reported as far as possible.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
c) The Investigator **must** sign the written report for each serious adverse event before forwarding it to the Sponsor.	❑	❑
d) At each visit, or study assessment, AEs and SAEs that might have occurred since the previous visit or assessment should be reported and documented in the subject's CRF and clinical notes.	❑	❑
e) At the completion of the study, follow up as required by the protocol and as clinically indicated **all** ongoing adverse events.	❑	❑

2. ***Documenting an AE***

a) Document the event in an unambiguous way as far as possible. For example, the subject may say that they "felt sick". This can be interpreted in many ways: either they felt nauseated or they may have felt unwell, or they may even have been vomiting!	❑	❑
b) Ask the subject the duration of the event. If the subject cannot remember, then document as accurately as possible in the subject's hospital or clinic notes any relevant information given by the subject.	❑	❑
c) Record the details of any treatment and/or concomitant medication (s) given to the subject at the time of the adverse event.	❑	❑
d) Document the outcome of the adverse event.	❑	❑
e) Clearly document any actions taken with respect to the adverse event.	❑	❑
f) Ensure that the Investigator/Co-Investigator documents the causality between the investigational drug(s) and the event.	❑	❑

3. ***Documenting a SAE***

a) Report the details of the SAE to the Sponsor within 24 hours of the event occurring in accordance with ICH GCP guidelines, or in any event, as soon after you have identified it has occurred.	❑	❑
b) Respond promptly to requests for follow-up information from the Monitor or Sponsor as a more detailed, written report and/or an autopsy report, in the case of death, will usually be required.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
c) Document the outcome of the adverse event.	❑	❑
d) Clearly document any actions taken with respect to the adverse event.	❑	❑
e) Ensure that the Investigator/Co-Investigator documents the causality between the investigational drug(s) and the event.	❑	❑
f) Ensure that the Investigator reports to the IEC/IRB all incidences of SAE in accordance with the local requirements of the IEC/IRB.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: T7

MONITORING VISITS

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: T7

MONITORING VISITS

I. Purpose

This procedure describes the preparation for and the procedures to follow during monitoring visits.

II. Other Related Procedures

SOP T3: Investigational Products Accounting and Dispensing
SOP T4: Case Report Form Completion
SOP T6: Adverse Event and Serious Adverse Event Reporting
SOP T7: Monitoring Visits
SOP T8: Data Clarification

III. Procedures

Monitoring a study is 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, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP) and the applicable regulatory requirement(s). Monitoring visits will normally be arranged in advance by the Monitor with the Investigator and/or other staff as appropriate, soon after the first patient is enrolled. Depending on the study, visits will probably take place approximately every four to six weeks, However, depending on the length of the study and its progress, the interval between monitoring visits may be prolonged or shortened.

	Yes	No*
1. ***Prior to the Monitoring Visit***		
a) Use the monitoring visit checklist shown in Appendix A of this SOP to update the study and prepare information for the monitoring visit.	❑	❑
b) Ensure that all the relevant documents relating to the study are gathered together before the planned visit.	❑	❑
c) Where possible, try to get all the CRFs up to date, including any outstanding corrections from the last or previous visit.	❑	❑
d) Make sure that all source documents are available, including those from other departments, e.g. Radiology, Cardiology etc. which may be relevant to the study.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
e) Locate a room or quiet area with a desk that can be set aside for use by the Monitor during the monitoring visit.	❑	❑
f) Prepare details of numbers of patients screened and enrolled in the study and of any other outstanding business requiring discussion.	❑	❑
2. *During the Monitoring Visit*		
a) If required by the Monitor, the Investigator, Co-Investigator and/or the CRC should be available on the day of the visit, in order to clarify any details and answer any queries raised by the Monitor.	❑	❑
b) It is preferable that the Investigator is always available for at least a proportion of each monitoring visits.	❑	❑
c) The Monitor will normally require time to go through the CRFs and associated source documents alone, with a meeting with the appropriate site staff afterwards to discuss any problems or outstanding business.	❑	❑
d) The Monitor may also wish to examine facilities at the study site and check the storage of the study medication and drug accountability. Check whether this is the case, and make an appointment with the staff in other departments that may be involved. In any event, accompany the Monitor on such visits to the departments if required.	❑	❑
3. *After the Monitoring Visit*		
a) Ensure that all source documents are returned to the respective departments.	❑	❑
b) Check that any missing data identified by the Monitor and any corrections that need to be performed are done promptly; they are easier to do when the points are fresh in your mind.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Appendix A

MONITORING VISIT CHECKLIST

Protocol Number: _____ Date of Protocol: _____
dd / mm / yy

Sponsor's Name: _____ Date of Monitoring Visit: _____
dd / mm / yy

Patient Recruitment Summary:

Total No. of subjects/patients recruited into the study: _____

No. of new subjects/patients recruited since last visit: _____

No. of potential subjects/patients anticipated or screened since last visit: _____

Total No. of subjects/patients completed: _____

Total Number of dropouts since last visit: _____

Total No. of dropouts from study: _____

Since Last Monitoring Visit	Yes	No
1. Is there any outstanding business to discuss?	❑	❑
2. Have there been any adverse events?	❑	❑
3. Have there been any protocol violations?	❑	❑
4. Are all the CRFs up to date?	❑	❑
5. Have all CRF corrections been made since the last visit?	❑	❑
6. Are all source documents available?	❑	❑
7. Have there been any protocol amendments?	❑	❑
8. Any changes to the Subject Patient Information Sheet or Informed Consent Form?	❑	❑
9. Has the contents of the Investigator's File been checked?	❑	❑
10. Is a room/quiet area available for the arranged time of the visit?	❑	❑

Room number/name: _____

	initials	*initials*	*initials*
Who will be available during the monitoring visit?	_____	_____	_____

Post Visit

Names of Monitor and any accompanying colleague _____

_____

Duration of visit _____ hours

Any outstanding tasks as result of visit? ❑ Yes ❑ No *Record details on reverse of this page*

Checklist completed by: _____ on _____(date)

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: T8

DATA CLARIFICATION

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: T8

DATA CLARIFICATION

I. Purpose

To describe the procedures to be conducted before and during data clarification.

II. Other Related Procedures

SOP T4: Case Report Form Completion
SOP T7: Monitoring Visits

III. Procedures

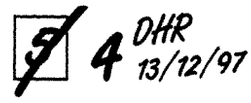
Different companies have different standard operation procedures for data clarification. However, the following procedures are commonly used for data clarification.

Data clarification will be performed by the trial Monitor with the CRC/Investigator responding to the query raised by the Data Management personnel of the Sponsor or the CRO. All queries raised will be recorded on a data clarification form (Appendix A). The Monitor will usually bring this form to the study site and verify the queries against the source documents with the CRC/ Investigator. Data clarification may be performed during regular monitoring visits or specially scheduled visits.

	Yes	No*
1. *Prior to the Visit for Data Clarification*		
a) The CRC should establish with the Monitor which trial subjects' data needs to be clarified, and ensure that the appropriate hospital records and/or relevant source documents of the subjects are available during the visit.	❑	❑
2. *During the Visit for Data Clarification*		
a) Identify the data in the CRF for each query on the data clarification form.	❑	❑
b) Check each of the queries against the source documents.	❑	❑
c) For queries where no changes are required, the Investigator should leave the data in the CRFs unchanged but still sign the data clarification form.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
d) For queries that need to be changed/corrected, the correct information or data should be recorded on the resolution section of the Data Clarification Form which should then be signed by the Investigator. The Investigator should correct the wrong data on the CRF by crossing it out with a single straight line, write down the correct data alongside, initial and date change.	❑	❑



Correcting data in a CRF

e) Corrections to the CRFs may be performed by the CRC if the Investigator is absent during the visit. However, the Investigator should verify that all the corrections made on the CRF and also the Data Clarification Form have been endorsed and approved by him/her.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Appendix A

DATA CLARIFICATION FORM

Study _____

Investigator _____ Monitor _____

Patient No _____ Patient Initials _____

Sheet No _____

Date	Query No	CRF Page No	Query / Action Required	Resolution	Investigator Sign & Date	Monitor Sign & Date

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: SC1

STUDY CLOSURE VISIT

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: SC1

STUDY CLOSURE VISIT

I. Purpose

To describe the procedures to be conducted before, during and after the Study Closure Visit.

II. Other Related Procedures

SOP T3: Investigational Products Accounting and Dispensing
SOP T4: Case Report Form Completion
SOP T7: Monitoring Visits
SOP SC2: Archiving of Study Data

III. Procedure

The study closure visit is the final monitoring visit usually performed four to six weeks after the last follow-up of the last subject in the study site. The preparation and procedures for the Study Closure Visit are more or less the same to that of a regular Monitoring Visit.

	Yes	No*
1. *Prior to the Study Closure Visit*		
a) If this visit also includes a regular Monitoring Visit, please refer to SOP T7.	❑	❑
b) Check that any remaining CRFs or Data Clarification Forms, have been completed and verified by the Investigator.	❑	❑
c) Ensure that all the essential documents are available and filed in the Investigator's File.	❑	❑
d) Make sure the drug accountability is up-to-date. Prepare all returned drugs or empty drug containers if return is needed for the monitor to collect.	❑	❑
e) Prepare any remaining specimens to be delivered to overseas laboratory if there is any.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
2. *During the Study Closure Visit*		
a) Facilitate the Monitor in the final check of the availability of all essential documents kept at the site.	❑	❑
b) Facilitate the Monitor in the final check on the accountability of the study drug/device.	❑	❑
c) Discuss with the Monitor the retention and archiving of all the essential trial documents, source data documents and CRFs. Follow any agreement made with the Sponsor on the archiving of trial documents during the pre-study phase.	❑	❑
3. *After the Study Closure Visit*		
a) Plan and prepare for archiving of all the trial documents. Please refer to SOP SC2 for archiving of study data.	❑	❑
b) Make sure the IEC/IRB is notified of the completion of the trial. If the trial is terminated due to other reasons, the notification must also include the reasons for discontinuation. The Investigator should also prepare and sign a Final Study Report and submit it to the IEC/IRB. A copy of the Final Study Report should also be sent to the Sponsor.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Section	*Comments*

Effective Date: _____

Issue Date _____

SOP No: SC2

ARCHIVING OF STUDY DATA

APPROVED BY: _____

Investigator

_____

Signature/Date

REVISIONS.

No.	*Section No*	*Page No*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: SC2

ARCHIVING OF STUDY DATA

I. Purpose

To describe the procedure for archiving the study documents at the end of a clinical trial.

II. Other Related Procedures

SOP SC1: Study Closure
SOP QA2: Audits
SOP QA3: Inspections

III. Procedures

	Yes	No*
Discuss and agree with the Sponsor as early as possible the procedure(s) and the exact requirements needed for archiving so that the necessary arrangement can be made.	❑	❑
Access to documentation and other study materials should only be allowed to the Investigator, the study personnel and the Regulatory Authorities.	❑	❑
Complete the checklist shown in Appendix A to determine the required study documents that need to be archived, as well as the location of the archived documents.	❑	❑
Advise the Sponsor of any new arrangements associated with the archiving of the study data.	❑	❑
Make any necessary arrangements to transfer the responsibility for the archived documents to the Investigator's successor in the event that he or she leaves the department before or after the study.	❑	❑
Check that the coded subject list containing the subjects full names, year of birth, and subject code number, together with the subject consent forms are archived along with all the data that will be archived.	❑	❑
Note that essential documents as defined in the ICH GCP Guidelines must be retained until notification from the Sponsor is received that they no longer need to be retained.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
Note, for studies on unlicensed products, essential documents must be kept by the Investigator for at least 2 years after the Sponsor's last marketing application in an ICH region. The Sponsor will inform the Investigator when this is the case, but in any event, the Investigator should expect to keep documentation for around 10-15 years.	❑	❑
Clearly mark in the subject(s) hospital records or clinic notes that he/she has taken part in a clinical trial and that the information should not be destroyed until the Investigator has given written consent to destroy them.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Appendix A

CHECKLIST FOR ARCHIVING STUDY DOCUMENTS

Are the following study documents archived at the study site?

	Yes	No*	N/A		Yes	No*	N/A
Investigator's Brochure	❑	❑	❑	Copies of Signed CRFs	❑	❑	❑
Investigator Brochure Update	❑	❑	❑	SAE Reports	❑	❑	❑
Signed Protocol	❑	❑	❑	Regulatory Documents	❑	❑	❑
Signed Protocol Amendments	❑	❑	❑	Investigator CV	❑	❑	❑
Regulatory Approval Documents	❑	❑	❑	Co-Investigator CV	❑	❑	❑
Recruitment Advertisement	❑	❑	❑	Lab Reference Ranges	❑	❑	❑
Consent Forms	❑	❑	❑	Lab Reference Range Updates	❑	❑	❑
Patient Information Sheet	❑	❑	❑	Laboratory Quality Control Data	❑	❑	❑
Sample CRF	❑	❑	❑	Code Break Procedure	❑	❑	❑
Sample Diary Card	❑	❑	❑	Subject Screening Log	❑	❑	❑
Sample Questionnaire	❑	❑	❑	Subject Identification Code List	❑	❑	❑
Insurance/Indemnity Statement	❑	❑	❑	Subject Enrollment Log	❑	❑	❑
Ethics Committee Approval	❑	❑	❑	Drug Accountability Records	❑	❑	❑
Ethics Committee Composition	❑	❑	❑	Meeting Reports	❑	❑	❑
Notifications to Ethics Committee	❑	❑	❑	Signature Sheet	❑	❑	❑
Safety Updates from Sponsor	❑	❑	❑	Trial Initiation Report	❑	❑	❑
Drug Destruction or Return Log	❑	❑	❑	Trial Report	❑	❑	❑
Contact Notes and Letters	❑	❑	❑	Record of Retained Samples	❑	❑	❑

Name of Investigator: _____
(Forename) (Surname)

Precise Location/Address of Archived Documents: _____

Archive for Subject Source Documents, If different from above address: _____

Date of earliest possible destruction of archived documents: _____

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Description of Archived Document	*Comments*

Section	*Comments*

Effective Date _____

Issue Date: _____

SOP No: QA1

INDEPENDENT DATA MONITORING

APPROVED BY:

_____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No*	*Page No*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP

Date	*Signed*	*Date*	*Signed*
1		3.	
2.		4.	

SOP No: QA1

INDEPENDENT DATA MONITORING

I. Purpose

The purpose of an Independent Data Monitoring Committee (IDMC) is to assess at intervals the progress of a clinical trial, the safety data and the critical efficacy endpoints. The overall aim is to recommend to the Sponsor whether to continue, modify or stop a trial based on the data of either the present trial or from other trials on similar compounds.

II. Other Related Procedures

SOP P1: Preparation of Clinical Trial Protocol and Protocol Amendments
SOP P3: Review and Validation of Clinical Trial Protocol

III. Procedures

An IDMC is a separate entity from an EC and its composition should include clinical trial scientists knowledgeable in the appropriate disciplines including Medical Statistics and Medical Ethics. An IDMC will examine not only trial data but also relevant evidence from other sources. It's recommendation to the Sponsor should be based on the interpretation of the results of an ongoing trial and the existing scientific data relevant to such interpretation. The IDMC is also sometimes referred to as a Data and Safety Monitoring Board (DSMB), Monitoring Committee (MC) or Data Monitoring Committee (DMC).

The main objectives of the IDMC are to:

		Yes	No*
1.	Ensure that patients in the trial are protected and that their interests are not made secondary to the interests of scientific investigations.	❑	❑
2.	Ensure that evaluation of interim results and decision making is made competently based on thorough evaluation.	❑	❑
3.	Ensure that credibility of trial reports and ethics of trial conduct are above reproach with no plausible appearance of professional or financial conflicts of interest.	❑	❑
4.	Enable physicians entering patients to remain free of knowledge of interim efficacy data.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: QA2

AUDITS

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: QA2

AUDITS

I. Purpose

The purpose of this SOP is to describe the requirements for an Audit at the study site.

II. Other Related Procedures

All SOPS, as Auditors will probably Audit against the SOPs in place at the site.

III. Procedures

An Audit is a systematic and independent examination of trial related activities and documents that determines whether a trial or its related activities were conducted, and the data recorded, analysed and accurately reported according to the protocol, Sponsor and Investigator's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

Who will perform the Audit?

In general, a member of the Quality Assurance (QA) department of the Sponsor will undertake an Audit. This group has to be independent of the Sponsor's department that is responsible for setting up and managing the clinical trial programme. The head of the QA department often reports directly to the senior management of the Sponsor. In some circumstances, the Sponsor may contract out the Audit to an external consultant.

The Audit Timetable

In the first instance, the Auditor will inform the Sponsor's study Monitor that an Audit is likely to take place. Usually, the Monitor will immediately inform the Investigator and the Auditor may contact the Investigator directly to inform him/her that an Audit is to take place, together with a suggested date and agenda.

Once the Audit date has been agreed the Monitor will contact the Investigator or his/her CRC to make an appointment for a pre-Audit visit to the Investigator study site. At this meeting the Monitor should undertake a careful briefing regarding what will happen on the day of the Audit, and who needs to be present. The Monitor will also undertake a thorough 'Monitoring Visit'.

Remember, that the Monitor is being assessed also and he/she will want to ensure that the study is going well, the protocol is being followed, the CRFs are well completed and up-to-date, and that the study files are in order.

	Yes	No*

Prior to the Audit

(a) The Investigator should notify all those who need to be aware that an Audit is to take place.

The following list gives some examples of who might need to be informed:

• Co-Investigator(s)	❑	❑
• CRC	❑	❑
• Study Administrator	❑	❑
• Pharmacy	❑	❑
• Laboratory	❑	❑
• Technical Departments (e.g. X-Ray, ECG if appropriate)	❑	❑
• Medical Records	❑	❑
• Institutional Quality Assurance Personnel (if available)	❑	❑

(b) Whilst the Monitor will be a great help in preparing the investigational team for an Audit, the Investigator should also call a meeting of those involved to ensure that everyone in the team is aware of the following:

• That there is to be an Audit	❑	❑
• The purpose of the Audit	❑	❑
• When the Audit is to take place and who should be present or be available if required	❑	❑
	❑	❑

(c) Conduct a thorough review of the following prior to the Audit:

• Study Procedures	❑	❑
• Study Protocol	❑	❑
• CRFs	❑	❑
• Source Data	❑	❑
• Study Documentation	❑	❑

Preparation for the Audit

(a) Check that suitable facilities are made available for the Auditor. The Auditor will need to have an office or a quiet area in which to work, meet people and examine records. Access to a photocopier may be a necessary requirement. ❑ ❑

(b) Ensure that all the requested documentation is available for the Auditor. ❑ ❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

		Yes	No*
(c)	Ensure that all trial team personnel are available on the day of the Audit.	❑	❑
(d)	Make sure that you have a copy of the most up to date IB and a signed copy of the final protocol including any protocol amendments.	❑	❑
(e)	Locate the letter of approval from the IEC/IRB and check that it refers to the final version of the protocol for the study.	❑	❑
(f)	Identify any protocol amendments and locate IEC/IRB approval letters for these. Record dates of implementation of each protocol amendment and check that the date supersedes the date of approval.	❑	❑
(g)	Check that there is documentation to confirm that any other information required by the IEC/IRB has been supplied (e.g. notification of serious unexpected Adverse Events).	❑	❑
(h)	Ensure that the list of study personnel is up-to-date and accurately reflects all personnel who have been involved in the study (no matter how minor their roles). Check that the CV's are on file for anyone undertaking assessments, completing CRFs or obtaining consent.	❑	❑
(i)	Make sure that the log of subjects enrolled in the study is up-to date and complete. If a log of subjects screened is being kept, make sure that this is also current.	❑	❑
(j)	Inspect all completed consent forms and check that these have been signed and dated by the subject and the person taking consent. The date of consent should be prior to any study related procedures. Check that this is the case.	❑	❑
(k)	Review the eligibility criteria for all subjects who have entered the study. Make detailed notes regarding any subject that do not satisfy the study inclusion criteria.	❑	❑
(l)	Check that each CRF has been fully completed and that all data are legible.	❑	❑
(m)	Check CRFs for inconsistencies regarding medical history, diagnoses, concomitant medications and dates of visits.	❑	❑
(n)	Make sure that all corrections in the CRF have been signed and dated.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

		Yes	No*
(o)	For each subject in the study, check the patient files, nursing records etc. for evidence of Adverse Events and ensure that details of all Adverse Events have been recorded in the CRF.	❑	❑
(p)	Determine whether or not the Adverse Events observed are defined as serious (refer to the protocol for Adverse Event definitions) and ensure that all serious Adverse Evens are reported to the Sponsor.	❑	❑
(q)	Confirm that there is no outstanding documentation relating to any Adverse Events and check that all events have been followed up adequately.	❑	❑
(r)	If drug accountability is being undertaken by the Investigator, check that all medication packs are accounted for. A high return of unused material in patient supplies is expected. If the pharmacy is dealing with this aspect, visit the pharmacy and ensure that dispensing and return records are available.	❑	❑
(s)	Observe study conduct: are the assessments being undertaken as per the protocol, are data reliable, are there any fatal flaws in trial conduct?	❑	❑
(t)	Ensure that the Investigator and each member of the study team is aware that the Auditor will be looking for evidence that each person dealing with the study, particularly the Investigator, can clearly identify the extent of their knowledge and degree of participation throughout the whole	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Section	*Comments*

Effective Date: _____

Issue Date: _____

SOP No: QA3

INSPECTIONS

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: QA3

INSPECTIONS

I. Purpose

The purpose of this SOP is to describe the requirements for an Inspection at the study site by the regulatory authorities from the USA, Europe or Japan.

II. Other Related Procedures

All SOPs

III. Procedures

Inspections performed by regulatory authorities are usually performed for three main reasons; a) to assure integrity of clinical study data, b) to assure subject's rights and safety, c) to permit sound decisions regarding efficacy and safety.The main objectives of a regulatory inspection are to determine compliance of clinical investigators with GCP guideline(s) and regulations, to assess if monitoring procedures have been satisfactorily implemented by a Sponsor or CRO and to assess whether data submitted to the regulator from specific studies are substantiated by appropriate records.

1. *Prior to the Inspection*

	Yes	No*
(a) The first step in preparing for the Inspection is to notify all individuals and groups involved with the conduct of the clinical trial.	❑	❑
(b) The Sponsor should also be notified and advised that a regulatory Inspection is imminent and likely to take place within a time period of for instance two weeks.	❑	❑
(c) Notify the EC/IRB as they may also be visited during the Inspection.	❑	❑
(d) Prepare a list of all subjects enrolled, including name, address and or phone number, medical record number and dates enrolled and completed. This list can be given to the medical records department to request subject records and provided to the Inspector on request.	❑	❑
(e) Check that there is a signed consent form for each patient on whom any screening procedures were performed.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
(f) Organise the regulatory files according to the following headings:		
• Protocol	❑	❑
• IRB Files	❑	❑
• Initial Approval Letter	❑	❑
• Amendment Approval Letter	❑	❑
• Informed Consent Forms	❑	❑
• Correspondence or Status Reports	❑	❑
• Sponsor Correspondence	❑	❑
• Monitoring Log	❑	❑
• Laboratory Documentation	❑	❑
• Laboratory Normal Values	❑	❑
• Certification and Accreditation Certificates	❑	❑
• List of Expiry Dates For Trial Medication	❑	❑
• Test Article Accountability	❑	❑
(g) The CRF and supporting source documents for each patient enrolled in the study and who received the test article should be reviewed for completeness. Data correction forms for each altered case report form documenting the date and initials of the individual making the correction. Organise the patient's/subjects CRF from Medical Records study chart and all supporting source documents in the same fashion for each patient. Check that each subject enrolled has the following documented information:		
• Condition of subject at time of study entry documenting the condition or disease under investigation	❑	❑
• Record of exposure to trial medication	❑	❑
• All concomitant medications and treatments	❑	❑
• Observations and clinical assessments of the subject while on the trial medication	❑	❑
• Laboratory reports	❑	❑
• Diagnostic test results e.g. X-ray's, ECG	❑	❑
• Autopsy report (if applicable)	❑	❑
(h) Ensure that all the members of the research team meet within a day or two of the scheduled inspection.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

	Yes	No*
2. *Organisation of facilities prior to the Inspection*		
(a) Ensure that adequate facilities such as a quiet working environment are provided for the Inspector to work.	❑	❑
(b) If possible ensure the Inspector has easy access to a photocopier machine without having to ask for it.	❑	❑
3. *During the Inspection*		
(a) Ensure that the appropriate study site personnel make themselves available in person, by pager, or telephone to answer any questions during the ongoing inspection.	❑	❑
(b) Be prepared to the study team summary of responsibilities (see Appendix A).	❑	❑
(c) If asked questions by the Inspector, talk and act confidently about your area of responsibility.	❑	❑
(d) Provide correct information to the inspection in a timely manner.	❑	❑
(e) Seek clarification if you do not fully understand any questions.	❑	❑
(f) Do not answer questions if you are not the correct person to give a proper answer.	❑	❑
(g) Finally, don't make statements that cannot be supported.	❑	❑
4. *After the Inspection*		
The Inspector will provide a formal report to the Sponsor, and the Sponsor, Investigator and Institution should address any severe criticisms.	❑	❑

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP.

Appendix A

EXAMPLE OF A STUDY PERSONNEL AND RESPONSIBILITIES LIST

Title	Name	Responsibilities
Investigator	Doctor XXXX MD Present Position Tel No. Email	Overall supervision of study. Sponsor and IRB communications. Conduct weekly meetings to discuss study progress.
Co-Investigator	Dr. XXX.XXXX MD Present Position Tel No. Email	Subject screening and enrolment. Performs clinical evaluations, documents, reports and follow-up adverse events.
CRC	Nurse XXXXX RN Present Position Tel. No. Email	Explains study procedures to subject/patient; obtains informed consent; schedules follow-up appointments; collects clinical data; performs day to day study procedures.
Technician	Mr/Ms. XXXXXX BS Present Position Tel No Email	Process and ship blood and urine specimens.
Pharmacist	Mr/Ms. XXXX Pharm. D Present Position Tel No. Email	Receive trial medication. Dispenses trial medication to subjects. Maintain trial medication logs. Store returned drugs from subjects/patients Meets with Monitors.

* If the answer is NO to any of the above, specify reason(s) on the last page of this SOP

Section	*Comments*

Effective Date _____

Issue Date _____

SOP No: CP1

MEASUREMENT OF BLOOD PRESSURE

APPROVED BY

_____
Investigator

_____
Signature/Date

REVISIONS

No	*Section No*	*Page No*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP

Date	*Signed*	*Date*	*Signed*
1		3	
2		4	

SOP No: CP1

MEASUREMENT OF BLOOD PRESSURE

I. Purpose

To ensure that the method used to measure blood pressure in a clinical study is performed in an accurate and standardised manner.

II. Other Related Procedures

None

III. Procedures

a) The following staff (or grades of staff) are permitted to carry out this procedure: medically qualified staff, staff with nursing qualifications, and trained technicians.

b) The procedure should be carried out in accordance with the times defined in the study protocol.

c) To measure the blood pressure of a sitting subject/patient, the subject/patient must have been sitting down for at least five minutes. To measure the blood pressure of a standing subject/patient, the subject/patient must have been standing for at least two minutes.

d) The systolic blood pressure should be calculated from the mean of three consecutive measurements taken at one-minute intervals. None of the three measurements should deviate by more than 5 mmHg from the mean value.

e) The blood pressure measurement should take place in a quiet room; the subject's/patient's arm should be held at heart level.

f) The manometer should be at eye level so that the calibrations on the scale are easy to read.

g) The cuff must be of adequate size. The width of the inflatable part should be at least 40% and the length at least 80% of the arm circumference.

h) Localise the brachial artery (medial upper arm) by palpation and wrap the cuff carefully around the upper arm. The middle of the inflatable part should lie directly over the brachial artery. Do not rely on any markings on the cuff — check the midline yourself by folding the cuff in half. The lower edge of the cuff should be approximately 2.5 cm above the elbow.

i) Ascertain the maximum inflation pressure by finding out the pressure with which the radial pulse is no longer palpable during rapid inflation of the cuff (palpable systolic pressure). The maximum cuff pressure is 30 mmHg above this value.

j) Quickly and uniformly release the pressure. Wait 15 to 30 seconds before re-inflating the cuff.

k) Place a stethoscope over the elbow, underneath the cuff on the palpable brachial artery. The ear pieces of the stethoscope should be pointing forwards.

l) The bell of the stethoscope should be applied with light pressure to ensure that the entire bell is in contact with the skin. Undue pressure can cause distortion of sounds.

m) Inflate the cuff evenly and quickly to the maximum cuff pressure, as determined above.

n) Release the cuff pressure at a rate of 2 to 3 mm Hg per second.

o) Read off the systolic blood pressure at the point where you hear at least two consecutive beats (Phase 1 of the Korotkow sounds).

p) The blood pressure must always be given as an even number — read off at the next 2 mm Hg marking.

q) When the Phase V Korotkow sound is no longer audible, you can read off the diastolic blood pressure. Wait until the pressure is 10 to 20 mm Hg lower to ensure that this sound is no longer audible and then quickly release the pressure.

r) Make a note of the position of the subject/patient (sitting or standing) and also which arm was used to measure the blood pressure.

s) Wait one minute and repeat the above procedure on the same arm. It is important to wait one minute to ensure that there is no remaining venous congestion.

IV. Specific problems

a) *Auscultatory gap*
In some subjects/patients — especially those with hypertension — the normal sounds at high cuff pressure over the brachial artery can become temporarily silent during reduction of the pressure, only to reappear at lower cuff pressures. This early and temporary loss of pulse sounds is known as the auscultatory gap and occurs in the late stages of Phases I and II. This auscultatory gap can in certain circumstances be up to 40 mm Hg, and there is therefore the danger of significantly underestimating the systolic pressure or overestimating the diastolic pressure. The existence of an auscultatory gap can be excluded by palpating the disappearance of the radial pulse during inflation of the cuff.

b) *Effect of arm position*
The blood pressure in the arm increases with the lowering of the arm below heart level, and decreases when the arm is raised. With indirect blood pressure measurement, the arm should be held so that the bell of the stethoscope is at heart level. Heart level is the mid- point between the fourth intercostal space and left lower edge of the sternum. You should pay particular

attention in standing patients to the position of the brachial artery in relation to the heart level. If the patient is lying on their back on a flat surface with a slightly raised head, it can be assumed that the brachial artery is at heart level. In sitting position, the arm should be placed on a table at a level just above the hips.

c) *Patients with above average upper arm circumference (>41 cm)*
When a standard cuff is used in subjects/patients with above average upper arm circumference, it can result in falsely elevated blood pressure measurements. This applies particularly when small cuffs are used, because the compressible soft tissue of the upper arm causes an excessive loss in cuff pressure. This problem can be minimised by the use of cuffs with a width of 40 to 50% of the measured upper arm circumference (or by excluding these patients from the study). In subjects/ patients who are not overweight, a normal adult cuff (width 15 cm) is adequate. A blood pressure measurement on the lower arm is not recommended because falsely elevated blood pressure values often result.

Effective Date: _____

Issue Date: _____

SOP No: CP2

SPIROMETRY TESTING

APPROVED BY: _____

Investigator

_____

Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: CP2

SPIROMETRY TESTING

I. Purpose

To obtain Spirometry data of the highest quality and achieve proper interpretation of the results.

II. Other Related Procedures

None

III. Procedures

a) The following staffs (or grades of staff) are permitted to carry out this procedure: medically qualified staff, staff with nursing qualifications, trained Technicians.

b) The procedure should be carried out in accordance with times defined in the study protocol.

c) In order to assure acceptable spirometry data with a sufficient level of accuracy as well as precision, those qualified personnel performing the procedures should coach each subject/patient to perform maximal expiratory maneuvers with each measurement.

d) For each maneuver the subject/patient should be in a standing position and wear a nose clip.

e) The subject/patient takes a full deep breath (i.e. to total lung capacity) and blow out forcefully, without hesitations with maximal effort until all air is expelled from the lungs.

f) The operator should continue coaching the subject/patient throughout the procedure (e.g. "blow out hard...blow.... blow...")

g) In order for a spirometry measurement to be judged acceptable, it should conform to the American Thoracic Society standards for acceptability. The criteria of which implies;

   i. An adequate start of the test
   ii. Adequate expiratory time (at least 6 seconds)
   iii. Adequate Peak Expiratory Flow Rate (PEFR)
   iv. No evidence of interruption by coughing, glottis closure, obstruction by the tongue or false teeth.

IV. Reproducibility Criteria

a) To be considered acceptable, only the best two of three acceptable spirograms that have Forced Expiratory Volume in 1 second (FEV1) values that do not vary by more than 5% of the largest value, or more than 100 ml, whichever is greater, should be recorded.

b) An exception to this requirement is where a set of maneuvers does not have to meet the reproducibility criterion if the subject/patient, by giving the maximal effort develops bronchcoconstriction on each subsequent maneuver. In this case, less than three maneuvers are allowed, and the values from those obtained will still be recorded, but only the first FEV1 will be considered the best.

V. Reporting of Data

a) For the purposes of analysis, the largest FEV1 and the largest Forced Vital Capacity (FVC) from the acceptable and reproducible maneuvers (regardless of whether they were obtained from the same curve or not) will be considered the true value for that series of measurements.

b) Every effort should be made to ensure adequate spirometry performance. The Subject/patients should be excluded if they cannot perform acceptable spirometry maneuvers. However, an individual study day should not be terminated because of quality difficulties.

VI. Quality Control

a) The site is encouraged to prepare the subject/patients for individual measurements of spirometry according to standard criteria.

b) The spirometer used should meet American Thoracic Society (ATS) standards for performance.

c) Calibration and maintenance logs must be maintained for each spirometer.

d) Calibration of the spirometer must be performed at least once a week.

e) It is recommended that calibration be performed every day that spirometry data is collected.

f) The same instrument and operator should be used throughout the study.

VII. Predicted Values

For predicted values, reference should be made to the local values that are used.

Effective Date: _____

Issue Date: _____

SOP No: CP3

MEASUREMENT OF BODY WEIGHT AND HEIGHT

APPROVED BY: _____
Investigator

_____
Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: CP3

MEASUREMENT OF BODY WEIGHT AND HEIGHT

I. Purpose

To ensure that the method used to measure body weight and height in a clinical study is performed in an accurate and standardised manner.

II. Procedures for Measurement of Body Weight

Mechanical or electronic digital scales are used for measuring body weight.

1. *Infants/Babies*

a) Ensure the reading of the electronic digital scale starts from zero or the pointer of an ordinary scale points sharply at zero before the measurement is taken.

b) Prepare a warm environment before taking off the clothing, diaper and/or shoes of the infant/baby.

c) Nude weight is preferable for measuring the body weight of an infant/baby less than one year of age.

d) Put the infant/baby on the scales gently.

e) Do not take the reading shown on the scale if the baby is moving. Comfort or tease the infant/baby so as to make him/her settle down.

f) In case the baby/infant struggles on the scale, making the reading inconsistent, it is better to weigh the mother and the child together, then weigh the mother alone. The baby's weight can thus be calculated by the difference of the weight of the mother and baby, and the weight of the mother.

g) Read off the measurement to the nearest 10 grams.

2. *Children/Adults*

a) Ensure that the reading of the electronic digital scale starts from zero or the pointer of an ordinary scale points sharply to zero before taking the measurement.

b) Minimal clothing is acceptable during the measurement for children older than one year, but diaper or shoes must be taken off before the measurement.

c) Adult subjects should take off any heavy clothing, shoes and belongings before standing or sitting on the scale. If body weight is an important end point in the trial, adult subjects should wear minimal clothing during the measurement.

d) Read off the measurement to the nearest 10 grams.

3. *Validation of the measurement*

The accuracy of the scale should be ensured by checking its calibration regularly (once per week) in controlled conditions, using an object such as a bag of saline solution. The variation of the scale reading should not be more than 0.05 grams for digital electronic scales and 0.1 kg for mechanic scales.

III. Procedures for Measurement of Length/Height

1. *Infants/Babies*

Supine length is measured for subjects below two years of age. It is measured using a measuring board consisting a flat horizontal board with a metric scale fixed to one side, a vertical fixed head plate firmly attached at one end, and a sliding foot plate at the other end.

a) Put the baby on the measuring board in a lying position. Comfort or tease the baby so as to make him/her calm down.

b) An assistant should hold the baby's head in contact with the fixed head plate and at the same time apply gentle upward pressure to the baby's mastoid processes.

c) The person performing the measurement should keep the knees of the baby fully extended with one hand and the other hand is used to bring the sliding foot plate to the baby's soles. Minimal force should be used in order to avoid excessive pressure on the soft tissue of the soles.

d) Read the measurement from the metric scale fixed to the side of the foot plate.

e) In order to ensure a very accurate measurement, it is recommended that the whole measuring procedure is performed five times. In between the measurements, readjust the baby in the standard position whenever necessary. The mean of the four last measurements is regarded as the supine length of that examination.

2. *Children/Adults*

Standing height is measured for those subjects older than two years of age. or an earlier age if the infant can stand independently. It can be measured using an ordinary standing stadiometer.

a) Ask the subject to take off his/her shoes and ask him/her to stand straight on the stadiometer.

b) The subject is urged to stand straight so that his/her heels, buttocks, and shoulders are in contact with the vertical backboard of the stadiometer.

c) The person performing the measurement should apply gentle upward pressure to the subject's mastoid processes over the cheeks so as to stretch the spine of the subject. This procedure will decrease postural and diurnal variation of body height.

d) The upper limbs of the subject should be relaxed with the palms facing medially.

e) Slide down the head plate until it touches the subject's head. Minimal force should be used to do this.

f) While the subject is in this position, ask him/her to take a deep breath so as to straighten the spine.

g) Read off the measurement indicated on the metric scale by the sliding plate.

h) If the subject has obvious signs of asymmetry in the legs, two heights should be record: one standing on the longer leg with the shorter leg supported by a suitable block, and the other measurement on the shorter leg with the longer leg stand partially flexed.

3. *Validation of the measurements*

a) When length/height is the end-point of the study, the within- and between-measurer variation in length/height measurement should be validated.

b) Validation could be performed by looking at the mean and standard deviation among the measurements of a phantom by different measurers (between-measurer) and by the same measurer (within-measurer). The mean values and standard deviation indicate the replicability and repeatability of the measurement technique.

c) For repeated measurement sessions in in the same subject it is ideal to have the measurement done by the same measurer to avoid too large measurer variation.

Effective Date: _____

Issue Date: _____

SOP No: CP4

VENEPUNCTURE (ADULTS)

APPROVED BY: _____

Investigator

_____

Signature/Date

REVISIONS:

No.	*Section No.*	*Page No.*	*Initials/Date*

DATES OF NEXT REVIEW OF THIS SOP:

Date	*Signed*	*Date*	*Signed*
1.		3.	
2.		4.	

SOP No: CP4

VENEPUNCTURE (ADULTS)

I. Purpose

To ensure that a proper and standardised technique is used in performing venepuncture in adults in a clinical study

II. Other Related Procedures

None

III. Procedures

Venepuncture is the primary technique and method used for acquiring blood samples for laboratory testing.

1. *Preparation of the Puncture Site(s)*

a) Ensure that the phlebotomy station or tray which includes all the blood taking materials (gloves, tourniquet, vacutainer, syringes, and needles etc) is well organised and ready.

b) Make a positive subject identification

c) Label all the specimen collection tubes with the information requested by the Sponsor.

d) Make sure the subject is either lying down or sitting in a comfortable position with the ventral surfaces of the arm up

e) Wash hands

f) Tie or attach a tourniquet tightly but not so that it is uncomfortable for the subject, approximately 3-5 inches above a potential venepuncture site **DO NOT** leave the tourniquet on for more than 1-2 minutes

g) Identify a viable vein by palpating or feeling the vein that rebounds (bounces) when pushed or tapped on The most common site selected is the antecubital area of the arm, where the basilic, cephalic and medial cubital veins are the most prominent and usually nearer to the surface of the skin

h) Decide the method to use There are three basic methods of venipuncture: vacutainer procedure, syringe technique, and hand/butterfly technique.

i) Assemble the required equipment.

j) Put gloves on and follow universal precautions.

k) Swab the intended puncture site with an alcohol wipe in a concentric circular motion working from the inside out, and repeat if the arm is particularly dirty.

l) Let the site dry for 30 to 60 seconds.

m) Do not re-palpate vein after cleansing.

2. ***Methods of performing Venipunctures***

A. *Vacutainer Procedure*

Vacutainer tube contains a vacuum which, when connected to a needle and a blood vessel is accessed, will aspirate blood from the vein into the tube.

a) Stabilise the chosen vein between the index finger and thumb.

b) Orientate the needle at approximately 15° angle to the arm, immediately over and in the direction of the vein.

c) Insert the needle quickly and smoothly with the bevel facing upwards.

d) Stabilize the apparatus so that the needle does not move.

e) Engage the first tube, remove when full and repeat for additional tubes.

f) If no blood enters the tube, slowly draw the needle back until the bevel is close to exiting the skin, re-palpate the vein to relocate it, re-direct the needle and slowly push the needle in further.

g) If re-direction is unsuccessful or the subject exhibits undue pain, abort the blood draw and attempt in another location.

h) Disengage last tube before withdrawing needle.

i) Untie tourniquet.

j) Withdraw needle.

k) Apply gauze and pressure to the puncture area or have the subject apply pressure for 3 to 5 minutes. The arm may be raised above the heart level to control bleeding.

l) Dispose of the needle immediately into the Sharps container.

m) Dress the puncture site with adhesive tape over the gauze or Band-Aids.

B. *Syringe Technique*

The syringe is a mechanical device consisting of a plunger that fits tightly into a cylinder. As the plunger is drawn back suction is created. If a needle is attached and inserted into a vein, the suction created draws blood into the syringe.

a) Stabilise the chosen vein between the index finger and thumb.

b) Orientate the needle at approximately 15° angle to the arm, immediately over and in the direction of the vein.

c) Watch for a blood flashback in the needle hub, indicating that the needle is in position in the vein correctly.

d) Stabilise the apparatus so that the needle does not move.

e) Draw back on the plunger slowly and steadily to aspirate the desired volume of blood.

f) Untie the tourniquet.

g) Withdraw the needle. Immediately after clearing the skin, draw back on the syringe plunger slightly to prevent dripping of blood from the needle.

k) Apply gauze and pressure to the puncture area or have the subject apply pressure for 3 to 5 minutes. The arm may be raised above the heart level to control bleeding.

l) Properly transfer specimen to the required tubes.

m) Dispose of the needle immediately after use into the Sharps container.

n) Dress the puncture site with tape over gauze or use a Band-Aid plaster.

C. *Hand/Butterfly Needle Technique*

Butterfly Needle Technique is an alternate method for collecting blood in small veins, infants and young children. Hand veins are most conveniently drawn with a butterfly.

a) Select the largest vein available on the dorsal side of the hand.

b) Stabilise the vein between the index finger and thumb.

c) Squeeze the two wings of the butterfly together between the thumb and index finger in such a manner that the bevel of the needle is positioned up.

d) Orientate the needle at a 10° to 15° angle to the hand, immediately over and in the direction of the vein.

e) Insert the needle with a smooth, deliberate stroke.

f) Watch for blood to flashback in the butterfly tubing, indicating that the needle has entered the vein. Advance the needle slightly to "thread" the needle into the vein a little more.

g) Steady the needle, if necessary with one hand while drawing back on the syringe plunger with the other.

h) After drawing sufficient specimen, untie the tourniquet.

g) Withdraw the needle. Immediately after clearing the skin, draw back on the syringe plunger slightly to prevent dripping of blood from the needle.

k) Apply gauze and pressure to the puncture area or have the subject apply pressure for 3 to 5 minutes. The arm may be raised above the heart level to control bleeding.

l) Properly transfer specimen to required tubes.

m) Dispose of the butterfly needle immediately after use into the Sharps container.

n) Dress the puncture site with adhesive tape over the gauze or Band-Aids.

SOP No: A1

PREPARATION, APPROVAL AND REVIEW OF SOPS

I. Purpose

To describe the procedure for preparing, approving and distributing SOPs and to describe the procedure for dealing with revisions and for conducting of regular review of SOPs.

II. Other Related Procedures

All SOPs

III. Procedure

a) The Investigator or any person delegated by the Investigator is responsible for ensuring that SOPs are prepared, reviewed, revised and approved and is also responsible for authorising the content of each particular SOP.

b) Before the conduct of each trial the SOPs to which the trial will be conducted should be up to date. Deficiencies requiring amendments to the SOPs should be dealt with at the earliest opportunity, but no later than the next SOP review. SOPs should be reviewed three months after the first implementation and annually thereafter.

c) All SOPs should be prepared according to a standard format, which should be defined.

d) Each SOP should be prepared (authored) by someone competent to do so and eventually signed off by that individual.

e) Each SOP should be reviewed at draft stage by staff who will use it.

f) The Investigator should review each SOP, and once he/she is satisfied that it is adequate, the Investigator should authorise it by signing it off.

g) Each SOP should show the date of preparation (i.e. when signed off by the author), the date of approval (i.e. when signed off by the Investigator) and the date it is effective from.

h) Each SOP should indicate whether it replaces a previous version and, if so, which.

i) All new SOPs should be reviewed for accuracy three months after first implementation.

j) All existing SOPs will be reviewed annually at a time specified.

k) Deficiencies identified in SOPs will be recorded and appropriate SOPs prepared or existing ones modified to address the deficiencies.

SOP No: A2

FORMAT FOR INVESTIGATOR's CV

I. Purpose

To describe the manner in which Curriculum Vitaes (CVs) for Investigators involved in clinical studies are written.

II. Other Related Procedures

None

III. Procedure

All Investigators working within a clinical study must submit an up to date short CV at the time of a IEC/IRB submission.

According to the Helsinki Declaration "Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and must never rest on the subject of the research, even thought the subject has given his or her consent."

Details of the particular format should include information such as present position, education, experience, professional qualifications, courses attended, conferences attended, teaching experience, clinical trials involvement and academic output.

A template for the Investigator's Short CV is given on the following page.

INVESTIGATOR's SHORT CV

NAME

Present Position

Year	Department and Institution Name
	Title
	address1
	address2
	address3
	address4
	Fax:
	Tel:
	E-Mail:

Education — undergraduate and postgraduate

Year	Institutes
	Degree in which subject

Experience

Year	Department and Institution Name
	Title

Professional qualification

Year	Association
	Member

Courses — clinical research methodology/trial/GCP/etc

Year	Title of the Course
	day/hour, Organisation, Country

Conferences – clinical research methodology/trial/GCP/etc

Year	Title of the Conference
	day/hour, Organisation, Country, speaker/participant

Teaching – clinical research methodology/trial/GCP/etc

Year	Topic
	hour, Organisation, Country

Clinical trials involvement

Year	Therapeutic area
	Number of patients
	Responsibility

Academic output

Publications in International Journals n= , in Local Journals n=
Book chapters n= , Letters n=
Invited speaker to International Meetings n= , to Local Meetings n=
Presentations at International Meetings n= , at Local Meetings n=

SOP No: A3

DECLARATION OF HELSINKI

Introduction

It is the mission of the physician to safeguard the health of the people. His or her knowledge and conscience are dedicated to the fulfillment of this mission. The Declaration of Geneva of the World Medical Association binds the physician with the words "The health of my patient will be my first consideration", and the International Code of Medical Ethics declares that "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient". The purpose of biomedical research involving human subjects must be to improve diagnostic, therapeutic and prophylactic procedures and the understanding of the etiology and pathogenesis of disease. In current medical practice, most diagnostic, therapeutic or prophylactic procedures involve hazards. This applies especially to biomedical research.

Medical progress is based on research which ultimately must rest in part upon experimentation involving human subjects. In the field of biomedical research a fundamental distinction must be realized between medical research in which the aim is essentially diagnostic or therapeutic for a patient, and medical research the essential object of which is purely scientific and without direct diagnostic or therapeutic value to the person subjected to the research. Special caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected. Because it is essential that the results of laboratory experiments be applied to human beings to further scientific knowledge and to help suffering humanity, The World Medical Association has prepared the following recommendations as a guide to every physician in biomedical research involving human subjects. They should be kept under review in the future. It must be stressed that the standards as drafted are only as a guide to physicians all over the world. Physicians are not relieved from criminal, civil and ethical responsibilities under the laws of their own countries.

I . Basic Principles

1. Biomedical research involving human subjects must conform to generally accepted scientific principles and should be based on adequately performed laboratory and animal experimentation and a thorough knowledge of the scientific literature.

2. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol which should be transmitted for consideration, comment and guidance to a specially appointed committee independent of the investigator and the sponsor provided that this independent committee is in conformity with the laws and regulations of the country in which the research experiment is performed.

3. Biomedical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and

must never rest on the subject of the research, even thought the subject has given his or her consent.

4. Biomedical research involving human subjects cannot legitimately be carried out unless the importance of the objective is in proportion to the inherent risk to the subject.

5. Every biomedical research project involving human subjects should be preceded by careful assessment of predictable risks in comparison with foreseeable benefits to the subject or to others. Concern for the interests of the subject must always prevail over the interests of science and society.

6. The right of the research subject to safeguard his or her integrity must always be respected. Every precaution should be taken to respect the privacy of the subject and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

7. Physicians should abstain from engaging in research projects involving human subjects unless they are satisfied that the hazards involved are believed to be predictable. Physicians should cease any investigation if the hazards are found to outweigh the potential benefits.

8. In publication of the results of his or her research, the physician is obliged to preserve the accuracy of the results. Results of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

9. In any research on human beings, each potential subject must be adequately informed of the aims, methods, anticipated benefits and potential hazards of the study and the discomfort it may entail. He or she should be informed that he or she is at liberty to abstain from participation in the study and that he or she is free to withdraw his or her consent to participate at any time. The physician should then obtain the subject's freely-given informed consent, preferably in writing.

10. When obtaining informed consent for the research project, the physician should be particularly cautious if the subject is in a dependent relationship to him or her and may consent under duress. In that case, the informed consent should be obtained by a physician who is not engaged in the investigation and who is completely independent of this official relationship.

11. In case of legal incompetence, informed consent should be obtained from the legal guardian in accordance with national legislation. Where physical or mental incompetence makes it impossible to obtain informed consent, or when the subject is a minor, permission of the responsible relative replaces that of the subject in accordance with national legislation. Whenever the minor child is in fact able to give a consent, the minor's consent must be obtained in addition to the consent of the minor's legal guardian.

12. The research protocol should always contain a statement of the ethical considerations involved and should indicate that the principles enunciated in the present Declaration are complied with.

II. Medical Research Combined with Professional Care (Clinical Research)

1. In the treatment of sick persons, the physician must be free to use a new diagnostic and therapeutic measure, if in his judgment it offers hope of saving life, reestablishing health or alleviating suffering.

2. The potential benefits, hazards and discomfort of a new method should be weighed against the advantages of the best current diagnostic and therapeutic methods.

3. In any medical study, every patient — including those of a control group, if any —should be assured of the best proven diagnostic and therapeutic method.

4. The refusal of the patient to participate in a study must never interfere with the physician-patient relationship.

5. If the physician considers it essential not to obtain informed consent, the specific reasons for this proposal should be stated in the experimental protocol for transmission to the independent committee.

6. The physician can combine medical research with professional care, the objective being the acquisition of new medical knowledge, only to the extent that medical research is justified by its potential diagnostic or therapeutic value for the patient.

III. Non-Therapeutic Biomedical Research Involving Human Subjects (Non-Clinical Biomedical Research)

1. In the purely scientific application of medical research carried out on a human being, it is the duty of the doctor to remain the protector of the life and health of that person on whom biomedical research is being carried out.
2. The subjects should be volunteers—either healthy persons or patients for whom the experimental design is not related to the patient's illness.

3. The investigator or the investigating team should discontinue the research if in his/her or their judgment it may, if continued, be harmful to the individual.

4. In research on man, the interest of science or society should never take precedence over considerations related to the well-being of the subject.

Adopted by the 18th World Medical Assembly, Helsinki, 1961 and revised by the 29th WMA, Tokyo, 1975, the 35th WMA, Venice, 1983, and the 41st WMA, Hong Kong, 1989.

SOP No: A4

ICH GCP E6 GUIDELINES

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

Guideline for Good Clinical Practice

Recommended for Adoption
at Step 4 of the ICH Process
on 1 May 1996
by the ICH Steering Committee

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

TABLE OF CONTENTS

INTRODUCTION

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve the participation of human subjects. Compliance with this standard provides public assurance that the rights, safety and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki, and that the clinical trial data are credible.

The objective of this ICH GCP Guideline is to provide a unified standard for the European Union (EU), Japan and the United States to facilitate the mutual acceptance of clinical data by the regulatory authorities in these jurisdictions.

The guideline was developed with consideration of the current good clinical practices of the European Union, Japan, and the United States, as well as those of Australia, Canada, the Nordic countries and the World Health Organization (WHO).

This guideline should be followed when generating clinical trial data that are intended to be submitted to regulatory authorities.

The principles established in this guideline may also be applied to other clinical investigations that may have an impact on the safety and well-being of human subjects.

1. GLOSSARY

1.1 *Adverse Drug Reaction (ADR)*

In the pre-approval clinical experience with a new medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e. the relationship cannot be ruled out.

Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.2 *Adverse Event (AE)*

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.3 ***Amendment (to the protocol)***
See Protocol Amendment.

1.4 ***Applicable Regulatory Requirement(s)***
Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

1.5 ***Approval (in relation to Institutional Review Boards)***

The affirmative decision of the IRB that the clinical trial has been reviewed and may be conducted at the institution site within the constraints set forth by the IRB, the institution, Good Clinical Practice (GCP), and the applicable regulatory requirements.

1.6 ***Audit***
A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analyzed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.7 ***Audit Certificate***
A declaration of confirmation by the auditor that an audit has taken place.

1.8 ***Audit Report***
A written evaluation by the sponsor's auditor of the results of the audit.

1.9 ***Audit Trail***
Documentation that allows reconstruction of the course of events.

1.10 ***Blinding/Masking***
A procedure in which one or more parties to the trial are kept unaware of the treatment assignment(s). Single-blinding usually refers to the subject(s) being unaware, and double-blinding usually refers to the subject(s), investigator(s), monitor, and, in some cases, data analyst(s) being unaware of the treatment assignment(s).

1.11 ***Case Report Form (CRF)***
A printed, optical, or electronic document designed to record all of the protocol required information to be reported to the sponsor on each trial subject.

1.12 ***Clinical Trial/Study***
Any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of an investigational product(s), and/or to identify any adverse reactions to an investigational product(s), and/or to study absorption, distribution, metabolism, and excretion of an investigational product(s) with the object of ascertaining its safety and/or efficacy. The terms clinical trial and clinical study are synonymous.

1.13 ***Clinical Trial/Study Report***
A written description of a trial/study of any therapeutic, prophylactic, or diagnostic agent conducted in human subjects, in which the clinical and statistical description, presentations, and analyses are fully integrated into a single report (see the ICH Guideline for Structure and Content of Clinical Study Reports).

1.14 ***Comparator (Product)***
An investigational or marketed product (i.e., active control), or placebo, used as a reference in a clinical trial.

1.15 ***Compliance (in relation to trials)***
Adherence to all the trial-related requirements, Good Clinical Practice (GCP) requirements, and the applicable regulatory requirements.

1.16 ***Confidentiality***
Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity.

1.17 ***Contract***
A written, dated, and signed agreement between two or more involved parties that sets out any arrangements on delegation and distribution of tasks and obligations and, if appropriate, on financial matters. The protocol may serve as the basis of a contract.

1.18 ***Coordinating Committee***
A committee that a sponsor may organize to coordinate the conduct of a multicentre trial.

1.19 ***Coordinating Investigator***
An investigator assigned the responsibility for the coordination of investigators at different centres participating in a multicentre trial.

1.20 ***Contract Research Organization (CRO)***
A person or an organization (commercial, academic, or other) contracted by the sponsor to perform one or more of a sponsor's trial-related duties and functions.

1.21 ***Direct Access***
Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsor's monitors and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information.

1.22 ***Documentation***
All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records, and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken.

1.23 ***Essential Documents***

Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced (see 8. Essential Documents for the Conduct of a Clinical Trial).

1.24 ***Good Clinical Practice (GCP)***

A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected.

1.25 ***Independent Data-Monitoring Committee (IDMC) (Data and Safety Monitoring Board, Monitoring Committee, Data Monitoring Committee)***

An independent data-monitoring committee that may be established by the sponsor to assess at intervals the progress of a clinical trial, the safety data, and the critical efficacy endpoints, and to recommend to the sponsor whether to continue, modify, or stop a trial.

1.26 ***Impartial Witness***

A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject.

1.27 ***Independent Ethics Committee (IEC)***

An independent body (a review board or a committee, institutional, regional, national, or supranational), constituted of medical professionals and non-medical members, whose responsibility it is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial and to provide public assurance of that protection, by, among other things, reviewing and approving / providing favourable opinion on, the trial protocol, the suitability of the investigator(s), facilities, and the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

The legal status, composition, function, operations and regulatory requirements pertaining to Independent Ethics Committees may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP as described in this guideline.

1.28 ***Informed Consent***

A process by which a subject voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed and dated informed consent form.

1.29 ***Inspection***
The act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO's) facilities, or at other establishments deemed appropriate by the regulatory authority(ies).

1.30 ***Institution (medical)***
Any public or private entity or agency or medical or dental facility where clinical trials are conducted.

1.31 ***Institutional Review Board (IRB)***
An independent body constituted of medical, scientific, and non-scientific members, whose responsibility is to ensure the protection of the rights, safety and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trial protocol and amendments and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects.

1.32 ***Interim Clinical Trial/Study Report***
A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

1.33 ***Investigational Product***
A pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use.

1.34 ***Investigator***
A person responsible for the conduct of the clinical trial at a trial site. If a trial is conducted by a team of individuals at a trial site, the investigator is the responsible leader of the team and may be called the principal investigator. See also Subinvestigator.

1.35 ***Investigator / Institution***
An expression meaning "the investigator and/or institution, where required by the applicable regulatory requirements".

1.36 ***Investigator's Brochure***
A compilation of the clinical and nonclinical data on the investigational product(s) which is relevant to the study of the investigational product(s) in human subjects (see 7. Investigator's Brochure).

1.37 ***Legally Acceptable Representative***
An individual or juridical or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical trial.

1.38 ***Monitoring***
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, Standard Operating Procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s).

1.39 ***Monitoring Report***
A written report from the monitor to the sponsor after each site visit and/or other trial-related communication according to the sponsor's SOPs.

1.40 ***Multicentre Trial***
A clinical trial conducted according to a single protocol but at more than one site, and therefore, carried out by more than one investigator.

1.41 ***Nonclinical Study***
Biomedical studies not performed on human subjects.

1.42 ***Opinion (in relation to Independent Ethics Committee)***
The judgement and/or the advice provided by an Independent Ethics Committee (IEC).

1.43 ***Original Medical Record***
See Source Documents.

1.44 ***Protocol***
A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents. Throughout the ICH GCP Guideline the term protocol refers to protocol and protocol amendments.

1.45 ***Protocol Amendment***
A written description of a change(s) to or formal clarification of a protocol.

1.46 ***Quality Assurance (QA)***
All those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented (recorded), and reported in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirement(s).

1.47 ***Quality Control (QC)***
The operational techniques and activities undertaken within the quality assurance system to verify that the requirements for quality of the trial-related activities have been fulfilled.

1.48 ***Randomization***
The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias.

1.49 ***Regulatory Authorities***

Bodies having the power to regulate. In the ICH GCP guideline the expression Regulatory Authorities includes the authorities that review submitted clinical data and those that conduct inspections (see 1.29). These bodies are sometimes referred to as competent authorities.

1.50 ***Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR)***

Any untoward medical occurrence that at any dose:

- results in death,
- is life-threatening,
- requires inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity,

or

- is a congenital anomaly/birth defect

(see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.51 ***Source Data***

All information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies).

1.52 ***Source Documents***

Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories and at medico-technical departments involved in the clinical trial).

1.53 ***Sponsor***

An individual, company, institution, or organization which takes responsibility for the initiation, management, and/or financing of a clinical trial.

1.54 ***Sponsor-Investigator***

An individual who both initiates and conducts, alone or with others, a clinical trial, and under whose immediate direction the investigational product is administered to, dispensed to, or used by a subject. The term does not include any person other than an individual (e.g., it does not include a corporation or an agency). The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator.

1.55 ***Standard Operating Procedures (SOPs)***

Detailed, written instructions to achieve uniformity of the performance of a specific function.

1.56 ***Subinvestigator***
Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows). See also Investigator.

1.57 ***Subject/Trial Subject***
An individual who participates in a clinical trial, either as a recipient of the investigational product(s) or as a control.

1.58 ***Subject Identification Code***
A unique identifier assigned by the investigator to each trial subject to protect the subject's identity and used in lieu of the subject's name when the investigator reports adverse events and/or other trial related data.

1.59 ***Trial Site***
The location(s) where trial-related activities are actually conducted.

1.60 ***Unexpected Adverse Drug Reaction***
An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved investigational product or package insert/summary of product characteristics for an approved product) (see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

1.61 ***Vulnerable Subjects***
Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent.

1.62 ***Well-being (of the trial subjects)***
The physical and mental integrity of the subjects participating in a clinical trial.

2. THE PRINCIPLES OF ICH GCP

2.1 Clinical trials should be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

2.2 Before a trial is initiated, foreseeable risks and inconveniences should be weighed against the anticipated benefit for the individual trial subject and society. A trial should be initiated and continued only if the anticipated benefits justify the risks.

2.3 The rights, safety, and well-being of the trial subjects are the most important considerations and should prevail over interests of science and society.

2.4 The available nonclinical and clinical information on an investigational product should be adequate to support the proposed clinical trial.

2.5 Clinical trials should be scientifically sound, and described in a clear, detailed protocol.

2.6 A trial should be conducted in compliance with the protocol that has received prior institutional review board (IRB)/independent ethics committee (IEC) approval/favourable opinion.

2.7 The medical care given to, and medical decisions made on behalf of, subjects should always be the responsibility of a qualified physician or, when appropriate, of a qualified dentist.

2.8 Each individual involved in conducting a trial should be qualified by education, training, and experience to perform his or her respective task(s).

2.9 Freely given informed consent should be obtained from every subject prior to clinical trial participation.

2.10 All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.

2.11 The confidentiality of records that could identify subjects should be protected, respecting the privacy and confidentiality rules in accordance with the applicable regulatory requirement(s).

2.12 Investigational products should be manufactured, handled, and stored in accordance with applicable good manufacturing practice (GMP). They should be used in accordance with the approved protocol.

2.13 Systems with procedures that assure the quality of every aspect of the trial should be implemented.

3. INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE (IRB/IEC)

3.1 *Responsibilities*

3.1.1 An IRB/IEC should safeguard the rights, safety, and well-being of all trial subjects. Special attention should be paid to trials that may include vulnerable subjects.

3.1.2 The IRB/IEC should obtain the following documents:
Trial protocol(s)/amendment(s), written informed consent form(s) and consent form updates that the investigator proposes for use in the trial, subject recruitment procedures (e.g. advertisements), written information to be provided to subjects, Investigator's Brochure (IB), available safety information, information about payments and compensation available to subjects, the investigator's current curriculum vitae and/or other documentation evidencing qualifications, and any other documents that the IRB/IEC may need to fulfil its responsibilities.

The IRB/IEC should review a proposed clinical trial within a reasonable time and document its views in writing, clearly identifying the trial, the documents reviewed and the dates for the following:

- approval/favourable opinion;
- modifications required prior to its approval/favourable opinion;
- disapproval/negative opinion; and
- termination/suspension of any prior approval/favourable opinion.

3.1.3 The IRB/IEC should consider the qualifications of the investigator for the proposed trial, as documented by a current curriculum vitae and/or by any other relevant documentation the IRB/IEC requests.

3.1.4 The IRB/IEC should conduct continuing review of each ongoing trial at intervals appropriate to the degree of risk to human subjects, but at least once per year.

3.1.5 The IRB/IEC may request more information than is outlined in paragraph 4.8.10 be given to subjects when, in the judgement of the IRB/IEC, the additional information would add meaningfully to the protection of the rights, safety and/or well-being of the subjects.

3.1.6 When a non-therapeutic trial is to be carried out with the consent of the subject's legally acceptable representative (see 4.8.12, 4.8.14), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials.

3.1.7 Where the protocol indicates that prior consent of the trial subject or the subject's legally acceptable representative is not possible (see 4.8.15), the IRB/IEC should determine that the proposed protocol and/or other document(s) adequately addresses relevant ethical concerns and meets applicable regulatory requirements for such trials (i.e. in emergency situations).

3.1.8 The IRB/IEC should review both the amount and method of payment to subjects to assure that neither presents problems of coercion or undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

3.1.9 The IRB/IEC should ensure that information regarding payment to subjects, including the methods, amounts, and schedule of payment to trial subjects, is set forth in the written informed consent form and any other written information to be provided to subjects. The way payment will be prorated should be specified.

3.2 *Composition, Functions and Operations*

3.2.1 The IRB/IEC should consist of a reasonable number of members, who collectively have the qualifications and experience to review and evaluate the science, medical aspects, and ethics of the proposed trial. It is recommended that the IRB/IEC should include:

(a) At least five members.

(b) At least one member whose primary area of interest is in a nonscientific area.

(c) At least one member who is independent of the institution/trial site.

Only those IRB/IEC members who are independent of the investigator and the sponsor of the trial should vote/provide opinion on a trial-related matter.

A list of IRB/IEC members and their qualifications should be maintained.

3.2.2 The IRB/IEC should perform its functions according to written operating procedures, should maintain written records of its activities and minutes of its meetings, and should comply with GCP and with the applicable regulatory requirement(s).

3.2.3 An IRB/IEC should make its decisions at announced meetings at which at least a quorum, as stipulated in its written operating procedures, is present.

3.2.4 Only members who participate in the IRB/IEC review and discussion should vote/provide their opinion and/or advise.

3.2.5 The investigator may provide information on any aspect of the trial, but should not participate in the deliberations of the IRB/IEC or in the vote/opinion of the IRB/IEC.

3.2.6 An IRB/IEC may invite nonmembers with expertise in special areas for assistance.

3.3 *Procedures*

The IRB/IEC should establish, document in writing, and follow its procedures, which should include:

3.3.1 Determining its composition (names and qualifications of the members) and the authority under which it is established.

3.3.2 Scheduling, notifying its members of, and conducting its meetings.

3.3.3 Conducting initial and continuing review of trials.

3.3.4 Determining the frequency of continuing review, as appropriate.

3.3.5 Providing, according to the applicable regulatory requirements, expedited review and approval/favourable opinion of minor change(s) in ongoing trials that have the approval/favourable opinion of the IRB/IEC.

3.3.6 Specifying that no subject should be admitted to a trial before the IRB/IEC issues its written approval/favourable opinion of the trial.

3.3.7 Specifying that no deviations from, or changes of, the protocol should be initiated without prior written IRB/IEC approval/favourable opinion of an appropriate amendment, except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change of monitor(s), telephone number(s)) (see 4.5.2).

3.3.8 Specifying that the investigator should promptly report to the IRB/IEC:
(a) Deviations from, or changes of, the protocol to eliminate immediate hazards to the trial subjects (see 3.3.7, 4.5.2, 4.5.4).
(b) Changes increasing the risk to subjects and/or affecting significantly the conduct of the trial (see 4.10.2).
(c) All adverse drug reactions (ADRs) that are both serious and unexpected.
(d) New information that may affect adversely the safety of the subjects or the conduct of the trial.

3.3.9 Ensuring that the IRB/IEC promptly notify in writing the investigator/institution concerning:
(a) Its trial-related decisions/opinions.
(b) The reasons for its decisions/opinions.
(c) Procedures for appeal of its decisions/opinions.

3.4 *Records*

The IRB/IEC should retain all relevant records (e.g., written procedures, membership lists, lists of occupations/affiliations of members, submitted documents, minutes of meetings, and correspondence) for a period of at least 3 years after completion of the trial and make them available upon request from the regulatory authority(ies).

The IRB/IEC may be asked by investigators, sponsors or regulatory authorities to provide its written procedures and membership lists.

4. INVESTIGATOR

4.1 *Investigator's Qualifications and Agreements*

4.1.1 The investigator(s) should be qualified by education, training, and experience to assume responsibility for the proper conduct of the trial, should meet all the

qualifications specified by the applicable regulatory requirement(s), and should provide evidence of such qualifications through up-to-date curriculum vitae and/or other relevant documentation requested by the sponsor, the IRB/IEC, and/or the regulatory authority(ies).

4.1.2 The investigator should be thoroughly familiar with the appropriate use of the investigational product(s), as described in the protocol, in the current Investigator's Brochure, in the product information and in other information sources provided by the sponsor.

4.1.3 The investigator should be aware of, and should comply with, GCP and the applicable regulatory requirements.

4.1.4 The investigator/institution should permit monitoring and auditing by the sponsor, and inspection by the appropriate regulatory authority(ies).

4.1.5 The investigator should maintain a list of appropriately qualified persons to whom the investigator has delegated significant trial-related duties.

4.2 *Adequate Resources*

4.2.1 The investigator should be able to demonstrate (e.g., based on retrospective data) a potential for recruiting the required number of suitable subjects within the agreed recruitment period.

4.2.2 The investigator should have sufficient time to properly conduct and complete the trial within the agreed trial period.

4.2.3 The investigator should have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely.

4.2.4 The investigator should ensure that all persons assisting with the trial are adequately informed about the protocol, the investigational product(s), and their trial-related duties and functions.

4.3 *Medical Care of Trial Subjects*

4.3.1 A qualified physician (or dentist, when appropriate), who is an investigator or a sub-investigator for the trial, should be responsible for all trial-related medical (or dental) decisions.

4.3.2 During and following a subject's participation in a trial, the investigator/institution should ensure that adequate medical care is provided to a subject for any adverse events, including clinically significant laboratory values, related to the trial. The

investigator/institution should inform a subject when medical care is needed for intercurrent illness(es) of which the investigator becomes aware.

4.3.3 It is recommended that the investigator inform the subject's primary physician about the subject's participation in the trial if the subject has a primary physician and if the subject agrees to the primary physician being informed.

4.3.4 Although a subject is not obliged to give his/her reason(s) for withdrawing prematurely from a trial, the investigator should make a reasonable effort to ascertain the reason(s), while fully respecting the subject's rights.

4.4 *Communication with IRB/IEC*

4.4.1 Before initiating a trial, the investigator/institution should have written and dated approval/favourable opinion from the IRB/IEC for the trial protocol, written informed consent form, consent form updates, subject recruitment procedures (e.g., advertisements), and any other written information to be provided to subjects.

4.4.2 As part of the investigator's/institution's written application to the IRB/IEC, the investigator/institution should provide the IRB/IEC with a current copy of the Investigator's Brochure. If the Investigator's Brochure is updated during the trial, the investigator/institution should supply a copy of the updated Investigator's Brochure to the IRB/IEC.

4.4.3 During the trial the investigator/institution should provide to the IRB/IEC all documents subject to review.

4.5 *Compliance with Protocol*

4.5.1 The investigator/institution should conduct the trial in compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies) and which was given approval/favourable opinion by the IRB/IEC. The investigator/institution and the sponsor should sign the protocol, or an alternative contract, to confirm agreement.

4.5.2 The investigator should not implement any deviation from, or changes of the protocol without agreement by the sponsor and prior review and documented approval/favourable opinion from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to trial subjects, or when the change(s) involves only logistical or administrative aspects of the trial (e.g., change in monitor(s), change of telephone number(s)).

4.5.3 The investigator, or person designated by the investigator, should document and explain any deviation from the approved protocol.

4.5.4 The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favourable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted:
(a) to the IRB/IEC for review and approval/favourable opinion,
(b) to the sponsor for agreement and, if required,
(c) to the regulatory authority(ies).

4.6 *Investigational Product(s)*

4.6.1 Responsibility for investigational product(s) accountability at the trial site(s) rests with the investigator/institution.

4.6.2 Where allowed/required, the investigator/institution may/should assign some or all of the investigator's/institution's duties for investigational product(s) accountability at the trial site(s) to an appropriate pharmacist or another appropriate individual who is under the supervision of the investigator/institution.

4.6.3 The investigator/institution and/or a pharmacist or other appropriate individual, who is designated by the investigator/institution, should maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused product(s). These records should include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational product(s) and trial subjects. Investigators should maintain records that document adequately that the subjects were provided the doses specified by the protocol and reconcile all investigational product(s) received from the sponsor.

4.6.4 The investigational product(s) should be stored as specified by the sponsor (see 5.13.2 and 5.14.3) and in accordance with applicable regulatory requirement(s).

4.6.5 The investigator should ensure that the investigational product(s) are used only in accordance with the approved protocol.

4.6.6 The investigator, or a person designated by the investigator/institution, should explain the correct use of the investigational product(s) to each subject and should check, at intervals appropriate for the trial, that each subject is following the instructions properly.

4.7 *Randomization Procedures and Unblinding*

The investigator should follow the trial's randomization procedures, if any, and should ensure that the code is broken only in accordance with the protocol. If the trial is blinded, the investigator should promptly document and explain to the sponsor any premature unblinding (e.g., accidental unblinding, unblinding due to a serious adverse event) of the investigational product(s).

4.8 *Informed Consent of Trial Subjects*

4.8.1 In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki. Prior to the beginning of the trial, the investigator should have the IRB/IEC's written approval/ favourable opinion of the written informed consent form and any other written information to be provided to subjects.

4.8.2 The written informed consent form and any other written information to be provided to subjects should be revised whenever important new information becomes available that may be relevant to the subject's consent. Any revised written informed consent form, and written information should receive the IRB/IEC's approval/favourable opinion in advance of use. The subject or the subject's legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information should be documented.

4.8.3 Neither the investigator, nor the trial staff, should coerce or unduly influence a subject to participate or to continue to participate in a trial.

4.8.4 None of the oral and written information concerning the trial, including the written informed consent form, should contain any language that causes the subject or the subject's legally acceptable representative to waive or to appear to waive any legal rights, or that releases or appears to release the investigator, the institution, the sponsor, or their agents from liability for negligence.

4.8.5 The investigator, or a person designated by the investigator, should fully inform the subject or, if the subject is unable to provide informed consent, the subject's legally acceptable representative, of all pertinent aspects of the trial including the written information and the approval/ favourable opinion by the IRB/IEC.

4.8.6 The language used in the oral and written information about the trial, including the written informed consent form, should be as non-technical as practical and should be understandable to the subject or the subject's legally acceptable representative and the impartial witness, where applicable.

4.8.7 Before informed consent may be obtained, the investigator, or a person designated by the investigator, should provide the subject or the subject's legally acceptable representative ample time and opportunity to inquire about details of the trial and to decide whether or not to participate in the trial. All questions about the trial should be answered to the satisfaction of the subject or the subject's legally acceptable representative.

4.8.8 Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject or by the subject's legally acceptable representative, and by the person who conducted the informed consent discussion.

4.8.9 If a subject is unable to read or if a legally acceptable representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to subjects, is read and explained to the subject or the subject's legally acceptable representative, and after the subject or the subject's legally acceptable representative has orally consented to the subject's participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject or the subject's legally acceptable representative, and that informed consent was freely given by the subject or the subject's legally acceptable representative.

4.8.10 Both the informed consent discussion and the written informed consent form and any other written information to be provided to subjects should include explanations of the following:

(a) That the trial involves research.
(b) The purpose of the trial.
(c) The trial treatment(s) and the probability for random assignment to each treatment.
(d) The trial procedures to be followed, including all invasive procedures.
(e) The subject's responsibilities.
(f) Those aspects of the trial that are experimental.
(g) The reasonably foreseeable risks or inconveniences to the subject and, when applicable, to an embryo, fetus, or nursing infant.
(h) The reasonably expected benefits. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
(i) The alternative procedure(s) or course(s) of treatment that may be available to the subject, and their important potential benefits and risks.
(j) The compensation and/or treatment available to the subject in the event of trial-related injury.
(k) The anticipated prorated payment, if any, to the subject for participating in the trial.
(l) The anticipated expenses, if any, to the subject for participating in the trial.
(m) That the subject's participation in the trial is voluntary and that the subject may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the subject is otherwise entitled.
(n) That the monitor(s), the auditor(s), the IRB/IEC, and the regulatory authority(ies) will be granted direct access to the subject's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the subject, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the subject or the subject's legally acceptable representative is authorizing such access.

(o) That records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the subject's identity will remain confidential.
(p) That the subject or the subject's legally acceptable representative will be informed in a timely manner if information becomes available that may be relevant to the subject's willingness to continue participation in the trial.
(q) The person(s) to contact for further information regarding the trial and the rights of trial subjects, and whom to contact in the event of trial-related injury.
(r) The foreseeable circumstances and/or reasons under which the subject's participation in the trial may be terminated.
(s) The expected duration of the subject's participation in the trial.
(t) The approximate number of subjects involved in the trial.

4.8.11 Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects. During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

4.8.12 When a clinical trial (therapeutic or non-therapeutic) includes subjects who can only be enrolled in the trial with the consent of the subject's legally acceptable representative (e.g., minors, or patients with severe dementia), the subject should be informed about the trial to the extent compatible with the subject's understanding and, if capable, the subject should sign and personally date the written informed consent.

4.8.13 Except as described in 4.8.14, a non-therapeutic trial (i.e. a trial in which there is no anticipated direct clinical benefit to the subject), should be conducted in subjects who personally give consent and who sign and date the written informed consent form.

4.8.14 Non-therapeutic trials may be conducted in subjects with consent of a legally acceptable representative provided the following conditions are fulfilled:
(a) The objectives of the trial can not be met by means of a trial in subjects who can give informed consent personally.
(b) The foreseeable risks to the subjects are low.
(c) The negative impact on the subject's well-being is minimized and low.
(d) The trial is not prohibited by law.
(e) The approval/favourable opinion of the IRB/IEC is expressly sought on the inclusion of such subjects, and the written approval/ favourable opinion covers this aspect.

Such trials, unless an exception is justified, should be conducted in patients having a disease or condition for which the investigational product is intended. Subjects in these trials should be particularly closely monitored and should be withdrawn if they appear to be unduly distressed.

4.8.15 In emergency situations, when prior consent of the subject is not possible, the consent of the subject's legally acceptable representative, if present, should be requested. When prior consent of the subject is not possible, and the subject's legally acceptable representative is not available, enrolment of the subject should require measures described in the protocol and/or elsewhere, with documented approval/favourable opinion by the IRB/IEC, to protect the rights, safety and well-being of the subject and to ensure compliance with applicable regulatory requirements. The subject or the subject's legally acceptable representative should be informed about the trial as soon as possible and consent to continue and other consent as appropriate (see 4.8.10) should be requested.

4.9 *Records and Reports*

4.9.1 The investigator should ensure the accuracy, completeness, legibility, and timeliness of the data reported to the sponsor in the CRFs and in all required reports.

4.9.2 Data reported on the CRF, that are derived from source documents, should be consistent with the source documents or the discrepancies should be explained.

4.9.3 Any change or correction to a CRF should be dated, initialed, and explained (if necessary) and should not obscure the original entry (i.e. an audit trail should be maintained); this applies to both written and electronic changes or corrections (see 5.18.4 (n)). Sponsors should provide guidance to investigators and/or the investigators' designated representatives on making such corrections. Sponsors should have written procedures to assure that changes or corrections in CRFs made by sponsor's designated representatives are documented, are necessary, and are endorsed by the investigator. The investigator should retain records of the changes and corrections.

4.9.4 The investigator/institution should maintain the trial documents as specified in Essential Documents for the Conduct of a Clinical Trial (see 8.) and as required by the applicable regulatory requirement(s). The investigator/institution should take measures to prevent accidental or premature destruction of these documents.

4.9.5 Essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirements or by an agreement with the sponsor. It is the responsibility of the sponsor to inform the investigator/institution as to when these documents no longer need to be retained (see 5.5.12).

4.9.6 The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

4.9.7 Upon request of the monitor, auditor, IRB/IEC, or regulatory authority, the investigator/institution should make available for direct access all requested trial-related records.

4.10 *Progress Reports*

4.10.1 The investigator should submit written summaries of the trial status to the IRB/IEC annually, or more frequently, if requested by the IRB/IEC.

4.10.2 The investigator should promptly provide written reports to the sponsor, the IRB/IEC (see 3.3.8) and, where applicable, the institution on any changes significantly affecting the conduct of the trial, and/or increasing the risk to subjects.

4.11 *Safety Reporting*

4.11.1 All serious adverse events (SAEs) should be reported immediately to the sponsor except for those SAEs that the protocol or other document (e.g., Investigator's Brochure) identifies as not needing immediate reporting. The immediate reports should be followed promptly by detailed, written reports. The immediate and follow-up reports should identify subjects by unique code numbers assigned to the trial subjects rather than by the subjects' names, personal identification numbers, and/or addresses. The investigator should also comply with the applicable regulatory requirement(s) related to the reporting of unexpected serious adverse drug reactions to the regulatory authority(ies) and the IRB/IEC.

4.11.2 Adverse events and/or laboratory abnormalities identified in the protocol as critical to safety evaluations should be reported to the sponsor according to the reporting requirements and within the time periods specified by the sponsor in the protocol.

4.11.3 For reported deaths, the investigator should supply the sponsor and the IRB/IEC with any additional requested information (e.g., autopsy reports and terminal medical reports).

4.12 *Premature Termination or Suspension of a Trial*

If the trial is prematurely terminated or suspended for any reason, the investigator/institution should promptly inform the trial subjects, should assure appropriate therapy and follow-up for the subjects, and, where required by the applicable regulatory requirement(s), should inform the regulatory authority(ies). In addition:

4.12.1 If the investigator terminates or suspends a trial without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC, and should provide the sponsor and the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.2 If the sponsor terminates or suspends a trial (see 5.21), the investigator should promptly inform the institution where applicable and the investigator/institution should promptly inform the IRB/IEC and provide the IRB/IEC a detailed written explanation of the termination or suspension.

4.12.3 If the IRB/IEC terminates or suspends its approval/favourable opinion of a trial (see 3.1.2 and 3.3.9), the investigator should inform the institution where applicable and the investigator/institution should promptly notify the sponsor and provide the sponsor with a detailed written explanation of the termination or suspension.

4.13 *Final Report(s) by Investigator*

Upon completion of the trial, the investigator, where applicable, should inform the institution; the investigator/institution should provide the IRB/IEC with a summary of the trial's outcome, and the regulatory authority(ies) with any reports required.

5. SPONSOR

5.1 *Quality Assurance and Quality Control*

5.1.1 The sponsor is responsible for implementing and maintaining quality assurance and quality control systems with written SOPs to ensure that trials are conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirement(s).

5.1.2 The sponsor is responsible for securing agreement from all involved parties to ensure direct access (see 1.21) to all trial related sites, source data/documents , and reports for the purpose of monitoring and auditing by the sponsor, and inspection by domestic and foreign regulatory authorities.

5.1.3 Quality control should be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

5.1.4 Agreements, made by the sponsor with the investigator/institution and any other parties involved with the clinical trial, should be in writing, as part of the protocol or in a separate agreement.

5.2 *Contract Research Organization (CRO)*

5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO, but the ultimate responsibility for the quality and integrity of the trial data always resides with the sponsor. The CRO should implement quality assurance and quality control.

5.2.2 Any trial-related duty and function that is transferred to and assumed by a CRO should be specified in writing.

5.2.3 Any trial-related duties and functions not specifically transferred to and assumed by a CRO are retained by the sponsor.

5.2.4 All references to a sponsor in this guideline also apply to a CRO to the extent that a CRO has assumed the trial related duties and functions of a sponsor.

5.3 ***Medical Expertise***

The sponsor should designate appropriately qualified medical personnel who will be readily available to advise on trial related medical questions or problems. If necessary, outside consultant(s) may be appointed for this purpose.

5.4 ***Trial Design***

5.4.1 The sponsor should utilize qualified individuals (e.g. biostatisticians, clinical pharmacologists, and physicians) as appropriate, throughout all stages of the trial process, from designing the protocol and CRFs and planning the analyses to analyzing and preparing interim and final clinical trial reports.

5.4.2 For further guidance: Clinical Trial Protocol and Protocol Amendment(s) (see 6.), the ICH Guideline for Structure and Content of Clinical Study Reports, and other appropriate ICH guidance on trial design, protocol and conduct.

5.5 ***Trial Management, Data Handling, and Record Keeping***

5.5.1 The sponsor should utilize appropriately qualified individuals to supervise the overall conduct of the trial, to handle the data, to verify the data, to conduct the statistical analyses, and to prepare the trial reports.

5.5.2 The sponsor may consider establishing an independent data-monitoring committee (IDMC) to assess the progress of a clinical trial, including the safety data and the critical efficacy endpoints at intervals, and to recommend to the sponsor whether to continue, modify, or stop a trial.The IDMC should have written operating procedures and maintain written records of all its meetings.

5.5.3 When using electronic trial data handling and/or remote electronic trial data systems, the sponsor should:

(a) Ensure and document that the electronic data processing system(s) conforms to the sponsor's established requirements for completeness, accuracy, reliability, and consistent intended performance (i.e. validation).
(b) Maintains SOPs for using these systems.
(c) Ensure that the systems are designed to permit data changes in such a way that the data changes are documented and that there is no deletion of entered data (i.e. maintain an audit trail, data trail, edit trail).
(d) Maintain a security system that prevents unauthorized access to the data.

(e) Maintain a list of the individuals who are authorized to make data changes (see 4.1.5 and 4.9.3).
(f) Maintain adequate backup of the data.
(g) Safeguard the blinding, if any (e.g. maintain the blinding during data entry and processing).

5.5.4 If data are transformed during processing, it should always be possible to compare the original data and observations with the processed data.

5.5.5 The sponsor should use an unambiguous subject identification code (see 1.58) that allows identification of all the data reported for each subject.

5.5.6 The sponsor, or other owners of the data, should retain all of the sponsor-specific essential documents pertaining to the trial (see 8. Essential Documents for the Conduct of a Clinical Trial).

5.5.7 The sponsor should retain all sponsor-specific essential documents in conformance with the applicable regulatory requirement(s) of the country(ies) where the product is approved, and/or where the sponsor intends to apply for approval(s).

5.5.8 If the sponsor discontinues the clinical development of an investigational product (i.e. for any or all indications, routes of administration, or dosage forms), the sponsor should maintain all sponsor-specific essential documents for at least 2 years after formal discontinuation or in conformance with the applicable regulatory requirement(s).

5.5.9 If the sponsor discontinues the clinical development of an investigational product, the sponsor should notify all the trial investigators/institutions and all the regulatory authorities.

5.5.10 Any transfer of ownership of the data should be reported to the appropriate authority(ies), as required by the applicable regulatory requirement(s).

5.5.11 The sponsor specific essential documents should be retained until at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period however if required by the applicable regulatory requirement(s) or if needed by the sponsor.

5.5.12 The sponsor should inform the investigator(s)/institution(s) in writing of the need for record retention and should notify the investigator(s)/institution(s) in writing when the trial related records are no longer needed.

5.6 *Investigator Selection*

5.6.1 The sponsor is responsible for selecting the investigator(s)/institution(s). Each investigator should be qualified by training and experience and should have adequate resources (see 4.1, 4.2) to properly conduct the trial for which the investigator is selected. If organization of a coordinating committee and/or selection of coordinating investigator(s) are to be utilized in multicentre trials, their organization and/or selection are the sponsor's responsibility.

5.6.2 Before entering an agreement with an investigator/institution to conduct a trial, the sponsor should provide the investigator(s)/institution(s) with the protocol and an up-to-date Investigator's Brochure, and should provide sufficient time for the investigator/institution to review the protocol and the information provided.

5.6.3 The sponsor should obtain the investigator's/institution's agreement:

(a) to conduct the trial in compliance with GCP, with the applicable regulatory requirement(s) (see 4.1.3), and with the protocol agreed to by the sponsor and given approval/favourable opinion by the IRB/IEC (see 4.5.1);
(b) to comply with procedures for data recording/reporting;
(c) to permit monitoring, auditing and inspection (see 4.1.4) and
(d) to retain the trial related essential documents until the sponsor informs the investigator/institution these documents are no longer needed (see 4.9.4 and 5.5.12).

The sponsor and the investigator/institution should sign the protocol, or an alternative document, to confirm this agreement.

5.7 *Allocation of Responsibilities*

Prior to initiating a trial, the sponsor should define, establish, and allocate all trial-related duties and functions.

5.8 *Compensation to Subjects and Investigators*

5.8.1 If required by the applicable regulatory requirement(s), the sponsor should provide insurance or should indemnify (legal and financial coverage) the investigator/the institution against claims arising from the trial, except for claims that arise from malpractice and/or negligence.

5.8.2 The sponsor's policies and procedures should address the costs of treatment of trial subjects in the event of trial-related injuries in accordance with the applicable regulatory requirement(s).

5.8.3 When trial subjects receive compensation, the method and manner of compensation should comply with applicable regulatory requirement(s).

5.9 ***Financing***

The financial aspects of the trial should be documented in an agreement between the sponsor and the investigator/institution.

5.10 ***Notification/Submission to Regulatory Authority(ies)***

Before initiating the clinical trial(s), the sponsor (or the sponsor and the investigator, if required by the applicable regulatory requirement(s)) should submit any required application(s) to the appropriate authority(ies) for review, acceptance, and/or permission (as required by the applicable regulatory requirement(s)) to begin the trial(s). Any notification/submission should be dated and contain sufficient information to identify the protocol.

5.11 ***Confirmation of Review by IRB/IEC***

5.11.1 The sponsor should obtain from the investigator/institution:

(a) The name and address of the investigator's/institution's IRB/IEC.

(b) A statement obtained from the IRB/IEC that it is organized and operates according to GCP and the applicable laws and regulations.

(c) Documented IRB/IEC approval/favourable opinion and, if requested by the sponsor, a current copy of protocol, written informed consent form(s) and any other written information to be provided to subjects, subject recruiting procedures, and documents related to payments and compensation available to the subjects, and any other documents that the IRB/IEC may have requested.

5.11.2 If the IRB/IEC conditions its approval/favourable opinion upon change(s) in any aspect of the trial, such as modification(s) of the protocol, written informed consent form and any other written information to be provided to subjects, and/or other procedures, the sponsor should obtain from the investigator/institution a copy of the modification(s) made and the date approval/favourable opinion was given by the IRB/IEC.

5.11.3 The sponsor should obtain from the investigator/institution documentation and dates of any IRB/IEC reapprovals/re-evaluations with favourable opinion, and of any withdrawals or suspensions of approval/favourable opinion.

5.12 ***Information on Investigational Product(s)***

5.12.1 When planning trials, the sponsor should ensure that sufficient safety and efficacy data from nonclinical studies and/or clinical trials are available to support human exposure by the route, at the dosages, for the duration, and in the trial population to be studied.

5.12.2 The sponsor should update the Investigator's Brochure as significant new information becomes available (see 7. Investigator's Brochure).

5.13 *Manufacturing, Packaging, Labelling, and Coding Investigational Product(s)*

5.13.1 The sponsor should ensure that the investigational product(s) (including active comparator(s) and placebo, if applicable) is characterized as appropriate to the stage of development of the product(s), is manufactured in accordance with any applicable GMP, and is coded and labelled in a manner that protects the blinding, if applicable. In addition, the labelling should comply with applicable regulatory requirement(s).

5.13.2 The sponsor should determine, for the investigational product(s), acceptable storage temperatures, storage conditions (e.g. protection from light), storage times, reconstitution fluids and procedures, and devices for product infusion, if any. The sponsor should inform all involved parties (e.g. monitors, investigators, pharmacists, storage managers) of these determinations.

5.13.3 The investigational product(s) should be packaged to prevent contamination and unacceptable deterioration during transport and storage.

5.13.4 In blinded trials, the coding system for the investigational product(s) should include a mechanism that permits rapid identification of the product(s) in case of a medical emergency, but does not permit undetectable breaks of the blinding.

5.13.5 If significant formulation changes are made in the investigational or comparator product(s) during the course of clinical development, the results of any additional studies of the formulated product(s) (e.g. stability, dissolution rate, bioavailability) needed to assess whether these changes would significantly alter the pharmacokinetic profile of the product should be available prior to the use of the new formulation in clinical trials.

5.14 *Supplying and Handling Investigational Product(s)*

5.14.1 The sponsor is responsible for supplying the investigator(s)/institution(s) with the investigational product(s).

5.14.2 The sponsor should not supply an investigator/institution with the investigational product(s) until the sponsor obtains all required documentation (e.g. approval/favourable opinion from IRB/IEC and regulatory authority(ies)).

5.14.3 The sponsor should ensure that written procedures include instructions that the investigator/institution should follow for the handling and storage of investigational product(s) for the trial and documentation thereof. The procedures should address adequate and safe receipt, handling, storage, dispensing, retrieval of unused product from subjects, and return of unused investigational product(s) to the sponsor (or alternative disposition if authorized by the sponsor and in compliance with the applicable regulatory requirement(s)).

5.14.4 The sponsor should:
(a) Ensure timely delivery of investigational product(s) to the investigator(s).
(b) Maintain records that document shipment, receipt, disposition, return, and destruction of the investigational product(s) (see 8. Essential Documents for the Conduct of a Clinical Trial).
(c) Maintain a system for retrieving investigational products and documenting this retrieval (e.g. for deficient product recall, reclaim after trial completion, expired product reclaim).
(d) Maintain a system for the disposition of unused investigational product(s) and for the documentation of this disposition.

5.14.5 The sponsor should:
(a) Take steps to ensure that the investigational product(s) are stable over the period of use.
(b) Maintain sufficient quantities of the investigational product(s) used in the trials to reconfirm specifications, should this become necessary, and maintain records of batch sample analyses and characteristics. To the extent stability permits, samples should be retained either until the analyses of the trial data are complete or as required by the applicable regulatory requirement(s), whichever represents the longer retention period.

5.15 *Record Access*

5.15.1 The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection.

5.15.2 The sponsor should verify that each subject has consented, in writing, to direct access to his/her original medical records for trial-related monitoring, audit, IRB/IEC review, and regulatory inspection.

5.16 *Safety Information*

5.16.1 The sponsor is responsible for the ongoing safety evaluation of the investigational product(s).

5.16.2 The sponsor should promptly notify all concerned investigator(s)/institution(s) and the regulatory authority(ies) of findings that could affect adversely the safety of subjects, impact the conduct of the trial, or alter the IRB/IEC's approval/favourable opinion to continue the trial.

5.17 *Adverse Drug Reaction Reporting*

5.17.1 The sponsor should expedite the reporting to all concerned investigator(s)/institutions(s), to the IRB(s)/IEC(s), where required, and to the regulatory authority(ies) of all adverse drug reactions (ADRs) that are both serious and unexpected.

5.17.2 Such expedited reports should comply with the applicable regulatory requirement(s) and with the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.

5.17.3 The sponsor should submit to the regulatory authority(ies) all safety updates and periodic reports, as required by applicable regulatory requirement(s).

5.18 *Monitoring*

5.18.1 *Purpose*

The purposes of trial monitoring are to verify that:

(a) The rights and well-being of human subjects are protected.

(b) The reported trial data are accurate, complete, and verifiable from source documents.

(c) The conduct of the trial is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

5.18.2 *Selection and Qualifications of Monitors*

(a) Monitors should be appointed by the sponsor.

(b) Monitors should be appropriately trained, and should have the scientific and/or clinical knowledge needed to monitor the trial adequately. A monitor's qualifications should be documented.

(c) Monitors should be thoroughly familiar with the investigational product(s), the protocol, written informed consent form and any other written information to be provided to subjects, the sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

5.18.3 *Extent and Nature of Monitoring*

The sponsor should ensure that the trials are adequately monitored. The sponsor should determine the appropriate extent and nature of monitoring. The determination of the extent and nature of monitoring should be based on considerations such as the objective, purpose, design, complexity, blinding, size, and endpoints of the trial. In general there is a need for on-site monitoring, before, during, and after the trial; however in exceptional circumstances the sponsor may determine that central monitoring in conjunction with procedures such as investigators' training and meetings, and extensive written guidance can assure appropriate conduct of the trial in accordance with GCP. Statistically controlled sampling may be an acceptable method for selecting the data to be verified.

5.18.4 *Monitor's Responsibilities*

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 (see 4.1, 4.2, 5.6) 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 enroling 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 authorized to initial CRF changes for the investigator. This authorization should be documented.

(o) Determining whether all adverse events (AEs) are appropriately reported within the time periods required by GCP, the protocol, the IRB/IEC, the sponsor, and the applicable regulatory requirement(s).

(p) Determining whether the investigator is maintaining the essential documents (see 8. Essential Documents for the Conduct of a Clinical Trial).

(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.

5.18.5 *Monitoring Procedures*

The monitor(s) should follow the sponsor's established written SOPs as well as those procedures that are specified by the sponsor for monitoring a specific trial.

5.18.6 *Monitoring Report*

(a) The monitor should submit a written report to the sponsor after each trial-site visit or trial-related communication.

(b) Reports should include the date, site, name of the monitor, and name of the investigator or other individual(s) contacted.

(c) Reports should include a summary of what the monitor reviewed and the monitor's statements concerning the significant findings/facts, deviations and deficiencies, conclusions, actions taken or to be taken and/or actions recommended to secure compliance.

(d) The review and follow-up of the monitoring report with the sponsor should be documented by the sponsor's designated representative.

5.19 ***Audit***

If or when sponsors perform audits, as part of implementing quality assurance, they should consider:

5.19.1 *Purpose*

The purpose of a sponsor's audit, which is independent of and separate from routine monitoring or quality control functions, should be to evaluate trial conduct and compliance with the protocol, SOPs, GCP, and the applicable regulatory requirements.

5.19.2 *Selection and Qualification of Auditors*

(a) The sponsor should appoint individuals, who are independent of the clinical trials/systems, to conduct audits.

(b) The sponsor should ensure that the auditors are qualified by training and experience to conduct audits properly. An auditor's qualifications should be documented.

5.19.3 *Auditing Procedures*

(a) The sponsor should ensure that the auditing of clinical trials/systems is conducted in accordance with the sponsor's written procedures on what to audit, how to audit, the frequency of audits, and the form and content of audit reports.

(b) The sponsor's audit plan and procedures for a trial audit should be guided by the importance of the trial to submissions to regulatory authorities, the number of subjects in the trial, the type and complexity of the trial, the level of risks to the trial subjects, and any identified problem(s).

(c) The observations and findings of the auditor(s) should be documented.

(d) To preserve the independence and value of the audit function, the regulatory authority(ies) should not routinely request the audit reports. Regulatory authority(ies) may seek access to an audit report on a case by case basis when evidence of serious GCP non-compliance exists, or in the course of legal proceedings.

(e) When required by applicable law or regulation, the sponsor should provide an audit certificate.

5.20 ***Noncompliance***

5.20.1 Noncompliance with the protocol, SOPs, GCP, and/or applicable regulatory requirement(s) by an investigator/institution, or by member(s) of the sponsor's staff should lead to prompt action by the sponsor to secure compliance.

5.20.2 If the monitoring and/or auditing identifies serious and/or persistent noncompliance on the part of an investigator/institution, the sponsor should terminate the investigator's/institution's participation in the trial. When an investigator's/institution's participation is terminated because of noncompliance, the sponsor should notify promptly the regulatory authority(ies).

5.21 ***Premature Termination or Suspension of a Trial***

If a trial is prematurely terminated or suspended, the sponsor should promptly inform the investigators/institutions, and the regulatory authority(ies) of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC should also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

5.22 *Clinical Trial/Study Reports*

Whether the trial is completed or prematurely terminated, the sponsor should ensure that the clinical trial reports are prepared and provided to the regulatory agency(ies) as required by the applicable regulatory requirement(s). The sponsor should also ensure that the clinical trial reports in marketing applications meet the standards of the ICH Guideline for Structure and Content of Clinical Study Reports. (NOTE: The ICH Guideline for Structure and Content of Clinical Study Reports specifies that abbreviated study reports may be acceptable in certain cases.)

5.23 *Multicentre Trials*

For multicentre trials, the sponsor should ensure that:

5.23.1 All investigators conduct the trial in strict compliance with the protocol agreed to by the sponsor and, if required, by the regulatory authority(ies), and given approval/favourable opinion by the IRB/IEC.

5.23.2 The CRFs are designed to capture the required data at all multicentre trial sites. For those investigators who are collecting additional data, supplemental CRFs should also be provided that are designed to capture the additional data.

5.23.3 The responsibilities of coordinating investigator(s) and the other participating investigators are documented prior to the start of the trial.

5.23.4 All investigators are given instructions on following the protocol, on complying with a uniform set of standards for the assessment of clinical and laboratory findings, and on completing the CRFs.

5.23.5 Communication between investigators is facilitated.

6. CLINICAL TRIAL PROTOCOL AND PROTOCOL AMENDMENT(S)

The contents of a trial protocol should generally include the following topics. However, site specific information may be provided on separate protocol page(s), or addressed in a separate agreement, and some of the information listed below may be contained in other protocol referenced documents, such as an Investigator's Brochure.

6.1 *General Information*

6.1.1 Protocol title, protocol identifying number, and date. Any amendment(s) should also bear the amendment number(s) and date(s).

6.1.2 Name and address of the sponsor and monitor (if other than the sponsor).

6.1.3 Name and title of the person(s) authorized to sign the protocol and the protocol amendment(s) for the sponsor.

6.1.4 Name, title, address, and telephone number(s) of the sponsor's medical expert (or dentist when appropriate) for the trial.

6.1.5 Name and title of the investigator(s) who is (are) responsible for conducting the trial, and the address and telephone number(s) of the trial site(s).

6.1.6 Name, title, address, and telephone number(s) of the qualified physician (or dentist, if applicable), who is responsible for all trial-site related medical (or dental) decisions (if other than investigator).

6.1.7 Name(s) and address(es) of the clinical laboratory(ies) and other medical and/or technical department(s) and/or institutions involved in the trial.

6.2 ***Background Information***

6.2.1 Name and description of the investigational product(s).

6.2.2 A summary of findings from nonclinical studies that potentially have clinical significance and from clinical trials that are relevant to the trial.

6.2.3 Summary of the known and potential risks and benefits, if any, to human subjects.

6.2.4 Description of and justification for the route of administration, dosage, dosage regimen, and treatment period(s).

6.2.5 A statement that the trial will be conducted in compliance with the protocol, GCP and the applicable regulatory requirement(s).

6.2.6 Description of the population to be studied.

6.2.7 References to literature and data that are relevant to the trial, and that provide background for the trial.

6.3 ***Trial Objectives and Purpose***

A detailed description of the objectives and the purpose of the trial.

6.4 ***Trial Design***

The scientific integrity of the trial and the credibility of the data from the trial depend substantially on the trial design. A description of the trial design, should include:

6.4.1 A specific statement of the primary endpoints and the secondary endpoints, if any, to be measured during the trial.

6.4.2 A description of the type/design of trial to be conducted (e.g. double-blind, placebo-controlled, parallel design) and a schematic diagram of trial design, procedures and stages.

6.4.3 A description of the measures taken to minimize/avoid bias, including:
(a) Randomization.
(b) Blinding.

6.4.4 A description of the trial treatment(s) and the dosage and dosage regimen of the investigational product(s). Also include a description of the dosage form, packaging, and labelling of the investigational product(s).

6.4.5 The expected duration of subject participation, and a description of the sequence and duration of all trial periods, including follow-up, if any.

6.4.6 A description of the "stopping rules" or "discontinuation criteria" for individual subjects, parts of trial and entire trial.

6.4.7 Accountability procedures for the investigational product(s), including the placebo(s) and comparator(s), if any.

6.4.8 Maintenance of trial treatment randomization codes and procedures for breaking codes.

6.4.9 The identification of any data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data), and to be considered to be source data.

6.5 *Selection and Withdrawal of Subjects*

6.5.1 Subject inclusion criteria.

6.5.2 Subject exclusion criteria.

6.5.3 Subject withdrawal criteria (i.e. terminating investigational product treatment/trial treatment) and procedures specifying:
(a) When and how to withdraw subjects from the trial/ investigational product treatment.
(b) The type and timing of the data to be collected for withdrawn subjects.
(c) Whether and how subjects are to be replaced.
(d) The follow-up for subjects withdrawn from investigational product treatment/ trial treatment.

6.6 *Treatment of Subjects*

6.6.1 The treatment(s) to be administered, including the name(s) of all the product(s), the dose(s), the dosing schedule(s), the route/mode(s) of administration, and the treatment period(s), including the follow-up period(s) for subjects for each investigational product treatment/trial treatment group/arm of the trial.

6.6.2 Medication(s)/treatment(s) permitted (including rescue medication) and not permitted before and/or during the trial.

6.6.3 Procedures for monitoring subject compliance.

6.7 *Assessment of Efficacy*

6.7.1 Specification of the efficacy parameters.

6.7.2 Methods and timing for assessing, recording, and analysing of efficacy parameters.

6.8 *Assessment of Safety*

6.8.1 Specification of safety parameters.

6.8.2 The methods and timing for assessing, recording, and analysing safety parameters.

6.8.3 Procedures for eliciting reports of and for recording and reporting adverse event and intercurrent illnesses.

6.8.4 The type and duration of the follow-up of subjects after adverse events.

6.9 *Statistics*

6.9.1 A description of the statistical methods to be employed, including timing of any planned interim analysis(ses).

6.9.2 The number of subjects planned to be enrolled. In multicentre trials, the numbers of enrolled subjects projected for each trial site should be specified. Reason for choice of sample size, including reflections on (or calculations of) the power of the trial and clinical justification.

6.9.3 The level of significance to be used.

6.9.4 Criteria for the termination of the trial.

6.9.5 Procedure for accounting for missing, unused, and spurious data.

6.9.6 Procedures for reporting any deviation(s) from the original statistical plan (any deviation(s) from the original statistical plan should be described and justified in protocol and/or in the final report, as appropriate).

6.9.7 The selection of subjects to be included in the analyses (e.g. all randomized subjects, all dosed subjects, all eligible subjects, evaluable subjects).

6.10 ***Direct Access to Source Data/Documents***

The sponsor should ensure that it is specified in the protocol or other written agreement that the investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB/IEC review, and regulatory inspection(s), providing direct access to source data/documents.

6.11 ***Quality Control and Quality Assurance***

6.12 ***Ethics***

Description of ethical considerations relating to the trial.

6.13 ***Data Handling and Record Keeping***

6.14 ***Financing and Insurance***

Financing and insurance if not addressed in a separate agreement.

6.15 ***Publication Policy***

Publication policy, if not addressed in a separate agreement.

6.16 ***Supplements***

(NOTE: Since the protocol and the clinical trial/study report are closely related, further relevant information can be found in the ICH Guideline for Structure and Content of Clinical Study Reports.)

7. INVESTIGATOR'S BROCHURE

7.1 ***Introduction***

The Investigator's Brochure (IB) is a compilation of the clinical and nonclinical data on the investigational product(s) that are relevant to the study of the product(s) in human subjects. Its purpose is to provide the investigators and others involved in the trial with the information to facilitate their understanding of the rationale for, and their compliance with, many key features of the protocol, such as the dose, dose frequency/interval, methods of administration: and safety monitoring procedures. The IB also provides insight to support the clinical management of the study subjects during the course of the clinical trial. The information should be presented in a concise, simple, objective, balanced, and non-promotional form that enables a clinician, or potential investigator, to understand it and make his/her own unbiased risk-benefit assessment of the appropriateness of the proposed trial. For this reason, a medically qualified person should generally participate in the editing of an IB, but the contents of the IB should be approved by the disciplines that generated the described data.

This guideline delineates the minimum information that should be included in an IB and provides suggestions for its layout. It is expected that the type and extent of information available will vary with the stage of development of the investigational product. If the investigational product is marketed and its pharmacology is widely understood by medical practitioners, an extensive IB may not be necessary. Where permitted by regulatory authorities, a basic product information brochure, package leaflet, or labelling may be an appropriate alternative, provided that it includes current, comprehensive, and detailed information on all aspects of the investigational product that might be of importance to the investigator. If a marketed product is being studied for a new use (i.e., a new indication), an IB specific to that new use should be prepared. The IB should be reviewed at least annually and revised as necessary in compliance with a sponsor's written procedures. More frequent revision may be appropriate depending on the stage of development and the generation of relevant new information. However, in accordance with Good Clinical Practice, relevant new information may be so important that it should be communicated to the investigators, and possibly to the Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) and/or regulatory authorities before it is included in a revised IB.

Generally, the sponsor is responsible for ensuring that an up-to-date IB is made available to the investigator(s) and the investigators are responsible for providing the up-to-date IB to the responsible IRBs/IECs. In the case of an investigator sponsored trial, the sponsor-investigator should determine whether a brochure is available from the commercial manufacturer. If the investigational product is provided by the sponsor-investigator, then he or she should provide the necessary information to the trial personnel. In cases where preparation of a formal IB is impractical, the sponsor-investigator should provide, as a substitute, an expanded background information section in the trial protocol that contains the minimum current information described in this guideline.

7.2 *General Considerations*

The IB should include:

7.2.1 *Title Page*

This should provide the sponsor's name, the identity of each investigational product (i.e., research number, chemical or approved generic name, and trade name(s) where legally permissible and desired by the sponsor), and the release date. It is also suggested that an edition number, and a reference to the number and date of the edition it supersedes, be provided. An example is given in Appendix 1.

7.2.2 *Confidentiality Statement*

The sponsor may wish to include a statement instructing the investigator/recipients to treat the IB as a confidential document for the sole information and use of the investigator's team and the IRB/IEC.

7.3 *Contents of the Investigator's Brochure*

The IB should contain the following sections, each with literature references where appropriate:

7.3.1 *Table of Contents*

An example of the Table of Contents is given in Appendix 2

7.3.2 *Summary*

A brief summary (preferably not exceeding two pages) should be given, highlighting the significant physical, chemical, pharmaceutical, pharmacological, toxicological, pharmacokinetic, metabolic, and clinical information available that is relevant to the stage of clinical development of the investigational product.

7.3.3 *Introduction*

A brief introductory statement should be provided that contains the chemical name (and generic and trade name(s) when approved) of the investigational product(s), all active ingredients, the investigational product (s) pharmacological class and its expected position within this class (e.g. advantages), the rationale for performing research with the investigational product(s), and the anticipated prophylactic, therapeutic, or diagnostic indication(s). Finally, the introductory statement should provide the general approach to be followed in evaluating the investigational product.

7.3.4 *Physical, Chemical, and Pharmaceutical Properties and Formulation*

A description should be provided of the investigational product substance(s) (including the chemical and/or structural formula(e)), and a brief summary should be given of the relevant physical, chemical, and pharmaceutical properties.

To permit appropriate safety measures to be taken in the course of the trial, a description of the formulation(s) to be used, including excipients, should be provided and justified if clinically relevant. Instructions for the storage and handling of the dosage form(s) should also be given.

Any structural similarities to other known compounds should be mentioned.

7.3.5 *Nonclinical Studies*

Introduction:

The results of all relevant nonclinical pharmacology, toxicology, pharmacokinetic, and investigational product metabolism studies should be provided in summary form. This summary should address the methodology used, the results, and a discussion of the relevance of the findings to the investigated therapeutic and the possible unfavourable and unintended effects in humans.

The information provided may include the following, as appropriate, if known/ available:

- Species tested
- Number and sex of animals in each group
- Unit dose (e.g., milligram/kilogram (mg/kg))
- Dose interval
- Route of administration

- Duration of dosing
- Information on systemic distribution
- Duration of post-exposure follow-up
- Results, including the following aspects:
  - Nature and frequency of pharmacological or toxic effects
  - Severity or intensity of pharmacological or toxic effects
  - Time to onset of effects
  - Reversibility of effects
  - Duration of effects
  - Dose response

Tabular format/listings should be used whenever possible to enhance the clarity of the presentation.

The following sections should discuss the most important findings from the studies, including the dose response of observed effects, the relevance to humans, and any aspects to be studied in humans. If applicable, the effective and nontoxic dose findings in the same animal species should be compared (i.e., the therapeutic index should be discussed). The relevance of this information to the proposed human dosing should be addressed. Whenever possible, comparisons should be made in terms of blood/tissue levels rather than on a mg/kg basis.

(a) *Nonclinical Pharmacology*

A summary of the pharmacological aspects of the investigational product and, where appropriate, its significant metabolites studied in animals, should be included. Such a summary should incorporate studies that assess potential therapeutic activity (e.g. efficacy models, receptor binding, and specificity) as well as those that assess safety (e.g., special studies to assess pharmacological actions other than the intended therapeutic effect(s)).

(b) *Pharmacokinetics and Product Metabolism in Animals*

A summary of the pharmacokinetics and biological transformation and disposition of the investigational product in all species studied should be given. The discussion of the findings should address the absorption and the local and systemic bioavailability of the investigational product and its metabolites, and their relationship to the pharmacological and toxicological findings in animal species.

(c) *Toxicology*

A summary of the toxicological effects found in relevant studies conducted in different animal species should be described under the following headings where appropriate:

- Single dose
- Repeated dose
- Carcinogenicity
- Special studies (e.g. irritancy and sensitisation)
- Reproductive toxicity
- Genotoxicity (mutagenicity)

7.3.6 *Effects in Humans*

Introduction:

A thorough discussion of the known effects of the investigational product(s) in humans should be provided, including information on pharmacokinetics, metabolism, pharmacodynamics, dose response, safety, efficacy, and other pharmacological activities. Where possible, a summary of each completed clinical trial should be provided. Information should also be provided regarding results of any use of the investigational product(s) other than from in clinical trials, such as from experience during marketing.

(a) *Pharmacokinetics and Product Metabolism in Humans*

- A summary of information on the pharmacokinetics of the investigational product(s) should be presented, including the following, if available:
- Pharmacokinetics (including metabolism, as appropriate, and absorption, plasma protein binding, distribution, and elimination).
- Bioavailability of the investigational product (absolute, where possible, and/or relative) using a reference dosage form.
- Population subgroups (e.g., gender, age, and impaired organ function).
- Interactions (e.g., product-product interactions and effects of food).
- Other pharmacokinetic data (e.g., results of population studies performed within clinical trial(s).

(b) *Safety and Efficacy*

A summary of information should be provided about the investigational product's/products' (including metabolites, where appropriate) safety, pharmacodynamics, efficacy, and dose response that were obtained from preceding trials in humans (healthy volunteers and/or patients). The implications of this information should be discussed. In cases where a number of clinical trials have been completed, the use of summaries of safety and efficacy across multiple trials by indications in subgroups may provide a clear presentation of the data. Tabular summaries of adverse drug reactions for all the clinical trials (including those for all the studied indications) would be useful. Important differences in adverse drug reaction patterns/incidences across indications or subgroups should be discussed.

The IB should provide a description of the possible risks and adverse drug reactions to be anticipated on the basis of prior experiences with the product under investigation and with related products. A description should also be provided of the precautions or special monitoring to be done as part of the investigational use of the product(s).

(c) Marketing Experience

The IB should identify countries where the investigational product has been marketed or approved. Any significant information arising from the marketed use should be summarised (e.g., formulations, dosages, routes of administration, and adverse product reactions). The IB should also identify all the countries where the investigational product did not receive approval/registration for marketing or was withdrawn from marketing/registration.

7.3.7 *Summary of Data and Guidance for the Investigator*

This section should provide an overall discussion of the nonclinical and clinical data, and should summarise the information from various sources on different aspects of the investigational product(s), wherever possible. In this way, the investigator can be provided with the most informative interpretation of the available data and with an assessment of the implications of the information for future clinical trials.

Where appropriate, the published reports on related products should be discussed. This could help the investigator to anticipate adverse drug reactions or other problems in clinical trials.

The overall aim of this section is to provide the investigator with a clear understanding of the possible risks and adverse reactions, and of the specific tests, observations, and precautions that may be needed for a clinical trial. This understanding should be based on the available physical, chemical, pharmaceutical, pharmacological, toxicological, and clinical information on the investigational product(s). Guidance should also be provided to the clinical investigator on the recognition and treatment of possible overdose and adverse drug reactions that is based on previous human experience and on the pharmacology of the investigational product.

7.4 *APPENDIX 1*

TITLE PAGE *(Example)*

SPONSOR'S NAME

Product:
Research Number:
Name(s): Chemical, Generic (if approved)
Trade Name(s) (if legally permissible and desired by the sponsor)

INVESTIGATOR'S BROCHURE

Edition Number:
Release Date:

Replaces Previous Edition Number:
Date:

7.5 *APPENDIX 2*

TABLE OF CONTENTS OF INVESTIGATOR'S BROCHURE *(Example)*

Confidentiality Statement *(optional)*

Signature Page *(optional)*

1. Table of Contents
2. Summary
3. Introduction
4. Physical, Chemical, and Pharmaceutical Properties and Formulation
5. Nonclinical Studies
   - 5.1 Nonclinical Pharmacology
   - 5.2 Pharmacokinetics and Product Metabolism in Animals
   - 5.3 Toxicology
6. Effects in Humans
   - 6.1 Pharmacokinetics and Product Metabolism in Humans
   - 6.2 Safety and Efficacy
   - 6.3 Marketing Experience
7. Summary of Data and Guidance for the Investigator

NB: References on:
1. Publications
2. Reports

These references should be found at the end of each chapter

Appendices (if any)

8. ESSENTIAL DOCUMENTS FOR THE CONDUCT OF A CLINICAL TRIAL

8.1 *Introduction*

Essential Documents are those documents which individually and collectively permit evaluation of the conduct of a trial and the quality of the data produced. These documents serve to demonstrate the compliance of the investigator, sponsor and monitor with the standards of Good Clinical Practice and with all applicable regulatory requirements.

Essential Documents also serve a number of other important purposes. Filing essential documents at the investigator/institution and sponsor sites in a timely manner can greatly assist in the successful management of a trial by the investigator, sponsor and monitor. These documents are also the ones which are usually audited by the sponsor's independent audit function and inspected by the regulatory authority (ies) as part of the process to confirm the validity of the trial conduct and the integrity of data collected.

The minimum list of essential documents which has been developed follows. The various documents are grouped in three sections according to the stage of the trial during which they will normally be generated: 1) before the clinical phase of the trial commences, 2) during the clinical conduct of the trial, and 3) after completion or termination of the trial. A description is given of the purpose of each document, and whether it should be filed in either the investigator/institution or sponsor files, or both. It is acceptable to combine some of the documents, provided the individual elements are readily identifiable.

Trial master files should be established at the beginning of the trial, both at the investigator/institution's site and at the sponsor's office. A final close-out of a trial can only be done when the monitor has reviewed both investigator/institution and sponsor files and confirmed that all necessary documents are in the appropriate files.

Any or all of the documents addressed in this guideline may be subject to, and should be available for, audit by the sponsor's auditor and inspection by the regulatory authority(ies).

8.2 *Before the Clinical Phase of the Trial Commences*

During this planning stage the following documents should be generated and should be on file before the trial formally starts.

Title of Document	*Purpose*	*Located in Files of*	
		Investigator/ Institution	*Sponsor*
8.2.1 Investigator's brochure	To document that relevant and current scientific information about the investigational product has been provided to the investigator	X	X
8.2.2 Signed protocol and amendments, if any, and sample Case Report Form (CRF)	To document investigator and sponsor agreement to the protocol/ amendment(s) and CRF	X	X
8.2.3 Information given to trial subject - Informed Consent Form (including all applicable translations)	To document the informed consent	X	X
- any other written information	To document that subjects will be given appropriate written information (content and wording) to support their ability to give fully informed consent	X	X
- advertisement for subject recruitment (if used)	To document that recruitment measures are appropriate and not coercive	X	
8.2.4 Finacial aspects of the trial	To document the financial agreement between the investigator/ institution and the sponsor for the trial	X	X
8.2.5 Insurance statement (where required)	To document that compensation to subject(s) for trial-related injury will be available	X	X
8.2.6 Signed agreement between involved parties, e.g.:	To document agreements		
- investigator/institution and sponsor		X	X
- investigator/institution and CRO		X	X

	Title of Document	*Purpose*	*Located in Files of*	
			Investigator/ Institution	*Sponsor*
	- sponsor and CRO		X	(where required)
	- investigator/institution and authority(ies) (where required)		X	X
8.2.7	Dated, documented approval/ favourable opinion of Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the following: - protocol and any amendments - CRF (if applicable) - informed consent form(s) - any other written information to be provided to the subject(s) - advertisement for subject recruitment (if used) - subject compensation (if any) - any other documents given approval/ favourable opinion	To document that the trial has been subject to IRB/IEC review and given approval/favourable opinion. To identify the version number and date of the document(s)	X	X
8.2.8	Institutional Review Board/ Independent Ethics Committee composition	To document that the IRB/IEC is constituted in agreement with GCP	X	X (where required)
8.2.9	Regulatory authority(ies) authorisation/approval/ notification of protocol (where required)	To document appropriate authorisation/approval/notification by the regulatory authority(ies) has been obtained prior to initiation of the trial in compliance with the applicable regulatory requirement(s)	X (where required)	X (where required)

Title of Document	*Purpose*	*Located in Files of*	
		Investigator/ Institution	*Sponsor*
8.2.10 Curriculum vitae and/or other relevant documents evidencing qualifications of investigator(s) and sub-investigator(s)	To document qualifications and eligibility to conduct trial and/or provide medical supervision of subjects	X	X
8.2.11 Normal value(s)/range(s) for medical/laboratory/technical procedure(s) and/or test(s) included in the protocol	To document normal values and/or ranges of the tests	X	X
8.2.12 Medical/laboratory/technical procedures/tests - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document competence of facility to perform required test(s) , and support reliability of results	X (where required)	X
8.2.13 Sample of label(s) attached to investigational product container(s)	To document compliance with applicable labelling regulations and appropriateness of instructions provided to the subjects		X
8.2.14 Instructions for handling of investigational oroduct(s) and trial-related materials (if not included in protocol or Investigator's Brochure)	To document instructions needed to ensure proper storage, packaging, dispensing and disposition of investigational products and trial-related materials	X	X

Title of Document	*Purpose*	*Located in Files of*	
		Investigator/ Institution	*Sponsor*
8.2.15 Shipping records for investigational product(s) and trial-Related materials	To document shipment dates, batch numbers and method of shipment of investigational product(s) and trial-related materials. Allows tracking of product batch, review of shipping conditions, and accountability	X	X
8.2.16 Certificate(s) of analysis of investigational product(s) shipped	To document identity, purity, and strength of investigational product(s) to be used in the trial		X
8.2.17 Decoding procedures for blinded trials	To document how, in case of an emergency, identity of blinded investigational product can be revealed without breaking the blind for the remaining subjects' treatment	X	X (third party if applicable)
8.2.18 Master randomisation list	To document method for randomisation of trial population		X (third party if applicable)
8.2.19 Pre-trial monitoring report	To document that the site is suitable for the trial (may be combined with 8.2.20)		X
8.2.20 Trial initiation monitoring report	To document that trial procedures were reviewed with the investigator and the investigator's trial staff (may be combined with 8.2.19)	X	X

8.3 ***During the Clinical Conduct of the Trial***

In addition to having on file the above documents, the following should be added to the files during the trial as evidence that all new relevant information is documented as it becomes available

8.3.1 Investigator's brochure updates	To document that investigator is informed in a timely manner of relevant information as it becomes available	X	X

Title of Document	*Purpose*	*Located in Files of*	
		Investigator/ Institution	*Sponsor*
8.3.2 Any revision to: - protocol/amendment(s) and CRF - informed consent form - any other written information provided to subjects - advertisement for subject recruitment (if used)	To document revisions of these trial related documents that take effect during trial	X	X
8.3.3 Dated, documented approval/ favourable opinion of Institutional Review Board (IRB)/Independent Ethics Committee (IEC) of the following: - protocol amendment(s) - revision(s) of: - informed consent form - any other written information to be provided to the subject - advertisement for subject recruitment (if used) - any other documents given fapproval/avourable opinion - continuing review of trial (where required)	To document that the amendment(s) and/or revision(s) have been subject to IRB/IEC review and were given approval/favourable opinion. To identify the version number and date of the document(s)	X	X

Title of Document	*Purpose*	*Located in Files of*	
		Investigator/ Institution	*Sponsor*
8.3.4 Regulatory Authority(ies) Authorisations/approvals/ notifications where required for: - protocol amendment(s) and other documents	To document compliance with applicable regulatory requirements	X (where required)	X
8.3.5 Curriculum vitae for new Investigator(s) and/or sub-investigator(s)	(see 8.2.10)	X	X
8.3.6 Updates to normal value(s)/ range(s) for medical/laboratory/ technical procedure(s)/test(s) included in the protocol	To document normal values and ranges that are revised during the trial (see 8.2.11)	X	X
8.3.7 Updates of medical/laboratory/ technical procedures/tests - certification or - accreditation or - established quality control and/or external quality assessment or - other validation (where required)	To document that tests remain adequate throughout the trial period (see 8.2.12)	X (where required)	X
8.3.8 Documentation of investigational product(s) and trial-related materials shipment	(see 8.2.15.)	X	X
8.3.9 Certificate(s) of analysis for new batches of investigational products	(see 8.2.16)		X

Title of Document	*Purpose*	*Located in Files of*	
		Investigator/ Institution	*Sponsor*
8.3.10 Monitoring visit reports	To document site visits by, and findings of, the monitor		X
8.3.11 Relevant communications other than site visits - letters - meeting notes - notes of telephone calls	To document any agreements or significant discussions regarding trial administration, protocol violations, trial conduct, adverse event (AE) reporting	X	X
8.3.12 Signed Informed Consent Forms	To document that consent is obtained in accordance with GCP and protocol and dated prior to participation of each subject in trial. Also to document direct access permission (see 8.2.3)	X	
8.3.13 Source documents	To document the existence of the subject and substantiate integrity of trial data collected. To include original documents related to the trial, to medical treatment, and history of subject	X	
8.3.14 Signed, dated and completed Case Report Forms (CRF)	To document that the investigator or authorised member of the investigator's staff confirms the observations recorded	X (copy)	X (original)
8.3.15 Documentation of CRF corrections	To document all changes/additions or corrections made to CRF after initial data were recorded	X (copy)	X (original)
8.3.16 Notification by originating investigator to sponsor of serious adverse events and related reports	Notification by originating investigator to sponsor of serious adverse events and related reports in accordance with 4.11	X	X

Title of Document	*Purpose*	*Located in Files of*	
		Investigator/ Institution	*Sponsor*
8.3.17 Notification by sponsor and/or investigator, where applicable, to regulatory authority(ies) and IRB(s)/ IEC(s) of unexpected serious adverse drug reactions and of other safety information	Notification by sponsor and/or investigator, where applicable, to regulatory authorities and IRB(s)/IEC(s) of unexpected serious adverse drug reactions in accordance with 5.17 and 4.11.1 and of other safety information in accordance with 5.16.2 and 4.11.2	X (where required)	X
8.3.18 Notification by sponsor to investigators of safety information	Notification by sponsor to investigators of safety information in accordance with 5.16.2	X	X
8.3.19 Interim or annual reports to IRB/ IEC and authority(ies)	Interim or annual reports provided to IRB/IEC in accordance with 4.10 and to authority(ies) in accordance with 5.17.3	X (where required)	X
8.3.20 Subject screening log	To document identification of subjects who entered pre-trial screening	X	X
8.3.21 Subject identification code list	To document that investigator/institution keeps a confidential list of names of all subjects allocated to trial numbers on enrolling in the trial. Allows investigator/institution to reveal identity of any subject	X	
8.3.22 Subject enroment log	To document chronological enrolment of subjects by trial number	X	
8.3.23 Investigational products accountability at the site	To document that investigational product(s) have been used according to the protocol	X	X
8.3.24 Signature sheet	To document signatures and initials of all persons authorised to make entries and/or corrections on CRFs	X	X

Title of Document	Purpose	Located in Files of: Investigator/ Institution	Located in Files of: Sponsor
8.3.25 Record of retained body fluids/ tissue samples (if any)	To document location and identification of retained samples if assays need to be repeated	X	X

8.4 *After Completion or Termination of the Trial*

After completion or termination of the trial, all of the documents identified in sections 8.2 and 8.3 should be in the file together with the following

8.4.1	Investigational product(s) accountability at site	To document that the investigational product(s) have been used according to the protocol. To documents the final accounting of investigational product(s) received at the site, dispensed to subjects, returned by the subjects, and returned to sponsor	X	X
8.4.2	Documentation of investigational product destruction	To document destruction of unused investigational products by sponsor or at site	X (if destroyed at site)	X
8.4.3	Completed subject identification code list	To permit identification of all subjects enrolled in the trial in case follow-up is required. List should be kept in a confidential manner and for agreed upon time	X	
8.4.4	Audit certificate (if available)	To document that audit was performed		X
8.4.5	Final trial close-out monitoring report	To document that all activities required for trial close-out are completed, and copies of essential documents are held in the appropriate files		X
8.4.6	Treatment allocation and decoding documentation	Returned to sponsor to document any decoding that may have occurred		X

Title of Document	*Purpose*	*Located in Files of*	
		Investigator/ Institution	*Sponsor*
8.4.7 Final report by investigator to IRB/IEC where required, and where applicable, to the regulatory authority(ies)	To document completion of the trial	X	
8.4.8 Clinical study report	To document results and interpretation of trial	X (if applicable)	X


Faculty of Medicine
1887
Clinical Trials Centre
University of Hong Kong
臨床試驗中心