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STANDARD OPERATING PROCEDURES FOR CLINICAL INVESTIGATORS

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Final SOP status

UNDP/World Bank/WHO
Special Programme for Research and
Training in Tropical Diseases (TDR)

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Revised and approved by the Product Research and Development R&D Committee

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Clinical Development
Standard Operating Procedures (SOPs)

SOP Title: **Investigator's Responsibilities**

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Date **Signature**

Policy: All clinical studies supported by TDR will be carried out according to International Conference on Harmonisation (ICH)/WHO Good Clinical Practice standards, regulatory authorities requirements and TDR Standard Operating Procedures (SOPs).

All TDR investigators have an obligation to follow and adhere to the established TDR clinical study SOPs.

Note: When a trial is sponsored by another agency/pharmaceutical company, the Investigator may also be requested to follow their procedures in order to comply with company obligations. Agreement between all parties will be discussed before initiating the trial.

Scope: Clinical trials Phase I, II and III conducted by TDP/TDR.

Aims: To define Investigators' responsibilities and to provide instruction when performing clinical study(ies) supported by TDR to GCP (ICH) standards and under applicable regulatory requirements.

Applicable to: TDR investigators and as relevant UNAIDS investigators.

GLOSSARY

(ICH definition – International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use)

Adverse Drug Reaction (ADR)
In the pre-approval clinical experience with a new medicinal product or a product's 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' meaning 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.

Adverse event (AE)
Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product 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.

Applicable regulatory requirement(s)
Any law(s) and regulation(s) addressing the conduct of clinical trials of investigational products.

Approval (in relation to Institutional Review Boards)
The affirmative decision of the Institutional Review Board (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.

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 recorded, analysed and accurately reported, according to the protocol, sponsor's SOPs, GCP, and the applicable regulatory requirement(s).

Blinding
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).

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.

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.

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 ICH Guideline for structure and content of Clinical Study Reports).

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

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

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

Direct access
Permission to examine, analyse, 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 the sponsor’s proprietary information.

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.

Essential documents
Documents which individually and collectively permit evaluation of the conduct of a study and the quality of the data produced.

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.

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.

Independent Ethics Committee (IEC)
An independent body (an institutional, regional, national, or supranational review board or committee), constituted of medical professionals and non-medical members, whose responsibility it is to ensure 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, suitability of the investigator(s), facilities, and methods and materials 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.

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.

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).

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

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 materials to be used in obtaining and documenting informed consent of the trial subjects.

Interim clinical trial/study report
A report of intermediate results and their evaluation based on analyses performed during the course of a trial.

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.

Investigator
A person responsible for the conduct of a 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 Sub-investigator.

Investigator/institution
An expression meaning 'the investigator and/or institution, where required by the applicable regulatory requirements'.

Investigator's Brochure (IB)
A compilation of the clinical and nonclinical data on the investigational product(s) relevant to the study of the investigational product(s) in human subjects.

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.

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 applicable regulatory requirement(s).

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.

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.

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

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

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.

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.

Protocol amendment
A written description of a change(s) to, or formal clarification of, a protocol.

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

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.

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.

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. These bodies are sometimes referred to as competent authorities.

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
- results in important medical events that may not be immediately life-threatening or results in death or hospitalization but may jeopardize the patient or may require intervention to prevent the other outcomes listed above.

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).

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, laboratories and medico-technical departments involved in the clinical trial).

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

Standard Operating Procedures (SOPs)
Detailed, written instructions to achieve uniformity of performance of a specific function.

Study site/Trial site
The location(s) where trial-related activities are actually conducted

Sub-investigator
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 make important trial-related decisions (e.g. associates, residents, research fellows). See also Investigator.

Trial site/Study site
The location(s) where trial-related activities are actually conducted.

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*).

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

INVESTIGATOR STANDARD OPERATING PROCEDURE

Objectives:

- To provide the Investigator with general instruction to ensure that he/she understands and accepts the obligations incurred in undertaking the study.
- To ensure that the study is planned, set up, conducted, documented and reported according to the protocol, related SOPs, ICH GCP and applicable regulatory requirements.
- To ensure that the rights, safety, and welfare of study subjects are properly protected.
- To ensure that data are generated, collected and documented with accuracy, consistency and integrity.
- To ensure that the Investigator is acquainted with the study procedures, verification procedures, audits and inspection procedures.

PRIOR TO INITIATION OF THE STUDY

The Investigator should:

Be interested in the scientific aspects of the study and ensure that the study is responsive to the needs of public health within the country of the population in which it will be conducted.

Ensure the confidentiality of the product, the protocol and trial procedures by giving a confidentiality agreement in writing to TDP/TDR and/or sponsoring agencies.

Have sufficient time free from other obligations to prepare and conduct the trial. Clinical trials are time consuming and the Investigator should ensure that sufficient time can be dedicated to the study, including for informing and supervising study staff.

Review Investigator's Brochure and any up-to-date information on the investigational product. The Investigator must be familiar with the product, including pre-clinical toxicology, pharmacology, pharmacokinetics and up-to-date clinical data.

Review and discuss in detail, the ICH GCP guidelines, investigators' SOPs and protocol with the Clinical Monitor. The Investigator should clearly define:

- Factors that may alter the feasibility and acceptability of the trial.
- An adequate recruitment rate for the trial by providing retrospective data on numbers of patients who would have satisfied the proposed entrance criteria during preceding time periods.

Make sure that the procedures stated in the study protocol are applicable in his/her centre and fully understood. The Investigator should ask the Clinical Monitor to clarify any points of possible misunderstanding.

Make sure that there are sufficient medical, paramedical and clerical staff to support the study and deal with foreseeable emergencies.

- Provide a list of study personnel and functions in the study to the Clinical Monitor/Product Manager (Authorized Staff Form - ASF).
- Provide curriculum vitae of the Sub-co Investigators in the responsible laboratory.

Make sure that the physical location and facilities are sufficient to allow the study to be undertaken efficiently. Ensure:

- Confidentiality and safety conditions for trial subjects.
- Adequate equipment/facilities for subject follow-up, examination and care.
- Adequate facilities for product storage.
- Adequate facilities for laboratory assay. The laboratory assay should be validated under good laboratory practice (GLP) principles.
- Adequate facilities for retention of trial documents, ensuring confidentiality of all information about trial subjects and information supplied by TDR/sponsoring agencies.

Discuss the Case Report Form/SAE reporting forms and source documents in detail with the Clinical Monitor. Clearly define :

- Who will be responsible for CRF completion.
- Source documents/source data and access to source data.

Arrange archiving of trial documents according to GCP and regulatory requirements. It is important to check the duration of retention of patient records with the Institution's archive. In case the Institution's archive does not ensure retention of documents for the period of time requested by TDR/sponsor, the Investigator must arrange for the retention of the subjects' source documents/records for the period requested by TDR/sponsor and regulatory requirements.

Finalize informed consent forms and associated trial subject information materials (advertisements); establish procedures for application for local clearance (e.g. dean of the institution) and Independent Ethical Committee (IEC)/Institutional Review Board (IRB) approval.

Clearly define how subjects will be approached and informed, who will inform them, and what material will be used. The informed consent form and all information (leaflet written in simple language, video) should be developed collaboratively with head members of the study population/ community to ensure methods are appropriate.
In case of the need for screening tests, including biological specimen collection, before entering a trial, two types of consent form should be developed: one for biological specimen collection and analysis, and one for participation in the study after obtaining satisfactory laboratory results and respecting inclusion criteria.
As a rule, the advertisement must not make reference to TDR or the compound, nor make any claims.
Informed consent and advertisements must be submitted to TDR for review and must be included in documentation submitted to the Independent Ethical Committee and/or Institutional Review Board (IEC/IRB).

Make sure that the local ethics committee fulfils the ICH GCP requirements.

ICH GCP Composition and Operations of IEC/IRB

The IRB/IEC should determine the authority under which it is established and the composition (names and qualifications)of its members, which 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.
- At least five members.
- At least one member whose primary interest is in a non-scientific area.
- At least one member who is independent of the trial site.

An IEC/IRB may invite nonmembers with expertise in special areas to give assistance.

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

Only members who participate in review and discussion of the protocol, and who are independent of the investigator and the sponsor, can vote or provide opinion.

The IEC/IRB should perform initial and continual reviews of the trials according to the written operating procedures, and maintain records of activities and minutes of meetings.

The IEC/IRB should notify promptly, and in writing, all trial-related decisions and opinions, specifying the reasons for each.

See ICH Guidelines 3.2

Prepare the required documents to be submitted to the IEC/IRB:

Documents usually required by Ethics Committees

- Investigator Brochure and up-to-date safety information.
- Trial protocol (final version and amendments).
- Consent form(s) and subject information sheets.
- Subject recruitment procedures (e.g. advertisement
- Information on payment and compensation available to subjects.
- Current curriculum vitae for each investigator.
- Any other document requested by the IEC/IRB.

See *ICH Guidelines 3.1.2*

Obtain approval document from the Ethics Committee, which must identify the documents reviewed and state that the study is acceptable and can be initiated.

Send the approval document of the Ethics Committee, with a list of Committee members, to TDP/TDR/WHO as a supporting document for approval of the WHO Secretariat Committee on Research Involving Human Subjects (SCRIHS).

Prepare the application for Health Authority clearance in collaboration with TDR and other sponsoring agencies.

Prepare the application for product exportation/importation in collaboration with TDR and other sponsoring agencies.

If the IEC/IRB and others approve the trial, sign the final copy of the protocol and confirm in writing that he/she has read and understood, and will adhere to, the protocol, study procedures and ICH Good Clinical Practice, will collaborate with the monitor, and accords with TDR/sponsoring agencies on publications policy.

Submit requested documents to the Clinical Monitors, including:

- Signed agreement to comply with this SOP (page 1).
- Approved protocol, signed and dated.
- Approved informed consent form and other subject information, advertisement (local language and English translation).
- Investigator's and co-investigator's curriculum vitae (C.V.s).
- Authorized Staff Form (ASF).
- Product exportation/importation authorization.
- Laboratory certification/list of normal laboratory ranges, dated and signed by Investigator.
- Technical services agreement (TSA), signed and dated.
- Signed agreement that the product will not be used before the Trial Initiation Monitoring Visit has been made and authorization obtained from the TDR Clinical Coordinator (if applicable).
- Signed FDA 1572 form (if applicable, e.g. study under Investigational New Drug - IND).

DURING THE STUDY

The trial can be initiated (begin screening and/or enrolment of trial subjects) only after the Clinical Monitor has satisfactorily conducted a Trial Initiation Monitoring Visit and the TDR Clinical Coordinator has given written authorization.

Investigator's File, Including Storage and Retention

On initiation of the study, the Investigator must prepare a file containing documents related to the trial. During the study, the Investigator is responsible for updating the File and regularly adding trial-related documents.

The Investigator should keep the File in a locked cabinet, in a secure area accessible only to the Investigator and authorized study staff. The Investigator File and associated source documents should be retained for the time agreed with TDR/sponsors. Patient identification codes should be kept for at least 15 years after completion of the trial. **Written approval from sponsors must be obtained prior to destroying records.**

The Investigator's File contains:

Administrative and Regulatory Documents

Composition of IEC/IRB.

Local regulatory requirements.

IEC/IRB and other authorities'written approval for all documents (protocol, informed consent(s) and any written information including advertisements for recruitment of study subjects).

IEC/IRB and other authorities' written approval for protocol amendments.

Correspondence with the Ethics Committee and the Authorities, including:

- Protocol submission.
- Amendment submission, if any.
- Protocol modification notification, if any.
- Interim report/written summaries of the trial, if applicable.
- Final Report/written summaries of the trial, if applicable.

Product importation authorization.

Correspondence about product importation.

For studies under IND, a copy of the completed and signed Form FDA 1572.

Investigator's and Co/Sub-investigators' C.V.s.

New Investigator and Sub-investigators' C.V.s, if appropriate.

Authorized Staff Form (ASF).

Technical Services Agreement (TSA) signed/dated by both parties.

Signed confidentiality agreement.

Signed agreement stating that products will not be used before the Trial Initiation Monitoring Visit has been made and approval from the TDR Clinical Coordinator obtained.

Copy of the insurance certificate/other insurance.

ICH GCP guideline.

TDR/TDP investigator's SOPs.

Study Archiving Form (copy).

Copy of the Investigator's interim report/written summaries of the trial to the IEC/IRB and authorities, if applicable.

Copy of the Investigator's final report/written summaries of the trial to the IEC/IRB and authorities, if applicable.

Correspondence and Monitoring

Correspondence with TDR/sponsoring agencies (including the telephone call, E-mail etc).

Notes of meetings with TDR/sponsoring agencies.

Summary list of site visits (copy).

Trial Initiation Monitoring Report (copy).

Notification by Investigator to TDR/Sponsor of serious adverse event and related reports.

Documentation of serious adverse event reporting by TDR/Sponsor to other investigators.

Correspondence about important requests.

Investigator interim report/summaries of the trial for TDR/sponsoring agencies, if applicable.

Investigator final report/summary of the trial for TDR/sponsoring agencies, if applicable.

Trial Documents

<u>General documents</u>

Investigator's brochure, with updates, if any.

Approved protocol and amendments, signed and dated by the Investigator(s) and sponsoring agencies, and new protocol amendments, if any.

Approved informed consent and any other written information including all translations, and advertisements for recruitment of study subjects.

Informed consent procedure.

Clinical Trial Final Report (if available during the Study Closeout Visit).

Data reporting

Blank CRF.

Blank SAE/UAE forms.

Blank source document if not existing on site.

Case Report Form completion procedure.

Adverse event reporting procedure.

Blank screening and enrolment log.

Product

Product certificate/batch release.

Certificate of extension of the batch expiry date, if applicable.

Dispatch notes (original) and acknowledgement of receipt (copy) (in case of new delivery).

Randomization list/envelope or acknowledgement of receipt.

Randomization list/envelope or randomization list/envelope retrieval certificate.

Code Breaking list/randomization envelope retrieval certificate.

Subject assignment list.

Product management procedure.

Product exportation/importation authorization

Product accountability log.

Product management form.

Return of unused products form, or product destruction certificate if destroyed on site.

Temperature recording log, if appropriate (especially for vaccines/biologicals).

Other products-related trial documents.

Laboratory specimens

Laboratory certification/normal ranges/update of normal values.

Reactive dispatch note and acknowledgement of receipt.

Specimen management procedures (collection, performing assay, storage, results).

Subject specimen collection log.

Shipment note, if appropriate.

Temperature recording log, if appropriate (deep frozen samples).

Record of retained laboratory specimens, if any, to document the location and identification of retained specimens if assays need to be repeated.

Other laboratory specimen related trial documents.

Trial supplies/equipment

Material/equipment dispatch note (original) and acknowledgement of receipt (copy).

Return of trial material/equipment certificate (copy).

Trial document dispatch note (original) and acknowledgement of receipt (copy) (CRFs, all trial logs).

Return of trial document certificate (copy).

Study Subjects Data and Documents

All signed and dated informed consent forms (for enrolled and screened subjects).

Study subject screening and/or enrolment log.

Study subject identification list.

Copy of all Case Report Forms (CRFs).

Copy of the Serious Adverse Event form.

Copy of documentation of CRF corrections.

All study subjects source documents including laboratory results.

Copy of all subjects CRFs retrieval certificate.

Screening and Recruitment of Study Subjects

It is important that the Investigator resolves all questions from his/her staff concerning the interpretation of inclusion/exclusion criteria.

The Investigator should be able to dedicate time to the recruitment of suitable trial subjects - the consultation time for recruitment of each subject is likely to be longer than the time required for normal consultation.

The Investigator must ensure the unbiased selection of an adequate number of suitable study subjects as defined by the Protocol.

The Investigator must allow study subjects who meet the inclusion criteria the opportunity to decide for themselves whether or not to be entered into the study.

The Investigator must document the identification of subjects who entered trial screening by completing a **subject screening/enrolment log.**

Obtain Informed Consent from All Trial Subjects

The concept of obtaining informed consent is considered to be the heart of GCP. Informed consent is the process by which a study subject voluntarily confirms his/her willingness to participate in the trial. Only study subjects who have fully understood all aspects of their participation in the trial can make proper judgements and give their consent to participate in the trial.

Information on disease prevention and transmission must be provided to the study subjects for the whole of the trial period.

Before any subject enters a trial, and before any study-related procedures begin, written informed consent must be obtained from the subject and/or his/her legally acceptable representative. In the case of a screening test which requires biological specimens to be collected prior to entering a trial, two types of consent form must be obtained, one for biological specimen collection and analysis, and the other for participation in the study after satisfactory laboratory results respecting the inclusion criteria have been obtained. Study subjects found ineligible at screening (for medical reasons) should receive supportive counselling, any necessary and available treatment and referral for continued counselling.

The Investigator can delegate the consent process to an appropriately qualified person; however, the Investigator should see the subject afterwards to ensure that the consent has been properly obtained. Verbal and written information given to the trial subject should be in simple terms and in his/her first language. Medical terms should be avoided.

The Investigator/designated person should perform informed consent procedures fully with each subject during recruitment:

- The informed consent form should be personally dated and signed by the trial subject and/or his/her legally acceptable representative as well as the Investigator/designated person responsible for the informed consent procedures.

- If the study subject and/or legally acceptable representative is (are) unable to read, an impartial witness for the Investigator should be present during the entire informed consent discussion. After oral approval by the study subject and/or legally acceptable representative, the witness must sign and personally date the informed consent form and attest that the information was accurately explained and apparently understood, and that informed consent was given freely by the subject and/or legally acceptable representative. The subject and/or

legally acceptable representative should personally sign and date the form if capable of doing so.

- The study subject and/or legally acceptable representative should be given a copy of the signed and dated informed consent form and any other written information.

- **The original signed and dated informed consent form should be kept in the Investigator's File with the study subject's data.**

Trial subjects and/or their legally acceptable representatives should be kept informed throughout the trial of any new findings or information about the tested product which might be of consequence to their participation in the trial. They should receive updates of the signed and dated consent form as well as copies of any amendments to the written information. Updates of the original signed and dated consent form should be kept in the Investigator's File.

INFORMED CONSENT PROCEDURES

- Give information regarding the trial to the subject/patient, making sure he/she understands that the study involves research.
- Give the purpose of the study, trial treatment and the probability for random assignment to each treatment.
- Explain in simple language the procedures to be followed, including invasive procedures.
- Explain the responsibilities of the subject/patient.
- List the expected risks or inconvenience to the subject/patient.
- List the expected benefits, making it clear if there is no intended clinical benefit to the subject.
- List the alternative treatment that may be available to subject.
- List the treatment available in the event of study-related injury.
- Discuss the anticipated prorated payment, if any, to the subject for participating in the trial.
- Discuss the anticipated expenses, if any, to the subject for participating in the trial.
- Let the patient know that the trial is voluntary and that he/she may refuse to participate or can withdraw from the trial at any time, without penalty or loss of benefits to which he/she is otherwise entitled.
- Let the subject/patient know that the Monitor, the Auditor, the IEC/IRB and the Regulatory Authority will be granted direct access to his/her 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.
- Assure the subject/patient that records identifying him/her will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available; and that, if the results of the trial are published, the subject's identity will remain confidential.
- Assure 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.
- Provide the name(s) of the person(s) to contact for further information regarding the trial and the rights of trial subjects, and in the event of trial-related injury.
- Explain to the subject/patient the foreseeable circumstances and/or reasons under which the his/her participation in the trial may be terminated.
- Provide the expected duration of the subject's participation in the trial.
- Provide the approximate number of study subjects involved in the trial.

(ICH GCP guidelines 4.8.10)

Protocol Compliance

Once the study has started, the Investigator must adhere to the Protocol and ensure that it is strictly followed. Deviations to protocol procedure(s) should not be made without the agreement of TDR/sponsoring agencies except when necessary to avoid immediate danger to a trial subject. Whenever the Investigator feels that changes are required, these can be suggested to, and discussed with, the Clinical Monitor/Clinical Coordinator. If changes are agreed by the Product Manager, Clinical Coordinator and Sponsor, then the change(s) can be made in form of a Protocol Amendment, signed by the Investigator and Sponsor, and appended to the original protocol.

The amendment should be described in an appropriate format, as follows:

PROTOCOL AMENDMENT FORMAT

- Protocol number and date.
- Protocol title.
- Date of approval of the amendment.
- Protocol amendment number.
- Text to be amended, with reference to the page, paragraph and line of the protocol.
- New text of the amendment.
- Signatures of the Investigator and Product Manager and/or Sponsor.

Amendments that are likely to affect the safety of a subject/patient or the conduct of a trial must be submitted in writing to the Ethics Committee. The changes cannot be implemented until the IEC/IRB has approved the amendment to the protocol. However, implementation of the change(s) may take place prior to IEC/IRB approval to avoid immediate danger(s) to the subject/patient. In this situation, the Investigator must immediately notify the Ethics Committee of the reasons for the changes and submit the proposed protocol amendment(s) to TDR/Sponsor for agreement and to IEC/IRB for approval. A copy of the IEC/IRB approval should be kept on file and a copy given to TDR/Sponsor.

In the case of minor modifications which do not have impact on the safety or burden requested of the subject/patient for participation in the trial, or which only impact on administrative activities, the modification might be considered a simple notification, which does not require formal approval.

Provide Medical Care for Trial Subjects

A qualified physician who is an investigator or sub-investigator must be responsible for all trial-related medical decisions:

- The Investigator should ensure that adequate medical care is provided to the trial subject for any adverse events, including clinically significant laboratory values related to the trial.
- The Investigator should inform the subject's primary physician about his/her participation in the trial if the subject has a primary physician and agrees that he/she be informed.

The Investigator should make a reasonable effort to ascertain the reason(s) for withdrawing prematurely from the trial, while fully respecting the subject's rights**.**

(ICH 4.3)

Randomization Procedures and Unblinding

The Investigator must follow the randomization procedures, if any. In the case of a randomized, controlled, double-blinded trial, the code is usually prepared in the form of numbered envelopes, each containing the identification of the corresponding treatment in order to enable the Investigator to open the code when needed, without identifying other patients' treatment (follow SOPs CT 06 – Breaking Code).

- Ensure that the code is broken only in accordance with the Protocol and mainly for medical reason(s).
- Premature unblinding must be reported to the Clinical Monitor immediately and should be documented in the File. The reason for premature unblinding of the investigational product should be given, e.g. due to a serious adverse event.
- At the end of the trial, the Investigator must return all the unbroken codes to the Clinical Monitor to prove that the study was blinded throughout

Safety Reporting

Trial subjects should be instructed to report any adverse event that they experience to the Investigator. Investigators should assess adverse events (AEs) at each visit. The AE is considered to be serious when it is fatal, life threatening, causes permanent disability, causes or prolongs hospitalization, or causes congenital anomaly (*see glossary*).

Terms for Causality Assessment

Not related
The experience is clearly related to other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

Unlikely

The experience was most probably produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy, and does not follow a known response pattern to the trial product.

Possible

The experience:

- follows a reasonable temporal sequence from the time of product administration,
- *and/or* follows a known response pattern to the trial product,
- *but* could have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

Probable

The experience:

- follows a reasonable temporal sequence from the time of product administration,
- *and/or* follows a known response pattern to the trial product,
- *and* could not have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy.

Most probable

The experience:

- follows a reasonable temporal sequence from the time of product administration,
- *and/or* follows a known response pattern to the trial product,
- *and* could not have been produced by other factors such as the patient's clinical state, therapeutic intervention or concomitant therapy,
- *and* either occurs immediately following trial product administration, or improves on stopping the product, or there is positive reaction at the application site.

Follow up of Adverse Event

The Investigator must ensure the safety of the trial subject. When a trial subject experiences AE(s), the following action should be taken:

- The occurrence of the AE(s) must be monitored carefully.
- The Investigator must provide the best possible care available and follow up the trial subject's adverse event until complete disappearance. Adverse event likely to be related to the product and persisting at the end of the trial, or any Serious Adverse Event occurring after termination of the trial and likely to be related to the product, should be followed up by the Investigator until its complete disappearance.
- A thorough investigation must be conducted to determine causality.
- The adverse event must be recorded in detail during the course of the trial, irrespective of the possible causal relationship with the investigational product.

Adverse Event Reporting Procedure

All adverse events occurring during the trial should be accurately reported in the appropriate section of the CRF.

Serious Adverse Event Reporting

All serious adverse events (SAEs) should be reported immediately (within 24 h) to the TDR Clinical Monitor and the TDR Clinical Coordinator and/or the TDR Product Manager, and, when appropriate, the other sponsors, by the Investigator, even if the adverse event is considered not to be related to treatment.

The Investigator must also comply with the local regulatory requirement(s) related to SAE reporting to health authorities, the regulatory authority and the IRB/IEC specified in the protocol.

The anonymity of the subjects shall be respected when forwarding all information.

(ICH 4.11)

- Notification should be made by faxing the Immediate Serious Adverse Event Report (specific form for the trial) and/or by telephone communication.
- The Investigator should send promptly, within five working days, the Serious Adverse Event Reporting Form, by fax or express mail, to the TDR Clinical Monitor and the TDR Clinical Coordinator and/or the TDR Product Manager, and when appropriate to the other sponsors.
- Any relevant information concerning the SAE that becomes available after the SAE report form has been sent (outcome, precise description of medical history, results of the investigation, copy of hospitalization report, etc.) should be forwarded as soon as possible to the TDR Clinical Monitor and the TDR Clinical Coordinator and/or the TDR Product Manager, and when appropriate, to the other sponsors. For reports of deaths, the Investigator should provide TDR/Sponsor/IRB/ IEC with any additional requested information e.g. autopsy reports and terminal medical reports.

Completion-validation of the Case Report Form

The Investigator must ensure the accuracy, legibility and completeness of data entry in the case report forms (CRFs) and in all other required report forms/logs. All CRFs and other required forms will be validated by the TDR Clinical Monitor during Monitoring Visits.

Completion

Only authorized study staff (name shown in authorized signatory form - ASF) are allowed to enter data into the CRF and other required report forms.

Ball-point pen must be used.

Capital letters must be used for all entries in the CRF.

All items must be completed by entering a number or text in the space provided.

When a subject is recruited into the trial, the initial and allocated numbers are entered in the CRF against the subject's name on the Subject Identification Code List**.** The subject's name should never be entered in the CRF to preserve confidentiality.

As far as possible, the results of assessment should be first be entered into the subject file and then transcribed into the CRF. This will allow data to be verified during the process of source data verification.

The CRF should be completed during subject participation.

Data reported on the CRFs that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

Case Report Form corrections

Only authorized study staff can make corrections.

Do not allow the Clinical Monitor/Sponsor to make correction in the CRF.

Corrections should not obscure the original entry:

- do not erase
- do not overwrite
- never use correcting fluids.

To make a correction:

- cross out the wrong entry with a single line.
- write the correct entry alongside/above/under the wrong entry.
- date the correction
- initial the correction
- explain the correction (if necessary).

Example:

~~PAZ~~ CL
PAT 9/11/98

Sex ~~1~~ 2 9/11/98
Male: 1Female:2

Date of vaccination ~~2/10/95~~
2/10/98

Site of injection: Left ☐ Right ☐
Missing data M.D. 9/11/98

Source data/documents

ICH international guidelines for Good Clinical Practice, and other applicable regulatory guidelines pertaining to clinical trials, require direct access to source data/documents for trial related monitoring, audits, IEC/IRB review, and regulatory inspection.

Source documents are all original documents, or certified copies containing data related to clinical trial activities (source data), necessary for the 'reconstruction and evaluation' of the trial.

Source Documents (non-exhaustive list)

- Informed consent.
- Subject medical file:
  - medical and medication history
  - serious adverse event
  - instrument printouts
  - traces and laboratory results
  - subjects visits dates.
- Subject identification list.
- Clinical and office charts.
- Product dispensing records, accountability.
- Laboratory notes.
- Trial agenda.
- Memoranda.

Source Data

The subject source documents should contain at least the following original data:

- Subject identification: family name, given name, date of birth, sex, and identification number in the trial.
- Protocol identification number/study reference.
- Name of product on test.
- Dates of first screening and/or enrolment in the trial.
- Dates of product administration and dosage.
- Date of assessment visit and name of individual responsible for making the assessment.
- Serious adverse event and related medication.
- Dates of laboratory sample collection.

Note
Before initiating the trial, the source document and source data will be clearly defined with the TDR Clinical Monitor. If no source document exist at the centre, one should be created.

- If the subject data are directly entered into the provided CRF, then the CRF becomes the source document. If this is the case, it should be stated clearly in the Protocol in order to avoid problems with verification of source data that may arise during audits by TDR QA personnel or inspections by regulatory authorities.
- Where a subject's diary exists, when subjects are asked to report eventual adverse event, medical consultation and medication during the trial, the diary must be validated by the Investigator and kept in the subject file.

In order to comply with Good Clinical Practice

The Investigator must guarantee that the monitor(s), the auditors and the regulatory authority(ies) will have direct access to source data/documents for verification of trial procedures and/or trial data.

The Investigator must pledge that the study subject will be informed both orally and in writing - in the consent form - that the monitor(s), auditors(s), IEC/IRB, and regulatory authority(ies) will be granted direct access to his/her original medical records, without violating the confidentiality, for verification of clinical trial procedures and/or data. By signing the informed consent form, the trial subject or legally acceptable representative is authorizing access to his/her medical records.

The Investigator is required to retain the patient identification list for a minimum of 15 years after completion or suspension of the trial (or a longer period if required by local regulations). The Investigator is required to retain all patient files and source documents for the maximum period of time permitted by the hospital, institution, or private practice, but for not less than 10 years, in order to meet international registration requirements (or

longer periods if required by local regulation). The Investigator should keep documents in a safe place and take measures to prevent accidental or premature destruction of source documents.

The Investigator should inform TDR and the Sponsor of any change of place of archiving. TDR and/or the Sponsor will inform the Investigator(s) when these documents no longer need to be retained.

Product Storage and Accountability

The Investigator may assign an appropriate person (pharmacist/nurse) to be responsible for investigational product storage and accountability at the trial site. The Investigator should ensure that the investigational product is properly received, stored and handled.

The Investigator/designated person must:

- Store the product in the condition that has been specified in writing by TDR/Sponsor and in accordance with the protocol and applicable regulatory requirement(s).
- Maintain records of the product's delivery, inventory and product return.
- Maintain up-to-date accountability on the trial 'Product Accountability log'.
- Ensure that the product is used only in accordance with the approved protocol.
- Document the use of the product by each subject, and if appropriate, check at regular intervals that each subject is following the instructions properly (compliance).
- Return any unused product to TDR/Sponsor at the end of the trial.

Premature Termination or Suspension of a Trial

In the case of premature termination/suspension of the trial for any reason, the Investigator should inform:

- the regulatory authority(ies), if applicable.
- the trial subject, assuring him/her appropriate treatment and follow-up.

If the Investigator terminates or suspends a trial without prior agreement of the Sponsor, then the Institution should:

- promptly inform and provide the sponsor and the IEC/IRB with a detailed written explanation of the termination or suspension.

If the Sponsor terminates/suspends a trial, then the Institution should:

- promptly inform and provide the IEC/IRB with detail written explanation of the termination or suspension.

If the IEC/IRB terminates or suspends its approval of a trial, then the Institution should:

- promptly notify and provide the sponsor with a detailed written explanation of the termination or suspension.

(ICH 4.12)

Progress and Final Reports

The Investigator should submit written summaries of the trial status to the IEC/IRB annually, or more frequently if requested by IEC/IRB.

The Investigator should provide written reports promptly to the Clinical Monitor/Sponsor and the IEC/IRB about any changes which significantly affect the conduct of the trial and/or increase the risk to the subjects.

The Investigator should provide the IEC/IRB, regulatory authority(ies) and TDR with a summary outcome and any reports required at the end of the trial.

References

ICH guideline for Good Clinical Practice, recommended for adoption at Step 4 of the ICH Process on 1 May 1996 by the ICH Steering Committee.

WHO guidelines for Good Clinical Practice (GCP) for trials on pharmaceutical products. World Health Organization, Geneva, 1995 (WHO Technical Report Series, No. 850: 97-137).

A practical guide to FDA GCP for investigators. Neher and Hutchinson, eds. Brookwood Medical Publications Ltd, Surrey, UK, 1993.

The trial investigator's GCP handbook: a practical guide to ICH requirements. Hutchinson, ed. Brookwood Medical Publications Ltd. Surrey, UK, 1997.

The clinical study site team: roles and Responsibilities. The Barnette International Self-Instructional Study-Site Curriculum, Barnett-Parexel, Philadelphia, USA, 1993.