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STANDARD OPERATING PROCEDURES FOR CLINICAL INVESTIGATORS

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R&D Committee

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Special Programme for Research and
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Clinical Development
Standard Operating Procedures (SOPs)

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Policy: All clinical studies supported by TDR will be carried out according to International Conference on Harmonisation (ICH)/WHO good clinical practice (GCP) 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: Phase I, II and III clinical trials conducted by the TDR unit on Product Research and Development (TDR/PRD).

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

Applicable to: TDR investigators and, where relevant, UNAIDS investigators.

GLOSSARY*

Adverse drug reaction (ADR)
In the pre-approval clinical experience with a new medicinal product or a product's new usage, 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 human subjects 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 (investigation) product, whether or not related to the medicinal (investigation) product.

Applicable regulatory requirement(s)
Any law(s) and regulation(s) addressing the conduct of clinical trials of investigation 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 were recorded, analysed and accurately reported, according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s).

*Unless otherwise stated, these definitions are derived from the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. *ICH Harmonised Tripartite Guidelines.*

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 investigation product(s), and/or to identify any adverse reactions to an investigation product(s), and/or to study the absorption, distribution, metabolism, and excretion of an investigation 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, GCP requirements, and the applicable regulatory requirements.

Confidentiality
Prevention of disclosure, to unauthorized 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 on 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; scans; X-rays; 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 in 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 (a review board or a committee, institutional, regional, national, or supranational), constituted of medical/scientific professionals and non-medical/non-scientific members, whose responsibility 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 the 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 Committee may differ among countries, but should allow the Independent Ethics Committee to act in agreement with GCP.

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 the 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.

Investigation 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 authorizations 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 non-clinical data on the investigation product(s) which is relevant to the study of the investigation 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.

Open trial
The opposite of a double-blind study, in that everyone knows what medication each patient is receiving. This may occur in a study involving either one or more than one treatment. (Definition from: Winslade J., Hutchinson D.R., 1992. *Dictionary of clinical research*. Surrey, UK: Brookwood Medical Publications Ltd.)

Opinion (in relation to an independent ethics committee)
The judgement and/or advice provided by an independent ethics committee (IEC).

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.

Protocol deviation/violation
Noncompliance with protocol requirements. This may include noncompliance with the following protocol provisions: inclusion and exclusion criteria, randomization procedures, blinding procedures, informed consent procedure, assignment of subject identification numbers, dosing and assessment schedules, reporting and procedures for adverse events, concomitant medications. (Definition from the authors)

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 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, has one or more of the following attributes:
– Results in death.
– Is life-threatening.
– Requires inpatient hospitalization or prolongation of existing hospitalization.
– Results in persistent or significant disability/incapacity.
– Is a congenital anomaly/birth defect.
– Results in an important medical event that may not be immediately life-threatening or does not directly result in death or hospitalization, but which 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, at the laboratories, and at 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 the 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, resident physicians, research fellows). See also 'investigator'.

Subject/trial subject
An individual who participates in a clinical trial, either as a recipient of the investigation 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.

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 investigation 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 (E2A)*).

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

INVESTIGATOR STANDARD OPERATING PROCEDURES

Objectives:

- To provide the investigator with general instructions 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 standard operating procedures (SOPs), International Conference on Harmonisation (ICH) good clinical practice (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.

The principal investigator is the one who will sign this document. He/she is responsible for sharing the information contained in this document with all of his/her team.

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 or 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 the Product Research and Development unit at TDR (TDR/PRD) and/or the other 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 time for informing and supervising study staff.

Review the investigator's brochure (IB) and any up to date information on the investigation product. The investigator must be familiar with the product, including preclinical toxicology, pharmacology, pharmacokinetics and up-to-date clinical data.

Review, and discuss in detail, the ICH GCP guideline, 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.

Ensure 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.

Ensure 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 (see annex 2, authorized signatory form).
- Provide his/her curriculum vitae and the curricula vitae of the sub-investigators and the head of the laboratory

Ensure that all persons assisting with the trial are adequately informed about the protocol, the investigation product(s), and their trial-related duties and functions.

Ensure 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 according to 'good clinical practice laboratory for clinical trials' (Annex A).
- Adequate facilities for retention of trial documents, ensuring confidentiality of all information about trial subjects and information supplied by TDR and/or other sponsoring agencies.

Discuss the case report form (CRF), serious adverse event (SAE) reporting form and source documents in detail with the clinical monitor (see annexes 3 and 4 for sample forms). Clearly define:

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

Arrange for 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 and/or other sponsors, the investigator must arrange for the retention of the subjects' source documents/records for the period requested by TDR and/or other sponsors and regulatory requirements.

Finalize the informed consent forms (see annex 5 for sample form) **and associated trial subject information materials (advertisements); and establish procedures regarding 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 the methods are appropriate.
- In case of the need for screening tests, including biological specimen collection, before entering a trial, two types of consent form can 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, or make any claims.
- Informed consent forms and advertisements must be submitted to TDR for review and must be included in documentation submitted to the IEC/IRB.

Ensure that the local ethics committee fulfils the ICH GCP requirements:

ICH GCP composition and operations of the Independent Ethics Committee (IEC) and Institutional Review Board (IRB)

The IEC/IRB 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.

The IEC/IRB may invite non-members 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
Guideline for GCP Part. 3.2

(See also: *Operational guidelines for ethics committees that review biomedical research.* Geneva, World Health Organization, 2000, TDR/PRD/ETHICS/2000.1)

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
Guideline for GCP Part. 3.1.2

Obtain the 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 TDR/PRD 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 and/or other sponsoring agencies on publication policy.

Submit requested documents to the clinical monitors, including:

- Signed agreement to comply with these SOPs (page 1; see also annex 6).
- Approved protocol, signed and dated.
- Approved informed consent form (see annex 5) and other subject information, and the advertisement (local language and English translation).
- Investigator's and co-investigator's curricula vitae.
- Authorized signatory form (see annex 2).
- 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 investigation new drug [IND]) (see annex 8).

DURING THE STUDY

The trial can be initiated (begin screening and/or enrolling 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 (see investigator's file form, annex 1). 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 and/or other sponsors. Patient identification codes should be kept for at least 15 years after completion of the trial. **Written approval from all sponsors must be obtained prior to destroying records.**

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 enter trial screening by completing a **subject screening/enrolment log** (see annexes 9 and 10).

Obtaining informed consent from 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 that requires the collection of biological specimens prior to entering a trial, two types of consent form can be obtained; one for biological specimen collection and analysis, and the other for participation in the study having obtained satisfactory laboratory results respecting the inclusion criteria. Study subjects found ineligible at screening (for medical reasons) should receive, if appropriate, supportive counselling, any necessary 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 (see annex 5 for a sample 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** (see annex 1) **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 the 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 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.

See ICH Guidelines
Guideline for GCP Part. 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 and/or other 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 the 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, 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 a 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 and/or other sponsors for agreement and to the IEC/IRB for approval. A copy of the IEC/IRB approval should be kept on the investigator's file and a further copy given to TDR and/or other sponsors.

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

Providing 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 abnormalities 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.

See ICH Guidelines
Guideline for GCP Part. 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 SOP 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 immediately to the clinical monitor and should be documented in the investigator's file. The reason for premature unblinding of the investigation 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 (AE) that they experience to the investigator. Investigators should assess 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

(Note: these categories and definitions are recommended by TDR; they may be modified according to the aims of the study and the nature of the trial product.)

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.

Insufficient data to assess

There is not enough clinical and/or laboratory information to suggest the relationship between the experience and the trial product.

Follow up of adverse event

The investigator must ensure the safety of the trial subject. When a trial subject experiences adverse event(s) (AEs), 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 its complete disappearance. An adverse event that is likely to be related to the product and that persists at the end of the trial, or any serious adverse event (SAE) 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 investigation product.

Adverse event reporting procedure

All adverse events occurring during the trial should be accurately reported in the appropriate annex of the case report form.

REPORTING OF SERIOUS ADVERSE EVENTS

The investigator should report all **serious adverse events** (SAEs) immediately (within 24h) to the TDR clinical monitor, the TDR clinical coordinator and/or the TDR product manager, and, when appropriate, the other sponsors, even if the adverse event is considered not to be related to the investigation product.

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 IEC/IRB.

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

See ICH Guidelines
Guideline for GCP Part. 4.11

- Notification should be made by faxing the alert form for SAE (specific form for the trial, see annex 3) and/or by telephone communication.
- The investigator should send promptly, within five working days, the serious adverse event report form (see annex 4), by fax or express mail, to the TDR clinical monitor, 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, 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 and/or other sponsors/IEC/IRB with any additional requested information, e.g. autopsy reports and terminal medical reports.

Completion and 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 (names shown in the authorized signatory form, see annex 2) are allowed to enter data into the CRF and other required report forms.

Ballpoint 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 to 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 protect confidentiality.

As far as possible, the results of assessment should 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 in the trial.

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 corrections in the CRF.

Corrections should not obscure the original entry:

- Do not erase.
- Do not overwrite.
- Never use correcting fluid.

To make a correction:

- Cross out the wrong entry with a single line.
- Write the correct entry alongside, above or under the wrong entry.
- Date the correction.
- Initial the correction.
- Explain the correction (if necessary).

Example:

~~PAZ~~
PAT *jk 29/03/02*

Sex *Male: 1 Female: 2*	~~1~~ 2	jk 29/03/99
Date of vaccination	~~2/10/95~~ 2/10/01 jk	
Site of injection:	Left ☐	Right ☐
Missing data	M.D. jk 29/03/02	

Source data and documents

ICH international guidelines for good clinical practice, and other applicable regulatory guidelines pertaining to clinical trials, require direct access to source data and 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 'reconstruction and evaluation' of the trial.

Source documents (non-exhaustive list)

Informed consent form.

Subject medical file:
- Medical and medication history.
- Outpatient or inpatient chart.
- Serious adverse event form.
- Instrument printouts.
- Traces and laboratory results.
- Subjects' visit 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: last name, first name, date of birth, sex, and identification number in the trial.
- Protocol identification number/study reference.
- Name of product on test.
- Date of first screening and/or enrolment in the trial.
- Dates of product administration and dosage.
- Dates of assessment visits and name of individual responsible for making the assessment.
- Serious adverse event(s) 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 documents exist at the centre, one should be created.

- If the subject data are directly entered into the provided CRF, then the CRF becomes a 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 quality assurance personnel or inspections by regulatory authorities.
- Where a subject's diary exists (when subjects are asked to report eventual adverse event(s), medical consultation and/or medication taken during the trial), the diary must be validated by the investigator and kept in the subject's file.

In order to comply with GCP:

The investigator must guarantee that the monitor(s), the auditors and the regulatory authority(ies) will have direct access to source data and 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 confidentiality, for the 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 for 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 for 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 the documents no longer need to be retained.

Product storage and accountability

The investigator may assign an appropriate person (pharmacist/nurse) to be responsible for investigation product storage and accountability at the trial site. The investigator should ensure that the investigation 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 and/or other sponsors and in accordance with the protocol and applicable regulatory requirement(s).
- Ensure that the storage temperature is maintained as specified in the protocol. There should be a daily temperature log.
- Maintain records of the product's delivery, inventory and 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 and/or other sponsors 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 of 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 a detailed 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.

See ICH Guidelines
Guideline for GCP Part. 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 the 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), TDR and/or other sponsors with a summary outcome and any reports required at the end of the trial.

References

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

Winslade J., Hutchinson D.R. *Dictionary of clinical research.* Surrey, UK: Brookwood Medical Publications Ltd. 1992.

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.

Operational guidelines for ethics committees that review biomedical research, Geneva, World Health Organization, 2000, TDR/PRD/ETHICS/2000.1

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.

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).

Annexes

[1] Annex A is a separate TDR annex. Annexes 1-10 form part of a global set of TDR annexes on standard operating procedures.

Annex 1

INVESTIGATOR'S FILE FORM

PROTOCOL TITLE:

Study ID No.
Sponsor:
Clinical monitor:
Tel: **Fax:** **Email:**

Investigation product:
Principal investigator:
Tel: **Fax:** **Email:**
Study site:

INVESTIGATOR'S and MONITOR'S SIGNATURE

To be signed during the closeout visit.

I hereby confirm that I have checked the content of the investigator's file against the information contained in this form and that the file is complete.

Monitor's signature: _____ **name:** _____

I hereby agree that the content of the investigator's file matches the information given on this form and I agree to retain the documents for the required period of time.

Investigator's signature: _____ **name:** _____

INVESTIGATOR'S FILE LOCATION

1. Administrative and regulatory documents:			
2. Correspondence and monitoring:			
3. Trial documents:			
a) General file:			
b) Data reporting:			
c) Products:			
d) Samples:			
e) Trial material / equipment:			
f) Study Subjects data and documents			
	YES	**NO**	**NA***
– Is/Are the trial documents storage room(s) adequate?	☐	☐	☐
– Is there a possibility of "locking" the storage place(s)?	☐	☐	☐
– Does/Do the storage place(s) have limited access?	☐	☐	☐

*NA: Not applicable

Annex 1 – *continued*

INVESTIGATOR'S FILE	On File		
The investigator's file should be checked and updated for the whole duration of the trial	**YES**	**NO**	**NA***
1. ADMINISTRATIVE AND REGULATORY DOCUMENTS			
• Composition of IEC/IRB who gave final approval	☐	☐	☐
• Local regulatory requirements	☐	☐	☐
• IEC/IRB and other authorities' written approval for all documents (protocol, informed consent and any other written information including advertisement for study subjects recruitment)	☐	☐	☐
• IEC/IRB and other authorities' written approval for protocol amendments	☐	☐	☐
• Correspondence with IEC/IRB and other authorities	☐	☐	☐
– Protocol submission	☐	☐	☐
– Amendment submission (if any)	☐	☐	☐
– Protocol modification notification (if any)	☐	☐	☐
– Interim report/written summaries of the trial	☐	☐	☐
– Documentation of serious adverse events reporting to the IEC/IRB/authorities	☐	☐	☐
– Termination of the study	☐	☐	☐
• Product importation authorization	☐	☐	☐
• Correspondence about product importation	☐	☐	☐
• For studies under IND, copy of the completed and signed form FDA 1572	☐	☐	☐
• Investigator and sub-investigators curriculum vitae (CV)	☐	☐	☐
• Copy of the up to date authorized signatory form (ASF)	☐	☐	☐
• Investigator agreement (TSA contract) signed and dated by both parties	☐	☐	☐
– Payment receipt	☐	☐	☐
• Signed confidential agreement	☐	☐	☐
• Signed agreement that products will not be used before the clinical trial initiation monitoring visit and approval from the TDR clinical coordinator	☐	☐	☐
• Copy of the insurance certificate/other insurance documents	☐	☐	☐
• ICH GCP Guideline	☐	☐	☐
• TDR/PRD investigator's SOPs	☐	☐	☐
• Other administrative and regulatory trial documents	☐	☐	☐
If yes, please specify _____			

*NA: Not applicable

Annex 1 – *continued*

INVESTIGATOR'S FILE	On File		
The investigator's file should be checked and updated for the whole duration of the trial	**YES**	**NO**	**NA***
2. CORRESPONDENCE AND MONITORING			
• Correspondence with TDR and/or other sponsoring agencies	☐	☐	☐
• Notes of meetings with TDR and/or other sponsoring agencies	☐	☐	☐
• Copy of the summary list of site visits	☐	☐	☐
• Trial initiation monitoring report	☐	☐	☐
• Notification by the investigator to TDR and/or other sponsors of serious adverse events and related reports	☐	☐	☐
• Documentation of serious adverse event reporting by TDR and/or other sponsors to other investigators	☐	☐	☐
• Correspondence about important requests	☐	☐	☐
• Investigator interim report/summaries of the trial for TDR and/or other sponsors	☐	☐	☐
3. TRIAL DOCUMENTS			
a) General documents			
• Copy of the investigator's brochure (version no.)	☐	☐	☐
• Copy of the approved protocol, signed and dated by all investigator(s) and sponsoring agencies (version no.)	☐	☐	☐
• Copy of the approved protocol amendment(s), signed and dated by all investigator(s) and sponsoring agencies (version no.)	☐	☐	☐
• One blank copy of the approved informed consent (IC) and any other written information including all translations and the advertisement for study subject recruitment	☐	☐	☐
• One blank copy of the approved revision of the informed consent (IC) and any other written information amendments including all translations and the advertisement for study subject recruitment	☐	☐	☐
• Informed consent procedure	☐	☐	☐
b) Data reporting			
• One blank copy of the CRF (version no.)	☐	☐	☐
• One blank copy of the SAE Forms (version no.)	☐	☐	☐
• One blank copy of the source document (version no.)	☐	☐	☐
• Case report form completion procedure	☐	☐	☐
• Adverse event reporting procedure	☐	☐	☐

*NA: Not applicable

Annex 1 – *continued*

INVESTIGATOR'S FILE	On File		
The investigator's file should be checked and updated for the whole duration of the trial	**YES**	**NO**	**NA***
c) Products			
• Product certificate/batch release	☐	☐	☐
• Certificate of extension of the batch expiry date	☐	☐	☐
• Product acknowledgement of receipts (copy)	☐	☐	☐
• Return of unused product form(s) (copy)	☐	☐	☐
• Product destruction certificate if destroyed on site, and TDR authorization	☐	☐	☐
• Product management procedures (administration, storage,)	☐	☐	☐
• Complete product accountability log (copy)	☐	☐	☐
• Complete product management log (copy)	☐	☐	☐
• Randomization list, envelopes and acknowledgement of receipts	☐	☐	☐
• Randomization list, envelopes and retrieval certificate	☐	☐	☐
• Copy of the temperature recording log if appropriate (especially for vaccines)	☐	☐	☐
• Other products related trial documents	☐	☐	☐
If yes, please specify _____			
d) Samples			
• Laboratory certification/normal ranges	☐	☐	☐
• Reactive acknowledgement of receipt	☐	☐	☐
• Specimen management procedures (collection, storage, results)	☐	☐	☐
• Temperature recording log if appropriate (e.g. deep freeze sample)	☐	☐	☐
• Shipment note (if appropriate)	☐	☐	☐
• Record of retained laboratory specimens (if any) To document location and identification of retained specimens if assays need to be repeated	☐	☐	☐
• Other laboratory specimen products-related trial documents	☐	☐	☐
If yes, please specify _____			

*NA: Not applicable

Annex 1 – *continued*

INVESTIGATOR'S FILE		On File		
The investigator's file should be checked and updated for the whole duration of the trial		**YES**	**NO**	**NA***
e) Trial material and equipment				
• Acknowledgement of receipt		☐	☐	☐
Specify material/equipment:		☐	☐	☐
		☐	☐	☐
		☐	☐	☐
• Return of trial material/equipment certificate (copy)		☐	☐	☐
Specify material/equipment:		☐	☐	☐
		☐	☐	☐
		☐	☐	☐
f) Study subjects' data and documents				
• Signed and dated informed consent forms (for all subjects)		☐	☐	☐
• Identification of screened and enrolled participants log		☐	☐	☐
• Identification of enrolled participants log		☐	☐	☐
• All case report forms (with copy of the CRF for terminated subjects)		☐	☐	☐
• Copy of the subject assignment list		☐	☐	☐
• Copy of the laboratory sample log		☐	☐	☐
• Copy of all serious adverse event forms		☐	☐	☐
• Documentation of CRF corrections		☐	☐	☐
• Copy of the completed CRFs retrieval certificate		☐	☐	☐
• All study subjects' source documents, including laboratory results		☐	☐	☐
COMMENTS AND ACTIONS:				

*NA: Not applicable

Annex 1 – *continued*

DOCUMENTS TO BE OBTAINED DURING THE PRE-TRIAL MONITORING VISIT

(or on agreed date _____ (*dd/mm/yy*) if not obtained during the pre-trial monitoring visit)

The investigator's file should be checked and updated for the whole duration of the trial	**YES**	**NO**	**NA***
• Composition of the Institutional Review Board/ Independent Ethics Committee	☐	☐	☐
• Local regulatory requirements	☐	☐	☐
• Form FDA 1572 For US studies (under IND) completed, signed and dated by all principal investigators who are to participate (can be sent before or after local IEC/IRB approval but a minimum of 45 days before product delivery date)	☐	☐	☐
• Investigator and sub-investigators curriculum vitae (CV)	☐	☐	☐
• Signed investigator SOP	☐	☐	☐
• Informed consent and any other written information including all translations and advertisement for study subject recruitment	☐	☐	☐
• Laboratory certification and accreditation	☐	☐	☐
• Laboratory technical procedure and normal ranges	☐	☐	☐
Other documents			
Please specify:			
•	☐	☐	☐
•	☐	☐	☐
•	☐	☐	☐
•	☐	☐	☐

COMMENTS AND ACTIONS:

*NA: Not applicable

Annex 1 – *continued*

DOCUMENTS TO BE OBTAINED DURING THE PRE-TRIAL MONITORING VISIT

(or on agreed date _____ (*dd/mm/yy*) if not obtained during the pre-trial monitoring visit)

These documents should be submitted to TDR before initiation of the trial. A copy of the approval should be given as soon as possible in order to finalize / print all trial documents and prepare product packaging.	**YES**	**NO**	**NA***
• Technical services agreement, signed and dated	☐	☐	☐
• Signed approved protocol (can be collected during the initiation visit)	☐	☐	☐
• Composition of IEC/IRB who gave approval	☐	☐	☐
• IEC/IRB and other authorities' written approval for all documents (protocol, informed consent and any other written information including advertisement for study subject recruitment)	☐	☐	☐
• Product importation authorization	☐	☐	☐
• Signed agreement that products will not be used before the written approval by the TDR Clinical Coordinator	☐	☐	☐
• Authorized signatory form (ASF) (can be collected during the initiation visit)	☐	☐	☐
Other documents			
Please specify:			
•	☐	☐	☐
•	☐	☐	☐
•	☐	☐	☐
•	☐	☐	☐

COMMENTS AND ACTIONS:

Follow up actions	**Person(s) responsible**

*NA: Not applicable

Annex 2

AUTHORIZED SIGNATORY FORM

STUDY STAFF AND AUTHORIZED STAFF FOR TRIAL DOCUMENT COMPLETION

Principal investigator: **Centre:**
Sponsor:
Title of the trial:

Investigation product:

Last name	First name	Function	Role in the trial	Authorized to fill in the trial documents?	Signature	Initials
				Yes |__| No |__| If yes, specify:	**Date of signature:** _____/_____/_____ *dd / mm / yy*	

Investigator signature and date (to be signed and dated at the end of the trial): ..... **Date**_____/_____/_____ Page Nº

Annex 2 – *continued*

Last name	First name	Function	Role in the trial	Authorized to fill in the trial documents?	Signature	Initials
				Yes |__| No |__| If yes, specify: Yes |__| No |__| If yes, specify: Yes |__| No |__| If yes, specify:	**Date of signature:** _____/_____/____ **Date of signature:** _____/_____/____ **Date of signature:** _____/_____/____	

Investigator signature and date (to be signed and dated at the end of the trial): ..... **Date**_____/_____/_____ Page Nº

Annex 2 – *continued*

Last name	First name	Function	Role in the trial	Authorized to fill in the trial documents?	Signature	Initials
				Yes |__| No |__| If yes, specify: Yes |__| No |__| If yes, specify: Yes |__| No |__| If yes, specify:	**Date of signature:** _____/_____/____ **Date of signature:** _____/_____/__ __ **Date of signature:** _____/_____/____	

Investigator signature and date (to be signed and dated at the end of the trial): ..... **Date**_____/_____/_____ Page Nº

Annex 3

SERIOUS ADVERSE EVENT ALERT FORM

General information

Date of report (*dd-mm-yy*): _____

Source – Investigator/reporter name: _____/Signature_____

Address: _____

Tel. no.: _____ Fax no.: _____ Email: _____

Subject identification (initials of last name, first name): _____

Age (in years): _____ Date of birth, if known (*dd-mm-yy*): _____

Sex: _____

Race (white; black; oriental; other): _____

Hospital number (if applicable/available): _____

Protocol title: _____

Protocol no.: _____

Centre: _____

Subject number: _____

Adverse event

Description of event: _____

Onset date (*dd-mm-yy*): _____

Outcome(s): _____

Relationship to test product by the investigator / reporting physician: _____

Treatment required: _____

Concomitant medication

Name of medication: _____

Date started (*dd-mm-yy*): _____

Date discontinued (*dd-mm-yy*): _____

Dose: _____

Reason for use: _____

Route of administration: _____

Subject history

Relevant medical history; including laboratory, X-ray or ECG data.

Annex 4

SERIOUS ADVERSE EVENT REPORT FORM

PROTOCOL TITLE:	**Protocol ID no:**	**Centre:**

Trial information

Subject's study no. ⌊_⌊_⌊_⌋	**Investigation product:**	**Report type** ⌊_⌋ **1=Initial 2=Follow-up**

Adverse event information

1. Patient initials ⌊_⌊_⌊_⌋	2. Date of birth (*dd/mm/yy*) ⌊_⌊_⌊_⌊_⌋	3. Age (year) ⌊_⌊_⌋	4. Sex ⌊_⌋ 1 = female 2 = male	5. Height (cm) ⌊_⌊_⌋	6. Weight (kg) ⌊_⌊_⌋	7. Event onset (*dd/mm/yy*) ⌊_⌊_⌊_⌋

8. Adverse event in MEDICAL TERMS:

Expedited report criteria
(Tick all appropriate to event)

9.Patient died Date:_____ (*dd/mm/yy*)	10. Life-threatening	11. Prolonged hospitalization	12. Significant disability	13. Congenital anomaly	14. Other SAE

15. Description:

Suspected trial product information

16. Suspected product:	17. Daily dose at onset of event	18. Route of administration

19. Indication for use:

20.Therapy dates (*from/to, dd/mm/yy*)

21. Therapy duration until onset (*hh/dd/mm*)

22. Did the event abate after stopping product? ⌊_⌋ 1 = No 2 = Yes 3 = NA*

Concomitant drug(s)

23. Relevant concomitant drugs and dates of administration ⌊_⌋ 1 = No 2 = Yes
If yes, then list the name(s) and details

Drug name	Dose / Route	Unit / Schedule	Date started (*dd/mm/yy*)	Continue 1 = No 2 = Yes	Date discontinued (*dd/mm/yy*)	Reason for use

*NA: Not applicable

Annex 4 – *continued*

Serious Adverse Event Report Form	**Protocol ID no:**	**Centre:**

Other relevant history, laboratory findings and action taken

24. Other relevant history:

25. Relevant test/laboratory findings

Laboratory test	Unit	Date (*dd/mm/yy*)	Value	Comments on laboratory finding

26. Action taken by investigator:

__0 = none
__1 = Trial dosage change
__3 = Trial drug discontinued
__4 = Non-drug therapy
__5 = Concomitant drug discontinued
__6 = New drug therapy added
__7 = Prolonged hospitalization

27. Outcome: ⌊__⌋

1 = Completely recovered on (dd/mm/yy) _____
2 = Recovered with sequel
3 = Condition improving
4 = Condition still unchanged
5 = Condition deteriorated
6 = Death, autopsy done (*attach summary*)
7 = Death, autopsy not done

28. Causality assessment by investigator (is there any relationship with test product?): ⌊__⌋

0 = Not related
1 = Unlikely
2 = Possible
3 = Probable
4 = Most probable
5 = Insufficient data to assess

Annex 4 – *continued*

Serious Adverse Event Report Form	**Protocol ID no:**	**Centre:**

Information source

29. Name, address, telephone and email address of the investigator

Name: _____ Profession (speciality) _____

Address: _____

_____

_____

Tel: _____ Email: _____

Signature of investigator reporting event _____

Reporting date (*dd/mm/yy*) _____

Sponsor information

30. Name and address of reporting sponsor/manufacturer:

Name:
Address:

_____

_____

_____

31. Date received by sponsor (*dd/mm/yy*)	32. Date of this report (*dd/mm/yy*)
Signature_____	_____

Annex 5

EXAMPLE OF AN INFORMED CONSENT FORM

The doctor has confirmed that you have the skin disease called salak. As you probably know, this disease is very common in this area, and is transmitted by the bite of a sandfly. If not treated, your sores will probably increase in size and cause a lot of discomfort to you, but after some time they may heal by themselves, producing deep scars. Unfortunately, the medicines available for treatment are not very good – several injections are required, and you may experience vomiting and pain at the site of injection.

The Centre for Research and Training in Skin Diseases and Leprosy is looking for better drugs that can be given by mouth, and a cream that can be applied to the sores. From the experience we have had with the treatment of other skin diseases using a medicine called fluconazole and a cream that contains a drug called ketoconazole, we believe that this may also be a good treatment for salak.

The Centre is now inviting (recruiting) around 200 patients with salak to participate in a study to see whether this new treatment can be used to cure salak. If you agree to participate in the study, we will provide you with all the explanation you need, and you will receive special medical attention from the Centre.

In order to see if this medication really is good for salak, we need to compare the results of treatment with results from another group of patients who will receive some pills and a cream which look similar but have no effect on the sores. The doctors will examine each patient several times during the course of treatment. Neither the doctors nor the patients will know which medication and cream was given.

The treatment will be provided to you at no cost. It will consist of taking one pill a day and applying the cream twice a day. Depending on the type of disease you have, the treatment may last for a period of 6 or 12 weeks. You will have to come back here 3, 6 and 12 weeks after starting treatment to collect the medication, see the doctor, and have some laboratory tests done. Each time, the laboratory technician will prepare a slide from a scraping of your sores.

The Centre will compensate you if you have to leave your work to come here, and will pay for transportation between your home and the centre. We are going to pay careful attention in case the medication has any undesired effect on you, and a blood examination will be performed when you finish the treatment after 6 weeks, or after 6 and 12 weeks if you have to be treated for 12 weeks.

Only patients in good health will be invited to participate, and an initial blood test will be carried out to check your condition of health. The total amount of blood collected for examination each time will not be more than a regular syringe (10ml) full. You should know that this new treatment may produce, in more sensitive patients, some vomiting and skin rash. If you feel any discomfort, please come to the Centre at any time. The doctor will decide if you can continue the medication or should withdraw from the trial for safety reasons and be treated with an alternative drug. The Centre will be responsible for any additional treatment you may need as a consequence of this disease or the new treatment.

Annex 5 – *continued*

You are not obliged to enter into this study, and in this case the standard injectable medication will be offered to you, consisting of ……. injections of glucantime. On the other hand, if you agree to participate, we would very much like you to follow all the medical instructions, but you should know that you can leave the study at any time without any prejudice of health care in the future for you and your family.

All the information collected from you during the trial will be kept confidential. If the results of the trial are published, your identity will remain confidential.

This study has been approved by the Ministry of Health and Tehran University, which gave the approval on …….

If you have any further questions, you can contact a member of staff at the clinic of Dr …… Address …… Phone number ……

If any relevant information which could modify your participation in the trial should become available during the course of treatment, you will be informed by the physician.

In case of any urgency regarding the treatment, you can contact Dr …… at any time through his/her private telephone number…… home address:……

CONSENT FORM

I have read the information in this form, or it has been read to me. I have had the opportunity to ask questions about it and any questions that I have asked have been answered to my satisfaction. I know that I can refuse to participate in the study without penalty or loss of benefit to which I would have been otherwise entitled, or that if I agree to participate, I can drop out at any time without losing any benefits or services to which I or my family are entitled.

I freely agree to participate in the study. After signing below, I will receive a copy of this consent form.

By signing this form I agree that the data collected about me will be accessible to the sponsor's representatives (monitors/auditors/..), the ethics committee and the regulatory authorities.

PRINT NAME OF PARTICIPANT DATE AND SIGNATURE

_____ ____/____/_____(*dd/mm/yy*)

Subject inclusion no. _____ _____

Annex 5 – *continued*

PRINT NAME OF THE WITNESS

_____

DATE AND SIGNATURE

____/____/_____ (*dd/mm/yy*)

_____

PRINT NAME OF THE WITNESS

_____

DATE AND SIGNATURE

____/____/_____ (*dd/mm/yy*)

_____

Annex 6

AGREEMENT BETWEEN WHO/TDR AND THE INVESTIGATOR ON THECONDUCT OF THE WHO/TDR PROTOCOL

The investigator hereby confirms that he/she has read and understood the trial protocol, any amendments to the trial protocol, as well as the appendices to the trial protocol, and that these documents contain all details necessary to perform the trial. Unclear passages were clarified in a discussion between TDR and the investigator.

The investigator undertakes to delegate the whole study (or parts thereof) only to qualified personnel, to inform them about the study and their duties, and to supervise the correct conduct of the study. The persons involved in the conduct of the study are named in the "authorized signatory form".

The investigator agrees that WHO/TDR and health authority representatives should have free access to all documents of the study participant, if they so wish, to ascertain that the study is conducted in accordance with the protocol. Thus the existence of the study participant and his/her informed consent should be proved. The sponsors declare that neither WHO/TDR representatives nor personnel of the health authorities will handle data, which may identify the study participant outside the investigation site.

The investigator agrees to the protocol, amendments to the protocol, and appendices I-X in all details and will perform the study in accordance with these documents, with the Declaration of Helsinki, the ICH Guidelines on Good Clinical Practice (CPMP/ICH/135/95, Topic E6), and local regulations.

The investigator will treat the conduct and the results of this study as confidential. The filled out case report forms and all other study materials remain the property of TDR. Publications will be made in mutual agreement between the investigator and TDR.

Information related to the investigation should only be transferred to third persons after written consent from WHO/TDR has been obtained. This does not apply if the information transfer is mandatory (e.g. information of patients, submission to ethical committees).

Despite the above, it is the general policy of WHO/TDR to encourage publication of results from clinical investigations. The manuscript should be based on the final report of the study. According to good scientific practice, no interim data should be published. Prior to publication the manuscript should be sent to TDR for review and comment; TDR should comment within four weeks after submission of the manuscript.

Investigator's name and signature — date (*dd/mm/yy*)

_____ ____/____/____

WHO/TDR representative's name and signature: — date (*dd/mm/yy*)

_____ ____/____/____

Annex 8

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION **STATEMENT OF INVESTIGATOR** ***(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) Part 312)*** **(See instructions on reverse side.)**	Form Approved: OMB No 0910-0014 Expiration Date: September 30, 2002 See OMB Statement on Reverse. NOTE: No investigator may participate in an investigation until he/she provides the sponsor-with a completed, signed Statement of Investigator. Form FDA 1572 (21 CFR 312.53 (c)
1. Name and address of investigator	
2. Education, training, and experience that qualifies the investigator as an expert in the clinical investigation of the drug for the use under investigation. One of the following is attached: ☐ Curriculum vitae ☐ Other statement of qualifications	
3. Name and address of any medical school, hospital, or other research facility where the clinical investigation(s) will be conducted.	
4. Name and address of any clinical laboratory facilities to be used in the study.	
5. Name and address of the institutional review board (irb) that is responsible for review and approval of the study(ies).	
6. Names of the subinvestigators (e.g., research fellows, residents, associates) who will be assisting the investigator in the conduct of the investigation(s).	
7. Name and code number, if any, of the protocol(s) in the ind for the study(ies) to be conducted by the investigator.	

Form FDA 1572 (10/99) Previous edition is obsolete Page 1 of 2

Annex 8 – *continued*

8. Attach the following clinical protocol information.

For phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.

For phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

9. Commitments:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and i will ensure that the requirements relating to obtaining informed consent in 21 CFR part 50 and institutional review board (IRB) review and approval in 21 CFR part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an irb that complies with the requirements of 21 CFR part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. i also agree to promptly report to the irb all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, i will not make any changes in the research without irb approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR part 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572 STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach a curriculum vitae or other statement of qualifications as described in section 2.
3. Attach protocol outline as described in section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an investigational new drug application (IND).

10. SIGNATURE OF INVESTIGATOR 11. Date

WARNING: a willfully false statement is a criminal offense. U.S.C. title 18, sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
5516 Nicholson Lane
Kensington, MD 20859

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Form FDA 1572 (10/99) Previous edition is obsolete Page 2 of 2

Annex 9

IDENTIFICATION OF SCREENED AND ENROLLED PARTICIPANTS

Principal investigator: **Centre:**
Sponsor:
Title of the trial:

Investigation product:

Full name and 1st 3 letters	Full first name and 1st 2 letters	Date of birth *dd/mm/yy*	Address/coordinates	Screening number Date of visit	Inclusion number Date of inclusion	Comments
..... ⌊_⌊_⌊_⌋	..... ⌊_⌊_⌋	____/____/____		⌊_⌊_⌊_⌊_⌊_⌊ **Date:** ____/____/____ *dd / mm / yy*	⌊_⌊_⌊_⌊_⌊_⌊ **Date:** ____/____/____ *dd / mm / yy*	
..... ⌊_⌊_⌊_⌋	..... ⌊_⌊_⌋	____/____/____		⌊_⌊_⌊_⌊_⌊_⌊ **Date:** ____/____/____	⌊_⌊_⌊_⌊_⌊_⌊ **Date:** ____/____/____	

Investigator signature and date (to be signed and dated when this page is completed): ..... **Date**_____/_____/_____

Annex 9 – *continued*

Full name and 1st 3 letters	Full first name and 1st 2 letters	Date of birth *dd/mm/yy*	Address/coordinates	Screening number Date of visit	Inclusion number Date of inclusion	Comments
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	|__|__|__|__|__| Date: ____/____/____	
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	|__|__|__|__|__| Date: ____/____/____	
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	|__|__|__|__|__| Date: ____/____/____	
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	|__|__|__|__|__| Date: ____/____/____	

Investigator signature and date (to be signed and dated when this page is completed): .... **Date_____/_____/_____**

Annex 9 – *continued*

Full name and 1st 3 letters	Full first name and 1st 2 letters	Date of birth *dd/mm/yy*	Address/coordinates	Screening number Date of visit	Inclusion number Date of inclusion	Comments
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	|__|__|__|__|__| Date: ____/____/____	
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	|__|__|__|__|__| Date: ____/____/____	
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	|__|__|__|__|__| Date: ____/____/____	
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	|__|__|__|__|__| Date: ____/____/____	

Investigator signature and date (to be signed and dated when this page is completed): .... **Date_____/_____/_____**

Annex 10

IDENTIFICATION OF ENROLLED PARTICIPANTS

Principal investigator: **Centre:**
Sponsor:
Title of the trial:

Investigation product:

Full name and 1st 3 letters	Full first name and 1st 2 letters	Date of birth *dd/mm/yy*	Address/coordinates	Inclusion number Date of inclusion	Comments
..... ⌊_⌊_⌊_⌋	..... ⌊_⌊_⌋	____/____/____		⌊_⌊_⌊_⌊_⌊_⌊_⌋ **Date:** ____/____/____ *dd / mm / yy*	
..... ⌊_⌊_⌊_⌋	..... ⌊_⌊_⌋	____/____/____		⌊_⌊_⌊_⌊_⌊_⌊_⌋ **Date:** ____/____/____	

Investigator signature and date (to be signed and dated when this page is completed): ..... **Date**_____/_____/_____

Annex 10 – *continued*

Full name and 1st 3 letters	Full first name and 1st 2 letters	Date of birth *dd/mm/yy*	Address/coordinates	Inclusion number Date of inclusion	Comments
....	....	____/____/____		Date: ____/____/____	
....	....	____/____/____		Date: ____/____/____	
....	....	____/____/____		Date: ____/____/____	
....	....	____/____/____		Date: ____/____/____	

Investigator signature and date (to be signed and dated when this page is completed): .... **Date_____/_____/_____**

Annex 10 – *continued*

Full name and 1st 3 letters	Full first name and 1st 2 letters	Date of birth *dd/mm/yy*	Address/coordinates	Inclusion number Date of inclusion	Comments
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	
.... |__|__|__|	.... |__|__|	____/____/____		|__|__|__|__|__| Date: ____/____/____	

Investigator signature and date (to be signed and dated when this page is completed): .... **Date_____/_____/_____**

Annex A

GCP LABORATORY FOR CLINICAL TRIALS

Introduction

In an attempt to ensure that the data generated by clinical laboratories for TDR sponsored studies comply with GCP and other regulatory requirements, and that analytical tests, reporting, interpretation and verification are accurate, a set of criteria have been defined that should be applied when considering a laboratory's participation in a study.

Scope

All hospital/clinical laboratories which are to provide support for TDR clinical trials.

The term 'clinical laboratory' refers to laboratories performing in the following specialities and related areas:

– clinical chemistry
– haematology
– histopathology
– immunology (serology)
– microbiology
– pharmacokinetics.

Clinical laboratory standards

Personnel and organization

The work is to be undertaken by experienced laboratory personnel who are qualified for the task by education and training and are professionally directed by a pathologist or clinical scientist.

The number of suitably trained staff should be sufficient to perform the necessary laboratory procedures both in normal working hours and on an on-call basis, if required. The tests and procedures performed by both technical and non-technical staff must fall within their experience and training.

Qualification and training records should exist for all personnel. Training programmes should be available to ensure that a baseline standard of ability exists and that personnel are kept up to date with new assay techniques and equipment.

Quality control/assurance

Personnel within the laboratory who implement and monitor internal and external quality control/proficiency tests should have the authority to halt the release of results which do not meet the appropriate quality control standards.

All laboratories should have effective internal quality control and participate in proficiency test schemes, or hold accreditation by an appropriate professional or regulatory body where such a scheme is available.

Internal quality control measures should be implemented for all assays detailed in the clinical investigation protocol.

The laboratory should participate in at least one external quality control or proficiency testing scheme for all assays detailed in the clinical investigation protocol (where such schemes exist).

Laboratories should have validated and updated laboratory normal ranges or normal values.

Validations

The laboratories should follow the principles of good laboratory practice. All procedures should be designed to detect results that do not conform with the stipulated quality specifications. Samples should be stable throughout all analytical assessments. Each laboratory test must be validated to establish its performance characteristics in terms of frequency of malfunction, sensitivity, specificity, precision and reliability. Calibration and validation of methodologies should be maintained.

Facilities/equipment/maintenance

Provision should be made to restrict access to paper, magnetic and optical storage media.

Controls should be in place to ensure that faults in freezers/refrigerators that house temperature-sensitive clinical investigation samples and analytical reagents are rapidly identified and resolved.

Where a risk of contamination of TDR clinical investigation samples exists, suitable barrier measures should be in place to reduce the possibility of contamination.

Assay equipment should be suitable for those assays defined in the clinical investigation protocol.

Where methodology is specified by TDR/the sponsor, the laboratory should have sufficient capability, in terms of both personnel and facilities, for the execution of such assays.

The sample processing capability of the laboratory should be sufficient to ensure timely evaluation and reporting of results.

Apparatus should be periodically inspected, cleaned, maintained and calibrated according to the written procedures and manufacturers' recommendations. Calibration and maintenance of records should be routine.

Maintenance contracts should exist for all items of equipment for which user maintenance is not possible e.g. automated analysers or robotic equipment. Maintenance records should be retained.

Where the study protocol requires laboratory analyses to be performed frequently for **safety** purposes, arrangements should be in place for back-up assay facilities in the event of power or equipment failure.

Laboratory reagents must be appropriately labelled with expiry date, preparation date, identity and concentration. They must be stored under the appropriate conditions.

Standard operating procedures (SOPs)

The laboratory should have pre-established systematic procedures for sample collection, transport, preparation, identification, analysis, documentation and verification of laboratory data. There should be readily available written procedures covering, as a minimum requirement, the following key aspects of operations:

– cleaning, maintenance and calibration of laboratory equipment
– operation of laboratory equipment
– analytical methods
– data transformation techniques.

Procedures must be appropriate for their intended use, and compatible with the nature of the samples to be tested. Methods should be written, in the form of a manual or SOP, in a clear and unambiguous manner, such that an experienced analyst who is unfamiliar with the method is able to use the procedure and interpret the results. SOPs should follow a pre-established format which includes the following:

– title
– date of authorisations
– references
– basic principles
– apparatus and reagents
– procedural details
– safety precautions
– calculations and statistics
– quality assurance.

A policy should be in place defining the procedure to be followed in the event of abnormal results.

Sample handling/storage

Each clinical sample must be accompanied by appropriate documentation to clearly indicate from whom the sample was taken and what analyses should be performed on it.

Each sample received by the laboratory should be coded with a unique accession number that permits tracking of the sample through receipt, analysis and reporting.

Where required by the protocol, there should be sufficient refrigerators/freezers to ensure the safe storage of clinical investigation samples.

Reporting of results

A mechanism must be in place to ensure that all investigation personnel are informed promptly of the results of laboratory analyses. If a time period for the reporting of laboratory analyses is specified or implied by the study protocol, then procedures must be in operation to ensure compliance with these reporting requirements.

A procedure should be in place to alert investigation staff to any revision to laboratory normal ranges.

Manual or electronic checks must be in place to ensure that only technically valid results are released. All results must be checked/approved prior to release. In addition, any abnormal results must be reviewed by senior laboratory personnel prior to issue.

Source documentation requirements

Raw laboratory data, analysis request forms and reports of results must be retained in a manner consistent with the requirements of the study protocol.

Procedures should be in place to routinely back up data held in electronic form.

References

Organisation for Economic Co-operation and Development. OECD Principles of Good Laboratory Practice. *Environment Monograph,* 7: 45-48, 1992.

Susan Makkink. How to select a GCP compliant central laboratory. *Good Clinical Practice Journal,* 6 (1): 27-30, 1999.

Research and Development Unit, TDR

Clinical Development

Standard Operating Procedures (SOPs)

SOP title:	Breaking Code		
SOP No.:	CT 06		
SOP author(s):	Juntra Karbwang & Claire Pattou		
SOP approbation:			
SOP status:	Final	Revision due date:	September 2004
Status date:	10 April 2002		
Implementation date:	_____		
Document received by:	_____	_____ Date	_____ Signature

Policy: Medical need: Individual randomization codes must only be broken and revealed to investigators (or others responsible for managing the subject/patient) when identification of the study medication is required in order to manage a subject/ patient, i.e. when a medical emergency or serious medical condition has arisen.

Regulatory need.

Randomization code-breaks must be fully documented.

The clinical monitor will ensure that a system is in place to facilitate out-of-hours emergency contact between investigators and the clinical monitor/clinical co-ordinator/product manager.

Scope: All Phase I, II and III trials which are blinded to investigators.

Individual randomization codes, where the blind is to be broken on an individual basis due to a medical emergency/severe adverse event (SAE).

Applicable to: The clinical monitor/clinical co-ordinator/product manager, if contacted regarding the breaking of individual randomization codes.

Objective: To define the circumstances under which individual patient/subject randomization codes may be broken in the case of a medical emergency during a clinical study, and how to document this event.

Conducting the code-break procedures: Explain the code-break procedure to the staff at the study site during the study initiation visit:

- Make sure that the investigator knows that the code break will be performed only in the event of a medical emergency, when the physician in charge of a subject/patient feels that the patient cannot be treated adequately unless the identity of the investigation product is known or if the information is essential for further management of the other subjects/patients already included or to be included.
- It should be emphasized to the investigator that he/she must make every effort to contact the TDR clinical monitor prior to breaking the code. If this is not possible, and the situation is an emergency, the investigator may break the code and contact the TDR clinical monitor as soon as possible thereafter.

Following a request from the investigator or other physician in charge of the subject/patient, and when a set of individual codes is held at the sponsor's office, the individual code for the subject/patient in question should be broken and the investigator/physician informed of the medication.

Whoever is responsible for breaking the code will need to document the following:

- Protocol number.
- Study number.
- Subject/patient number.
- Date of code break.
- Identification and signature of person breaking the code.
- Identification of person(s) requesting the code break.
- Reason(s) for breaking the code.
- Investigator's signature.

The information should be recorded on an emergency code-break form (see Annex 26 for sample form) and directly on the case report form (CRF).

If the code is concealed in an envelope which is then opened, the person who broke the code must sign and date the envelope. If opened at the study site, the envelope will be returned to TDR/sponsor (after collection by the clinical monitor at the next site visit).

Provide all information regarding this event to the clinical co-ordinator/product manager.

If the randomization code was not declared in the investigator's initial serious adverse experience report, update the serious adverse experience worksheet once the blind is broken for the study.

Ensure that the clinical data management personnel are informed.

Ensure that all documentation relating to the code break is included in the study file.

TDR/PRD

TDR – Product Research and Development Unit – Clinical Development
SOP CT 06, 10 April 2002

EMERGENCY CODE BREAK FORM

PROTOCOL TITLE:

Study ID No:
Study Site:

Subject's Study No: .....
Subject's Initials: .....

Date of randomisation break: .....

Name/function of the person who break the code: .....

Name/function of the person requesting the code break: .....

REASON FOR BREAKING THE CODE

_____

_____

_____

_____

Signature of person breaking the code
Investigator's signature
(if not the investigator)

Date _____ Date _____

Note: *if available, the opened, signed and dated code envelope must be attached to this form.*

Manual for Completing the SAE Reporting Form

All Reports of Serious Adverse Events (SAEs) must be expedited and sent to the Clinical Monitor or Sponsor within 24 hours of identification of SAE occurrence

A serious adverse event is any untoward medical occurrence that, at any dose, has one or more of the following:

- results in death: **all** deaths on study defined as while on protocol therapy or within 30 days of the last dose. Deaths occurring later need not be reported unless they are a result of an event that started within the time frame covered by on study definition
- is life-threatening: it is defined as an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect?
- results in important medical events that may not be immediately life threatening or does not directly result in death or hospitalization but may jeopardize the patient or may require intervention to prevent on of the other outcomes listed above.

ICH Guideline – Clinical Safety Data Management (E2A)

Responsibility of Investigator when SAE Occurs

- All serious adverse events (SAEs) should be reported immediately by phone, fax (using form provided, (see Annex 3, page 236). The immediate report should be promptly followed by a detailed, written report (see Annex 4, page 237). The investigator should follow the AE report instructions agreed with TDR/sponsor and within time periods stated in the protocol. The investigator should also comply with the local regulatory requirement(s) related to the AE reporting to health authorities; regulatory authority and the IRB/IEC specified in the protocol.

- For reported deaths, the investigator should provide TDR/sponsor/IRB/IEC with any additional requested information, e.g. autopsy reports and terminal medical reports.

Procedures to Complete the SAE Form

- The SAE form must be completed in English.
- It should be legible, preferably typewritten
- Use black pen, if handwritten
- Avoid abbreviations
- Avoid leaving blank fields, use "N/A" instead
- Make sure that the information provided on the SAE form is consistent with the data recorded in the CRF and the source data.

Trial Information

Patient No.

- Enter the same number as on the CRF
- In the case of an SAE in an open trial: enter the patient number (entry number)
- If the SAE occurred **after randomization**: enter the randomization number, not the patient number. The randomization number is important for the code breaking.

Trial Product Name

- Enter the TDR/sponsor trial product under investigation in this trial. Not the suspected product, placebo, or comparator administered to the patient (see field no. 15)

Report type

- Immediate: detailed immediate data on this SAE is reported to TDR/sponsor after initial report of SAE
- Follow-up: this should be additional information that pertains to a specific SAE that has already been reported as immediate.

Adverse Event Information

1. **Patient initials**
   - Enter the initials of the patient. These initials must be the same as those on the CRF.

2. **Date of Birth**
   - Enter full birth date using digits (dd-mm-yy) as on CRF

3. **Age**
   - Enter patient's age in years at the time of the SAE

4. **Sex**
   - Provide correspond number in the space provided: 1 = female 2 = male

5. **Height**
   - Enter the height of the patient in centimetres in the space provided

6. **Weight**
   - Enter the weight of the patient at the time of onset of SAE, in kilograms

7. **Event onset**
   - Enter the date (dd-mm-yy) when the first sign/symptom of the SAE occurred

8. **Adverse events in medical terms**
   - Use precise medical terminology. This is important in order to allow a correct coding of the term(s) when data are entered into the data base
   - Enter the diagnosis whenever possible. If the diagnosis is not yet known, enter signs and symptoms that fulfil one of the SAE criteria. However, in such cases the diagnosis should be provided on a follow-up report.
   - Enter all information pertaining to aetiologies, course and treatment of SAE, which cannot be entered elsewhere on the form.
   - Do not use the term 'death', as this is the outcome of SAE. Use the medical term of the AE which resulted in death.

Expedited Report Criteria

Expedited Report Criteria (item 9 to 13)
- Tick the appropriate box in front of the number

9. **Death**, enter the date (dd-mm-yy) the patient died

10. **Life threatening**
    - An event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe

11. **Involved or prolonged inpatient hospitalization**

- If the patient had to be admitted to the hospital as inpatient or hospitalization of the patient had to be extended as a result of this AE, specify the reason for hospitalization in field no. 14 under 'Description'. If the patient was treated as an emergency case but not admitted as an inpatient, it is not considered as hospitalization. In this case, it should be considered under field no. 8.

12. **Significant disability**

- If it involved permanent and/or persistent or severe disability, which disrupts the patient's ability to carry out normal life functions. When an AE which results in 'an irreversible structural or functional impairment', specify disability (e.g. deafness) under field no. 14, 'Description'.

13. **Congenital anomaly/birth defect**

- Any anatomical malformation occurring in the offspring of a trial patient.

14. **Other SAE**

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

15. **Description of SAE**

- Use this field for a description of the SAE (nature, severity, course etc.) and for all additional associated sign/symptoms
- Enter all information pertaining to aetiologies, course, and treatment of the SAE, which cannot be entered elsewhere on the form.

Suspected Trial Product Information

16**. Suspected product**

- **Trial treatment not known/blinded:** enter 'code not open'
- **Trial treatment known:** if the code has been broken or if the patient received an open-label treatment, enter the respective trial treatment administered last before the time the SAE occurred *i.e. trial product, placebo, comparator*.

17. **Daily dose at onset of event**

- For open-label treatment or if the code has been broken, enter the daily dose of the suspected trial product the patient received last before the onset of the SAE

- Enter the total daily dose (value, unit) the patient received, regardless of schedule.

18. **Route of administration**
    - Enter the route by which the trial product was administered, *e.g. oral, intramuscular, subcutaneous, etc.*

19. **Indication for use**
    - This refers to the indication(s) for which the product is being studied in the trial or the indication for which the named patient treatment is being administered.

20. **Therapy dates (from/to)**
    - Start date: enter the date (dd-mm-yy) the patient started trial treatment with the suspected product
    - End date: enter the last date (dd-mm-yy) the patient received trial treatment with the suspected product
    - If the drug is not withdrawn: enter 'X' instead of end date.

21. **Therapy duration until onset**
    - If the SAE occurred during the treatment period of the trial, enter the time duration between first dose administered the product and onset of SAE. Indicate the unit in hours-days-months (h/d/m)
    - If the SAE occurred after the treatment period: enter 'NA' as the patient has not been under trial treatment at the onset of the event
    - If the SAE occurred during the run-in period, wash-out period or post-trial follow-up period, enter 'NA' as the patient has not been under trial treatment at the onset of the event.

22. **Did the event abate after stopping product?**
    - Write 0 for 'No' if SAE did not improve after stopping the trial product
    - Write 1 for 'Yes' if SAE improves spontaneously (i.e. without treatment) after stopping the trial product
    - If the treatment has not been withdrawn or if information is not yet available, write 3 for 'N/A'.

23. **Relevant concomitant drugs and dates of administration**
    - Indicate whether or not there is information on any relevant concomitant drugs taken by the patient
    - Enter only concomitant drugs which may have contributed to the occurrence and the course of the SAE. Provide detailed information of use.

Other relevant history, laboratory findings and action taken

24. **Other relevant history**
    - Enter patient's medical history and present condition which may have contributed to the occurrence or the course of the SAE.

25. **Relevant test/laboratory findings**
    - Enter only those test/lab findings that would help in the diagnosis, or describe the SAE, *e.g. increase in liver enzyme, etc.*
    - Enter details of laboratory tests and findings.

26. **Action taken by Investigator**
    - Tick one or more action(s) taken regarding the SAE.

27. **Outcome**
    - Provide numbers that correspond with the outcome. If the patient completely recovered, enter the date of complete recovery in the space provided.

28. **Causality assessment by Investigator**

    Provide causality assessment:

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

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

- **Most probable:** The event:
  - follows a reasonable temporal sequence from the time of product administration
  - ***and/or*** follows a known response pattern to the trial product
  - ***and*** could 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.

- **Insufficient data to assess:** There is not enough clinical and/or laboratory information to suggest the relationship of the event to the trial product.

Information Source

29. **Name, address, telephone and e-mail address of investigator reporting the SAE**
    - Enter the name, address, telephone number and e-mail address (if available) of the investigator who reports the SAE to Clinical Monitor/Clinical Co-ordinator/Product Manager/Sponsor
    - Sign and date (dd-mm-yy) of reporting.

Sponsor Information

30. **Name and address of reporting Sponsor/manufacturer**
    - Enter the name of the Clinical monitor/Product Manager/Sponsor who receives the SAE form from the investigator reporting the SAE.

31. **Date received by sponsor**
    - Enter the date (dd-mm-yy) the particular SAE report is received by TDR/Sponsor
    - If SAE was detected through reviewing the patient's CRF enter the date detection here.

32. **Date of this report**
    - This refers to the date (dd-mm-yy) on which this SAE case is released for local submission to the Health Authorities. The date has to be updated for each follow-up report.

TDR/PRD

TDR – Product Research and Development Unit – Clinical Development, June 2001

GCP Laboratory for Clinical Trials

Introduction

In an attempt to ensure that the data generated by clinical laboratories for TDR sponsored studies comply with GCP and other regulatory requirements, and that analytical tests, reporting, interpretation and verification are accurate, a set of criteria have been defined that should be applied when considering a laboratory's participation in a study.

Scope

All hospital and clinical laboratories providing support for TDR clinical trials.

The term 'clinical laboratory' refers to laboratories performing the following specialities and related areas:

- clinical chemistry
- haematology
- histopathology
- immunology (serology)
- microbiology
- pharmacokinetics.

Clinical laboratory standards

Personnel and organization

The work should be undertaken by experienced laboratory personnel who are qualified for the task by education and training, and who are professionally directed by a pathologist or clinical scientist.

The number of suitably trained staff should be sufficient to perform the necessary laboratory procedures both in normal working hours and on an on-call basis, if required. The tests and procedures performed by both technical and non-technical staff must fall within their experience and training.

Qualification and training records should exist for all personnel. Training programmes should be available to ensure that a baseline standard of ability exists and that personnel are kept up to date with new assay techniques and equipment.

Quality control assurance

Personnel within the laboratory who implement and monitor internal and external quality control and proficiency tests should have the authority to halt the release of results that do not meet the appropriate quality control standards.

All laboratories should have effective internal quality control and participate in proficiency test schemes, or hold accreditation by an appropriate professional or regulatory body where such a scheme is available.

Internal quality control measures should be implemented for all assays detailed in the clinical investigation protocol.

The laboratory should participate in at least one external quality control or proficiency testing scheme for all assays detailed in the clinical investigation protocol (where such schemes exist).

Laboratories should have validated and updated laboratory normal ranges or normal values.

Validations

The laboratories should follow the principles of good laboratory practice. All procedures should be designed to detect results that do not conform with the stipulated quality specifications. Samples should be stable throughout all analytical assessments. Each laboratory test must be validated to establish its performance characteristics in terms of frequency of malfunction, sensitivity, specificity, precision and reliability. Calibration and validation of methodologies should be maintained.

Facilities/equipment/maintenance

Provision should be made to restrict access to paper, magnetic and optical storage media.

Controls should be in place to ensure that faults in freezers and refrigerators housing temperature-sensitive clinical investigation samples and analytical reagents are rapidly identified and resolved.

Where a risk of sample contamination exists, suitable barrier measures should be in place to reduce the possibility of contamination.

Assay equipment should be suitable for those assays defined in the clinical investigation protocol.

Where methodology is specified by TDR and/or other sponsors, the laboratory should have sufficient capability, in terms of both personnel and facilities, for the execution of such assays.

The sample processing capability of the laboratory should be sufficient to ensure timely evaluation and reporting of results.

Apparatus should be periodically inspected, cleaned, maintained and calibrated according to the written procedures and manufacturers' recommendations. Calibration and maintenance of records should be routine.

Maintenance contracts should exist for all items of equipment for which user maintenance is not possible, e.g. automated analysers or robotic equipment. Maintenance records should be retained.

Where the study protocol requires laboratory analyses to be performed frequently for **safety** purposes, arrangements should be in place for back-up assay facilities in the event of power or equipment failure.

Laboratory reagents must be appropriately labelled with expiry date, preparation date, identity and concentration. They must be stored under the appropriate conditions.

Standard operating procedures (SOPs)

The laboratory should have pre-established systematic procedures for sample collection, transport, preparation, identification, analysis, documentation and verification of laboratory data. There should be readily available written procedures covering, as a minimum requirement, the following key aspects of operations:

- cleaning, maintenance and calibration of laboratory equipment
- operation of laboratory equipment
- analytical methods
- data transformation techniques.

Procedures must be appropriate for their intended use, and be compatible with the nature of the samples to be tested. Methods should be written, in the form of a manual or SOP, in a clear and unambiguous manner, such that an experienced analyst who is unfamiliar with the method is able to use the procedure and interpret the results. SOPs should follow a pre-established format which includes the following:

- title
- date of authorizations
- references
- basic principles
- apparatus and reagents
- procedural details
- safety precautions
- calculations and statistics
- quality assurance.

A policy should be in place defining the procedure to be followed in the event of abnormal results.

Sample handling/storage

Each clinical sample must be accompanied by appropriate documentation to clearly indicate from whom the sample was taken and what analyses should be performed on it.

Each sample received by the laboratory should be coded with a unique accession number that permits tracking of the sample through receipt, analysis and reporting.

Where required by the protocol, there should be sufficient refrigerators and freezers to ensure the safe storage of clinical investigation samples.

Reporting of results

A mechanism must be in place to ensure that all investigation personnel are informed promptly of the results of laboratory analyses. If a time period for the reporting of laboratory analyses is specified or implied by the study protocol, then procedures must be in operation to ensure compliance with these reporting requirements.

A procedure should be in place to alert investigation staff to any revision to laboratory normal ranges.

Manual or electronic checks must be in place to ensure that only technically valid results are released. All results must be checked and approved prior to release. In addition, any abnormal results must be reviewed by senior laboratory personnel prior to issue.

Source documentation requirements

Raw laboratory data, analysis request forms and reports of results must be retained in a manner consistent with the requirements of the study protocol.

Procedures should be in place to routinely back up data held in electronic form.

References

Organization for Economic Co-operation and Development. OECD Principles of Good Laboratory Practice. *Environment Monograph*, 7: 45-48, 1992.

Susan Makkink. How to select a GCP compliant central laboratory. *Good Clinical Practice Journal*, 6 (1): 27-30, 1999.

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