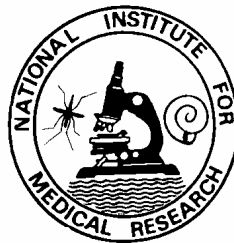


NATIONAL INSTITUTE OF MEDICAL RESEARCH



STANDARD OPERATING PROCEDURES
FOR
THE NATIONAL HEALTH RESEARCH ETHICS REVIEW COMMITTEE

2007

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FORMS FOR STANDARD OPERATING PROCEDURES

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ABBREVIATIONS

NIMR	National Institute for Medical Research
UN	United Nations
TANHER FORUM	Tanzania National Health Research Forum
NHRERC	National Health Research Ethics Review Committee
SOPs	Standard Operating Procedures
WHO	World Health Organization
DSMB	Data and Safety Monitoring Board
FDA	Food and Drug Authority
IRB	Institutional Review Board
NSR	Non-Significant Risk Device
PI	Principal Investigator
CIOMS	Council for International Organization of Medical Sciences
ICH	International Conference on Harmonization

FOREWORD

It is with great pleasure and satisfaction that we have established the Standard Operating procedures (SOPs) for the National Health Research Ethics Review Committee (NHRERC), a Sub-Committee of the Medical Research Coordinating Committee, the National Institute for medical Research, Tanzania.

The SOPs, by definition is a detailed written instruction to achieve uniformity and maintain standards in the performance of a specific function. In this particular case, these instructions have detailed procedures guiding the establishment of Institutional Health Research Review Committees or Boards (IRBs) and their basic functions. The document outlines procedures for: structuring and administering IRBs, and reviewing as well as monitoring research during the phase of implementation.

The development of the SOPs document began in 2004 at NIMR, just two years after the formation of NHRERC. Throughout the years, the document has been enriched by collective efforts from members of the NHRERC, members of health research institutions in Tanzania including academic and medical training institutions and other stakeholders.

The final developmental stages of this document included a National Consensus workshop organized by the Tanzania National Health Research Forum (TANHER Forum) in collaboration with NIMR in May 2005. The workshop participants included stakeholders from health research institutions in the country. This was followed by a Regional, East African Stakeholders Workshop organized by the African Malaria Network Trust (AMANET) in September 2005.

The Medical Research Coordinating Committee of NIMR during its 81st meeting held on 1st March 2006, at NIMR Headquarters, Dar es Salaam, approved the SOPs for use.

I wish to thank all partner Institutions and Stakeholders for their valuable contributions and collaboration without which this great achievement would not have been realized. I hope that as owners of the SOPs and implementers of research, we shall abide by the procedures we set for ourselves.

As a living document, the SOPs will be reviewed from time to time in the future and NIMR will endeavor to ensure the full participation of all stakeholders.

Dr Andrew Y Kitua
Chairman, MRCC
NIMR Director General

INTRODUCTION

Health research in Tanzania like in all developing countries and in particular Africa is increasing because of many discoveries that are being made in biomedical sciences and the new diagnostics procedure, drugs, vaccines and devices that need testing. However, much as this is a positive development, the high disease burden, ignorance, poverty and weak regulatory organs and ethical review frameworks, exposes people in these regions to abuse of human rights by researchers who may not be inclined to observing research ethics stipulated in the international guidelines. The situation is compounded more by limited awareness and knowledge among local health research scientists about existence of international guidelines or even understanding them for those who have ever come across or heard about them. It is against this background that the establishment of a National and Institutional Health Research Ethics Review Boards becomes necessary.

Health research international guidelines such as the Declaration of Helsinki, CIOMS, International Ethical Guidelines for Biomedical Research Involving Human Subjects, WHO and ICH Guidelines for Good Clinical Practices outline ethical and scientific standards for biomedical research. Compliance with these guidelines helps to ensure that the dignity, rights, safety, and well being for research participants are promoted and that the results of the investigations are credible.

All international guidelines require ethical and scientific review of biomedical research alongside informed consent and the appropriate protection of those unable to consent as essential measures to protect the individual persons and communities who participate in biomedical research and related fields involving human participants.

The purpose of this document is to outline the process for authorizing, reviewing, archiving, and amending SOPs for the NHRERC at NIMR. The procedures shall be written in immediate future tense using active verbs.

They shall be written so that a reader unfamiliar with the procedures would be able to duplicate the procedures accurately in proper time sequence by following the document.

THE TANZANIA HEALTH RESEARCH FORUM

The Tanzania National Health Research Forum (TANHER-FORUM) was established on 26th February 1999 as a way of implementing the recommendations of the Global Forum for Health Research. The Forum is an independent body supporting NIMR in its role of health research coordination and review without actually taking these functions away from NIMR.

The Forum ensures harmonization of guidelines for the conduct of health research in Tanzania and the review process including the health research review guidelines. In addition, the Forum works to enhance the translation of health research results into action.

TANHER-FORUM has two committees, the National Health Research Ethics Committee and the National Health Research Coordination Committee and NIMR is currently serving as the Secretariat to the Forum.

The role of the NHREC

The National Health Research Ethics Review Committee (NHRERC) was established in 2002 with the principal role of protecting research participants while taking into account the interests of the researcher and the research. Protection of research participants is based on three principles namely: respect of autonomy, beneficence and justice. The principle role of NHRERC is to analyse and assess the risk/benefits of research for the protection of research participants.

Mission statement

As a Committee set up to review, evaluate and decide on the ethical merits of the research protocols, the mission of the Committee is to ensure and guarantee the rights, dignity, safety and protection of all individuals and communities who participate in research activities. The committee is also committed to ensuring scientific merits of the research and protecting the rights of the researchers as well.

Functions of the NHREC

- Receiving reports for scientific review
- Receiving ethics contents of the proposals and give overall statement
- Advising the Medical Research Coordinating Committee on all matters of ethics in the research proposals
- Giving general advice to MRCC on any other matters related to clearance of the research proposals
- Develop and establish monitoring procedures for research
- Devise mechanisms for auditing health research

THE STANDARD OPERATING PROCEDURES (SOPs)

Under this part of the document the Standard Operating Procedures for health research ethics review have been articulated to give guidance to health research review committees in the protection and furtherance of the rights of research participants while taking cognizant of the key roles of relevant health research in improving the welfare of humankind.

SOP # 01: CONSTITUTING THE HEALTH RESEARCH ETHICS REVIEW COMMITTEE

This SOP describes procedures for constituting the NHRERC, its composition, terms of reference and ethical basis. It also gives membership conditions of appointment, resignation or disqualification and replacement.

Composition

The Committee consists of 15 members who collectively have the qualification and experience to review and evaluate the science, medical aspect, and ethics of research protocols. It is composed of both scientists and non-scientists with varying background to promote complete and adequate review of research protocols commonly received by NIMR. At least one member of the committee is a health scientist, one non health scientist (lawyer/social scientist) and one a community representative and ensures gender equity.

Terms of reference

The Committee operates within specified Standard Operating Procedure (SOPs), which are detailed, written instructions presented in a format that describes all activities and actions to be undertaken by an organization for achieving uniformity of the performance of specific functions. The aim of the SOPs and their accompanying checklists and forms is to simplify the organization and documentation of operation, whilst maintaining high standard of performance. They facilitate and support ethical review by improving the standard and uniformity of the decision-making and assure and gain the confidence of the public in the working of NHRERC.

SOPs promote transparency and efficiency in communication and operations of RECs. The following are terms of reference under which the Committee operates:

1. Review health research protocols submitted to it within a reasonable time and document its views in writing to the applicant(s), clearly identifying the study, the documents reviewed and the dates for the following:
 - i. Approval for commencement of the study
 - ii. Modifications required prior to its approval
 - iii. Disapproval
 - iv. Termination/suspension of any prior approval
2. Safeguard the dignity, rights, safety and well being of all study participants and communities. Special attention shall be paid to studies that may include vulnerable participants.
3. May request the investigator(s) to enlighten them on any aspect of the study but the researcher/investigator shall not participate in the deliberations of the Committee or in the voting of the Committee on any issue.
4. Obtain the following documents from investigator(s):
 - i. Summary of Protocol
 - ii. Study protocol(s) and/or amendment(s)
 - iii. Written informed consent forms and consent form updates that the investigator(s) proposes for use in the study
 - iv. Participant recruitment procedures
 - v. Written information to be provided to participants
 - vi. Available safety information
 - vii. Information about risks and benefits available to participants
 - viii. Research budget
 - ix. Curriculum vitae and composition of the research team
 - x. For research with external collaborators /investigators other conditions apply.

5. Consider the suitability of the investigator(s) for the proposed study by considering relevant qualification, training and experience, as documented by current curriculum vitae and/or by any other relevant documentation:
 - a) May request more information than is given when in the judgment of the additional information would assist them in taking a decision on the protocol or provide protection of the rights, safety and/or well-being of participants researchers.
 - b) Review both the amount and type of benefit to participants to ensure that such benefits do not present problems of coercion or undue influence on the study participants.
 - c) Concerns itself strictly on the scientific and ethical merits of submitted protocols for approval; executing the tasks free from bias or influence and not involving itself in the day to day administration, policy and other issues of NIMR.
 - d) Assists investigator(s) in the submission process. In this regard, the following items shall be made available to them by the Committee Secretariat:
 - i. Protocol submission forms and all relevant guidelines as stipulated in this Standard Operating Procedures (SOPs)
 - ii. Meeting almanac
 - iii. Committee membership list
 - iv. The National Research Guidelines
6. The Committee members and consultant reviewers shall be provided by the Committee Secretariat with all relevant SOPs to guide them in the review process of the protocols given to them.

Ethical and scientific basis

1. The Committee recognizes that the protocols it approves may also be approved by institutional review committees/community committees prior to submission to this Committee or their implementation in specific localities.
2. In evaluating protocols and ethical issues, the Committee is aware of the diversity of laws, cultures and practices governing research and medical practices in various communities in Tanzania
3. It attempts to inform itself where possible of requirements and conditions of the various localities where proposed research is being considered.
4. The Committee seeks to be informed, as appropriate, by institutional/community committees and researchers of the impact of the research it has approved
5. The Committee guided in its reflections, advices, and decisions by the ethical principles expressed in the *Declaration of Helsinki (1964 and as subsequent revisions)*
6. It makes further reference to the International Ethical Guidelines for Biomedical Research Involving Human Participants (CIOMS), the Belmont Report, and *European Convention on Human Rights and Biomedicine*.
7. The Committee has established its own SOPs based on Operational Guidelines for Ethics Committees that Review Biomedical Research (WHO) and the WHO & ICH Guidelines for Good Clinical Practices.
8. The Committee seeks to fulfil the requirements for international assurances and is established and functions in accordance with the national laws.

Membership Appointments

1. The Director General of NIMR is to be responsible for making appointments of Committee members
2. Members are selected in their personal capacities, based on their interest, ethical and/or scientific knowledge, and expertise, as well as on their commitment and willingness to volunteer the necessary time and effort for the Committee's work.

3. Members are appointed for a period of 4 years
4. Gradual replacement of members, the Chairperson
5. Membership may be renewed for up to two consecutive terms while ensuring staggering
6. Advisory committee will advise the Director General on appointments
7. Inclusion of religious representatives is a prerequisite.

Condition of Appointment

1. Willingness to publicize their identity, name, profession and affiliation to the Committee.
2. Willingness to sign a confidentiality agreement at the start of the term and abide by the confidential agreement regarding meeting deliberations, applications, protocol submissions, information on research participants and related matters which they have had the privilege to have as a result of being members of the Committee. The confidentiality protects the privacy and confidentiality of all parties whose information may be disclosed to the Committee in the course of its work.
3. Willingness to disclose in writing any interest or involvement – financial, professional, or otherwise – in a project or proposal under consideration.
4. Any member who has any vested interest in a proposal submitted to the Committee for review shall not participate in the deliberations on the protocol.

Resignation, Disqualification, Replacement of Members

1. Members may resign their position by submitting a letter of resignation to the Chairperson
2. Members may also be disqualified from continuance should the appointing authority provide written arguments to the other members and there is unanimous agreement
3. NIMR shall request for a replacement of any member under the following circumstances:

- i. Protracted illness of a member for a period of more than 6 months, which does not permit him/her to participate in the deliberations of the Committee.
- ii. Persistent absenteeism of a member without reasonable cause for a period of six months.
- iii. Voluntary withdrawal by a member.

SOP # 02: CONFIDENTIALITY/CONFLICT OF INTEREST AGREEMENT

The purpose of this procedure is to provide a form of Confidentiality/Conflict of Interest Agreement, who should read, keep in mind and sign it, when and where to sign and how the signed document be kept. This SOP covers the Agreement on both Confidentiality and Conflict of Interest, concerning activities and information of NHRERC.

It is the responsibility of all newly appointed Committee members and Consultant reviewers to read, understand, accept and sign the agreement stated on the Confidentiality/Conflict of Interest form (Form # 01) before beginning their tasks on conducting activities with NHRERC to protect the rights of the participants.

Detailed instructions

1. Newly appointed members or consultant reviewers shall:
 - i. Obtain two copies of the Agreement Form (Form # 01) from the Secretariat
 - ii. Read through the context of the form very carefully and fill in their names and their address in the blank
 - iii. Ask questions, if any and the Secretariat officer shall explain or clarify the context
 - iv. Sign and date both copies at the undersigned signature and give the forms back to a Compliance Officer to sign and date

- v. Keeps a copy as their records.
2. The Compliance Office shall keep a copy of the signed Agreement as the Institute's records in a Confidentiality/Conflict of Interest Agreement file and store in a secure cabinet with limited key holders.

SOP # 03: ADMINISTRATION AND FUNCTIONS OF THE COMMITTEE

The purpose of this SOP is to describe the administration, office bearers and their functions in the NHRERC. It therefore describes the Secretariat, functions of the Chairperson, Secretary, the Committee, Head of NIMR, Consultant reviewer and dissolution of the Committee.

Secretariat and Officers

1. The officers of the Committee shall comprise of the Chairperson and Secretary.
2. The Chairperson is elected from among appointed members of the Committee for each specific term and the Secretary shall always be an employee of NIMR.
3. The Chairperson shall be a respected person in the community, who has the qualifications of medical or social sciences, is concerned about human rights and ethical issues and is well informed in regulations relevant to the use of human subjects in research.
4. The Committee shall have a permanent secretariat at NIMR manned by the Committee Secretary and administrative supporting staff who are also employees of NIMR
5. NIMR shall also provide the necessary funding for the operations of the Committee.

Functions of the Secretariat

1. Organizing an effective and efficient tracking procedures for each proposal received.
2. Prepare, maintain, and distribute study files.
3. Organize Committee meetings regularly.

4. Prepare and maintenance of meeting agenda and minutes.
5. Maintain the Committee's documentation and archive.
6. Communicate with the Committee members and applicants.
7. Arrange for training for personnel and Committee members.
8. Organize the preparation, review, revision and distribution of SOPs and guidelines.
9. Provide the necessary administrative support for the Committee related activities to the Chairperson of the Committee e.g. communicating a decision to the applicant.
10. Providing updates on relevant and contemporary issues related to ethics in health research, as well as relevant contemporary literature to Committee members.

Responsibilities of Secretary

1. The Secretary shall be responsible for the oversight of Committee documents, records and archives.
2. Perform a pre-review of each submission of the Committee to ensure adherence to administrative submission requirements.
3. Undertake all administrative procedures in providing training and educational programs to new and continuing Committee members, and the scientific community in Tanzania on issue related to health research ethics. The training shall include programs about the basic principles of human subject protection, current literature and regulations and guidelines affecting the Committee and NIMR.
4. Support the Chair in preparing and providing a statement of assurance when required by the regulations guiding the establishment of the Committee.
5. Design and disseminate templates for Committee submission documents, including research protocols, informed consent materials, agreements and periodic and final reports.
6. Design and maintain a system for collecting and filing all Committee documents, including meeting minutes, member qualifications, protocol

submission versions, deviations from approved protocols, and periodic and final reports.

7. Assist the institution to recruit new Committee members
8. Prepare and submit annual Committee operational budget and plan to NIMR management in consultation with the Chair.
9. Accept, verify, duplicate and distribute all submitted items to the appropriate members for Committee review. Ensure that all required materials for submission are present and complete.
10. Create and distribute meeting agendas, and arrange meeting logistics.
11. Attend Committee meetings, take minutes during the meetings, and verify and distribute minutes in a timely manner.
12. Correspond with all submitting researchers at all times throughout the submission and review process, while remaining independent of the researcher's protocol operations. Advise submitting investigators on preparing and submitting protocols for review according to relevant SOPs.
13. Properly distribute and keep files of all correspondences.
14. Assist the Chair to conduct Committee meetings. Continually study and update staff about Committee operational regulations.
15. Be available for and attend any outside investigations or audits of the Committee.
16. Comply with requests during an investigation or audit.

Functions of the Chairperson

1. Chair Committee meetings in accordance with all regulations.
2. Prepare and provide a statement of assurance when required by the regulations guiding the establishment of the Committee.
3. Facilitate the provision of training and educational programs to new Committee and continuing Committee members and the health and social scientific community of the Tanzania. The training shall include programs

about the basic principles of human subject protection, current literature, regulations and guidelines affecting the Committee and NIMR.

4. Review and accept revisions that were made as per the committee recommendation pending protocol approval.
5. Determine submissions that could be exempted from review, and notify the Committee and the submitting investigator of such exemptions.
6. Perform expedited review of research that meets the expedited review criteria.
7. Assign responsibilities and duties to any other member in his or her absence and assign responsibilities to other members of the Committee.
8. Supervise the Secretary and ensure s/he is performing his/her task dutifully.

Responsibilities of Member of the Committee

1. Review, discuss and consider research protocols submitted for evaluation to safeguard the rights and well-being of study participants.
2. Review progress reports and monitor ongoing studies as appropriate.
3. Evaluate final reports and outcomes.
4. Support the executive in the discharge of their duties when called upon.
5. Maintain confidentiality of documents and deliberations of the Committee meetings.
6. Declare conflict of interest.
7. Participate in continuing education activities in biomedical ethics and research.
8. Undertake duties assigned to them by the Chair.
9. Attend meetings regularly and participate actively during deliberations.

Responsibility of the Head of NIMR

1. S/he shall prepare and provide a statement of assurance when required by the regulations guiding the establishment of the Committee.
2. S/he shall ensure the provision of the necessary logistic and financial support for the smooth operations of the Committee.
3. If s/he has an interest in a particular protocol, s/he shall not take part in the reviewing process of that protocol.
4. to provide necessary administrative support to the Committee

Dissolving the Committee

1. At any point in time, should NIMR cease to exist, the Committee is automatically dissolved.
2. The Director General of NIMR, following written notification to each member, may also dissolve the Committee at any time.

SOP # 04: COMMITTEE MEETING

This SOP describes procedure for scheduling meeting, distribution of agendas and meeting procedures. Except for unavoidable circumstances, the Committee shall meet once a month, at 10.00 hours promptly at NIMR HQ unless otherwise stated, provided materials have been submitted for review. In such a case, the Committee Chairperson shall provide an alternate meeting time and date and place.

1. A minimum of half the number of Committee members including at least one member whose primary concerns is in non-scientific areas and one medical scientist. If the protocol under review involves a target group of women, there must be a female member of the Committee present to form a quorum.
2. The Chair shall lead the meeting. In the absence of the Chairperson, the Vice Chairperson shall lead and shall be directed by the Chairperson prior to his/her departure shall lead the meeting.
3. The Secretary shall notify all Committee members of an upcoming meeting at least two weeks in advance by at least one of the following means: electronic mail, fax or carrier mail/messenger delivery.
4. The notification shall include a meeting agenda, which shall outline all protocol and related research submissions for consideration in the meeting, and shall include all related materials, including copies of protocols, informed consent materials, continuing and final reviews, safety reports, etc.
5. In the case where the Secretary is unsuccessful in routing the materials to Committee members, the Secretary shall at least notify the member(s) of the non-occurrence of the meeting, and shall arrange for alternative means of

material distribution. Whenever possible, the Secretary shall distribute the materials electronically.

6. The Secretary shall notify all Committee members of any changes in meeting time, date or agenda as soon as discovered.
7. Committee members shall keep an archive of all copies of meeting agenda and all other documents.

Meeting Procedure

1. The Chairperson or a delegated member of the Committee shall call the meeting to order only when a quorum of members are present. If a quorum is not formed, the meeting shall be rescheduled.
2. The Chairperson shall follow the agenda for the progress of the meeting. S/he may also choose to deviate from the agenda based on personal judgement. The meeting shall most likely follow the following order:
 - i. Adoption of provisional agenda
 - ii. Confirmation of minutes of the previous meetings
 - iii. Matters arising from previous minutes
 - iv. Discussion of new agendas
 - v. Action items (voting on protocols, acceptance of serious adverse events, periodic and annual reports, and final reports)
 - vi. Other matters
3. If the meeting is to review a new submitted protocol, the principal investigator of that protocol may be invited when deliberating on the protocol to answer questions that shall be raised by the board but must go out when decisions are made on the protocol.

Meeting Minutes

1. During Committee meetings, all deliberations shall be recorded in written meeting minutes or recorded electronically.
2. The minutes shall include a list of attendees, actions taken by the Committee, the decision or vote on those actions, including the number of members voting

for, against and abstaining, the basis for requiring changes in or disapproving research, and a written summary of the discussion of issues and their resolution.

3. The Secretary shall also include a summary of each considered protocol in the minutes.
4. The Secretary shall produce a hard copy of the minutes, sign and issue with a copy of the next meeting's agenda to all Committee members at least a week before the date of the subsequent meeting.
5. All Committee members shall review the minutes for accuracy and completeness.
6. The Committee members shall make recommendations to the minutes at the next Committee meeting.
7. The Chairperson shall confirm the accuracy and completeness and sign the minutes during the next meeting.
8. The Secretary shall archive the official minutes with the meeting's agenda and all relevant attachments.

SOP # 05 PROTOCOL REVIEW PROCEDURES

In this SOP, submission of protocols and review procedures are described. It is the responsibility of the Principal Investigator (PI) of a protocol to submit an application for assessment of a protocol following procedures as outlined in this SOP by filling in an Application Assessment Form (Form # 02). The Secretary is responsible for receiving and processing new protocol submissions, and for ensuring that the Form # 02 is adequately filled in and all elements required for consideration of the protocol are present.

Detailed Instructions

1. The submitting Investigator shall submit a research protocol with the following required documents:
 - i. Covering letter from the Head of affiliated institution where applicable
 - ii. Summary of the protocol

- iii. Wherever applicable, a full protocol pre-reviewed by a scientific committee from originating/affiliating institutions with the comments.
 - iv. Enrolment forms
 - v. Questionnaires
 - vi. Consent forms
 - vii. Curriculum Vitae of investigators
 - viii. Budget
 - ix. Insurance of research participants, Insurance Act of 1998.
2. Investigators must submit all documents at least three months prior to the commencement of the research study.
 3. The Chair is responsible for determining whether a submitted protocol qualifies for expedited review.
 4. Depending on the decision of the Chair on a particular protocol, primary reviewers would be appointed to review the protocol.

SOP # 06: PARTICIPATION OF PRINCIPAL INVESTIGATOR IN COMMITTEE MEETINGS AND VOTING PROCEDURE

The SOP provides conditions for participation of investigators in the Committee meetings when their protocols are being reviewed in special circumstances .

Detailed instructions

1. The Secretary shall notify all PIs of the meeting scheduled to consider their submissions at least two weeks before the meeting date. The Secretary shall also notify all PIs about their protocol's place in the agenda. An Associate Investigator may attend on the PI's behalf if necessary.
2. The PI may be invited into the meeting room during consideration of his or her protocol.
3. The PI may be invited to make a 15-20-minute presentation on the protocol under consideration. After the presentation, the PI shall remain in the meeting to answer any questions, concerns and suggestions from members.

4. After the question and answer period, the PI and any other attendees with a potential conflict of interest with the protocol or institution submitting shall leave the meeting during the decision/voting period.
5. Each Committee member shall vote/have a say for or against a protocol or abstain. An absentee member is allowed to send in his/her comments but cannot vote.
6. In order for a protocol to be approved, it shall receive the approval of a simple majority of those members present at the meeting. The Committee may also decide to postpone decisions on a protocol if more information or consideration is required.
7. After the Committee has voted on a protocol, the committee may invite the PI back into the meeting room for immediate notification of the voting results. The Committee may also decide to contact the PI by other means to communicate the results after the meeting.
8. If the Committee decides to disapprove a research proposal, the Committee shall include in its written notification to the investigator a statement of the reasons for its decision, and shall give the investigator an opportunity to respond in person or in writing.
9. If the PI is not satisfied with the committee's decision, the arbitration mechanism shall involve the PI presenting an appeal to the Arbitration Board, which in this case is MRCC.

SOP # 07: ASSESSMENT OF STUDY PROTOCOLS

This SOP describes how the HRERC reviews and assesses the protocol submitted for approval of the study. The Application Assessment Form (Form # 02) is designed to structure the protocol review process and to facilitate reporting recommendation and comments. This SOP applies to the assessment of all protocols submitted for review. The specific questions in the Application Assessment Form must be adequately addressed in the protocol itself and/or protocol-related documents under review. Relevant points made during discussion and deliberation about a specific protocol shall be recorded on the form. The decision reached by the

committee and the reasons for its decision shall be recorded on the Application Assessment Form.

It is the responsibility of the Secretariat/staff to record and file the decision, relevant points and deliberation about a specific protocol, including the reasons for that decision on the Application Assessment Form. The Chairperson of the HRERC shall sign and date to approve the decision in the form.

The Protocol in the Application Assessment Form shall be summarized recording general information about the protocol in the form (Form # 02) such as title of the protocol, protocol number and date, principal investigators and co-investigators, funding agency and project status whether new/revised/rejected version. Other information to be included in the summary shall be type of review whether regular, expedited or emergency, principal reviewer(s) from the Committee, brief summary of the study and comment by the Principal reviewer(s).

1. Study Design

The study design shall be reviewed with a view of evaluating the need for human participants for study, objectives of the study, and adequacy in literature review, appropriateness of the methodology proposed, inclusion/exclusion criteria, control arms (placebo, if any) and withdrawal or discontinuation criteria. Information on where to report a participant with unexpected disease(s) and state clearly how the PI should handle that case.

2. Qualification of investigators and study sites

Qualification of investigators shall be examined to see whether study and training background of the participating investigators relate to the study. The study sites shall also be examined for suitability of the study in terms of geographical distribution of the problem of under study and facility and infrastructure accessibility and availability at study sites to accommodate the study. Disclosure of potential conflicts of interest shall also be examined.

3. Review Study Participation

Under this item the assessment shall be done with a view of evaluating voluntary, non-coercive recruitment of participation. The following aspects shall be assessed to see if they have been adequately considered in the protocol:

- i. Procedures for obtaining informed consent
- ii. Contents of the patient information sheet
- iii. Contents and language of the informed consent document
- iv. Translation of the informed consent document to the local language
- v. Language be plain and easy to understand by the general public
- vi. Contact persons with physical address and phone numbers
- vii. Confidentiality
- viii. Risks -physical/mental/social
- ix. Benefits -to participants and to others
- x. Compensation -reasonable/ unreasonable
- xi. Involvement of vulnerable participants
- xii. Provisions for medical/psychosocial support
- xiii. Treatment for study related injuries
- xiv. Use of biological materials
- xv. The issue of insurance of health research participants, indemnity

4. Examination of Community Involvement and Impact

Ethical research conduct involving human participation requires community consultation, involvement of local researchers and institutions in the protocol design, analysis and publication of the results. It also requires contribution to development of local capacity for research and treatment and benefit to local communities and availability of study results. The protocol shall be examined to assess adequate consideration of these aspects.

Where the Committee had sought expert's advice on a protocol received for assessment, the Consultant shall also use Form # 02 in assessing the protocol

5. Making Decision by the Committee members

The guidance, advice and decision reached by the Committee members shall be summarized in the form (Form # 04). The summary shall include protocol title and date of review, checklist of documents reviewed, and decision reached by the Committee for example approved/approved with stipulation/recommended for resubmission after revision or rejected. Recommendations and/or suggestions, if any including reasons for disapproving a study (if so) shall be part of the summary. The summary shall also include a list of members participating in a review meeting.

6. Recording the Committee's decision

The Secretariat shall complete a decision form (Form # 04) and check the completeness and correctness of the assessment form. The Chairperson of the Committee shall sign and date. A copy of the completed decision form shall be made giving the original copy to the applicant. A copy of the decision form shall be kept in a file labelled, "Committee Decision" and the file returned to the appropriate shelf.

SOP # 08: REVIEW OF PROTOCOL AMENDMENT

The purpose of this procedure is to describe how protocol amendments are managed and reviewed by the NHRERC. This SOP applies to previously approved study protocols but later being amended and submitted for approval from NHRERC. Amendments made to protocols may not be implemented until reviewed and approved by the Committee. It is the responsibility of the Committee Secretariat to manage protocol amendments. Investigators may amend the contents of protocols from time to time. Protocol amendments must be submitted to the Committee for either "expedited" review (see SOP # 09).

Detailed instruction

1. The PI shall prepare the amendment package and submit to the Secretariat of the NHRERC.
2. Upon receipt of the amendment package, the Secretariat shall follow the receiving procedures in Management of Protocol Submission (SOP# 05) and Procedure for Maintaining Confidentiality of NHRERC Documents (SOP# 02).
3. A request on amendment memorandum of a protocol of an existing previously approved protocol shall state/describe the amendment made, provide the reason for the amendment, and state any untoward effects with original protocol and expected untoward effects because of the amendment.
4. The Secretariat shall check the original Amendment Submission Form (Form # 05) for completeness, presence of appropriate signatures, amended version of the protocol and appendix related documents. Changes or modifications in the amended version shall be underlined or highlighted.
5. The Secretariat shall then:
 - i. Inform the Chairperson of the Committee verbally and in writing.
 - ii. Keep "Sent" and "Received" mail related to the notification of the Chairperson in the protocol file under the Correspondence section
 - iii. Send the request for amendment memorandum and the protocol and related documents to the Chairperson within one working day of receipt of the Secretariat.
6. After review of the materials, the Chairperson shall determine whether the protocol requires expedited (SOP # 09) or full review (SOP # 05). Protocol amendment which increase risk to study participants, as judged by the Chairperson, such as a change in study design, may include but is not limited to:
 - i) Additional treatments or the deletion of treatments,
 - ii) Any changes in inclusion/exclusion criteria,

- iii) Change in method of dosage formulation, such as, oral changes to intravenous,
 - iv) Significant change in the number of subjects (for example there would be a significant increase if there are <20 participants enrolled, a change of 5% is significant; if there are >20 participants enrolled, a change of 20% is significant. Or there shall be a significant decrease if the decrease in the number alters the fundamental characteristics of the study),
 - v) Significant decrease or increase in dosage amount.
7. If the Chairperson decides the protocol requires full Committee approval, s/he shall indicate this decision on the Checklist, sign and date the form.
 8. If an amendment is received just prior to the Committee meeting, the Chairperson may decide to review the amendment in full Committee, even though the amendment may be expedited.
 9. Upon receiving the recommendation from the Chairperson, the Secretariat shall:
 - i) Place the protocol amendment request on the agenda for the next convened meeting and
 - ii) Distribute to each Committee member the amendment's revision documents to clearly identify each change and requested changes to the consent form, if applicable.
 10. The process outlined in the Application Assessment Form (SOP # 02) shall be used to review amended protocols and protocol-related documents.
 11. The Chairperson shall call for a vote on the proposed amendments
 12. The Secretary shall note recommendations for changes to the protocol and/or informed consent requested by Committee members in the minutes and communicated the decision to the clinical trial office or investigator in writing.
 13. If the Committee does not approve the protocol amendment, the notification to the investigator shall also state the reason for not approving the amendment.

14. If the NHRERC votes to require modifications to any of the documents, the specific changes required shall also be communicated to the investigator instructing him/her to make the necessary changes and resubmit the documents to Committee.
15. The Chairperson shall complete a decision form after the Committee has reached the decision.
16. The form and minutes of the meeting relevant to the discussion and decision reached shall be kept as an official record of the amendment review process.

Verbal communication and preliminary written communication of the decision and Completion of the Amendment Submission Form

1. The Chairperson shall notify verbally the Medical and Scientific Director of the Institute about the decision reached as soon as possible after the review, but no later than seven working days following the review.
2. The Chairperson shall send an electronic version and fax a copy of the Amendment Submission Form with his/her signature and date of approval to the Secretariat within one working day or whenever possible, but not later than three working days after the review has taken place.
3. The Chairperson must sign and date the original version of this form and return this to the Secretariat within three working days after the review.
4. The Secretariat shall assign a unique ID letter to the protocol number indicating that corresponds to the number of the amendment.
5. The Secretariat shall sign and date the original version of the form and send a signed and dated Amendment Submission Form to the Clinical Trials Office where applicable or the PI within seven working days.
6. The Clinical Trials shall then provide a “clean” copy (underlining and highlighting recommended/approved changes) of the protocol and protocol-related documents to the Secretariat as well as place the “clean” version on the LAN.

7. The Secretary shall place the original completed documents, the “clean” version of the protocol and related documents in the protocol file with the other documents pertaining to the amendment.

SOP # 09: Expedited Review

The SOP on expedited review is meant to give instruction on how expedited review shall be determined and done. The Chairperson in collaboration with the Secretariat shall determine which protocols may require expedited review. The following categories shall be qualified for an expedited review:

1. Research activities that present no risks to human subjects.
2. Minor changes in previously approved research protocol.
3. Modification/amendment of protocol
4. Protocol involves interviewing of non-confidential nature and not likely to harm the status or interest or not likely to offend the sensibility of study participants
5. Studies that involve collection of biological specimens by non-invasive means (e.g. Blood fluids, excreta, hair or nail in non-disfiguring or threatening manner)
6. Collection of data for research purposes through non-invasive procedures (not involving general anaesthesia or sedation), routinely employed in clinical practices and using medical devices which have been already approved for use. Examples of such procedures include application of EEG or ECG electrodes, acoustic testing, tests using the Doppler principle, non-invasive blood pressure and other routine clinical measurements.
7. Research involving data, documents or specimens that have been already collected or shall be collected for ongoing medical treatment or diagnosis.
8. Continuing review of a protocol previously approved with no modification to the original protocol and studies has taken place and no additional risk has been identified.

Detailed instructions

1. Expedited review shall be conducted by one or more experienced reviewers designated by the Chairperson from among members of the Committee in accordance with the requirements (SOP # 09). If the review involves a revised version, the selected members shall normally be those who reviewed the previous version of the protocol.
2. The expedited review shall be carried out on a complete study protocol with all required attachments as if it was being submitted for the first time (Form # 02). Results of the review process may be communicated to the PI before being discussed at a Committee meeting and reported retrospectively to the Committee meeting.
3. Expedited review shall take not longer than 4 weeks and if any member of the Committee raises a concern about a protocol that was expedited reviewed the protocol shall undergo a regular review. In an expedited review, the reviewers may exercise all of the authorities of the Committee except that the reviewers may not disapprove the research. A research activity may be disapproved only after review in accordance with the non-expedited procedure. The Secretary shall inform all members about the outcome of an expedited review as soon as practicable.

SOP # 10: Continuing Review

The purpose of continuing review is to review progress of the entire study, not just changes made so as to ensure continued protection of rights and welfare of research participants. The Committee members are responsible for determining whether the research is reviewed annually, or more frequently appropriate to the degree of risk. The Committee is also responsible for determining whether an independent data and safety monitoring board is required. The investigator of the research is responsible for keeping the Committee informed of significant findings that affect

the risk/benefit ratio and thus the need for more frequent review. The investigator is also responsible for following the continuing review procedures and deadlines.

Determination of Frequency of Continuing Review

1. At a research activity's initial review, the Committee shall determine:
 - i. How often it shall re-evaluate the research project. All research shall be reviewed at intervals appropriate to the degree of risk, but not less than once per year but at least once before the end of the data collection stage.
 - ii. The factors to be considered in setting the frequency of review should include the nature of the study, the degree of risk involved, and the vulnerability of the study subject population.
 - iii. Whether these studies need verification from sources other than the investigator that no material changes in the research have occurred.

2. The investigator shall utilize the continuing review form No. 11 to complete the annual review report and shall include all required elements, including the following:
 - i. Number and demographics of participants enrolled
 - ii. Changes in principal and/or associate investigator(s)
 - iii. A summary description of subject experiences
 - iv. All adverse events experienced
 - v. Numbers of and reasons for withdrawals from the research
 - vi. The research results obtained thus far
 - vii. A current risk-benefit assessment based on study results and
 - viii. Any new information since the Committee's last review.

3. If the investigator/researcher cannot provide any of the required information, s/he shall provide justification for the delay in the report, and a timetable for provision of the information. The investigator/researcher shall also submit a copy of the consent documents and procedures currently in use.

4. The investigator/researcher shall submit one hard copy of the continuing review report, with original signature. The investigator/researcher is also encouraged to submit an electronic copy of the review report via e-mail or disc.
5. Upon receipt of the continuing review report, the Secretary shall conduct a pre-committee review to ensure all the required elements are present. The Secretary shall work with the submitting investigator to ensure all elements are present before distribution of meeting items. The Secretary shall place the continuing review report on the next meeting's agenda.
6. The Chairperson may elect to invite an independent or alternate reviewer to the meeting. Committee members shall consider and vote upon all continuing review reports in full meeting utilizing the protocol voting procedure. The risk/benefit ratio may change over time. The criteria the Committee uses to approve or disapprove continuation of research are the same as the criteria for approval of an initial research project.
7. The Committee shall review the consent process and documents to determine whether they are still accurate and complete, whether new information that may have been obtained during the course of the study needs to be added, and whether documents being used by the investigator/researcher have current Committee approval. After reassessment, the Committee may require that the research be modified or halted. The Committee may also impose special precautions or relax special requirements it had previously imposed on the research protocol. They shall also determine whether there are any important new findings that might affect the willingness of participants to continue participating in the research. If so, they shall require the Investigator notify the participants of these findings. The Secretary shall archive continuing review reports and supporting materials with the relevant meeting minutes.

Timing of Continuing Review

1. If the Committee has not reviewed and approved a research study by the study's current expiration date, Committee approval has expired and research activities should stop. No new subjects may be enrolled in the study. However, if the investigator/researcher is actively pursuing renewal with the Committee and the Committee believes that an over-riding safety concern or ethical issue is not involved, the Committee may permit the study to continue for the brief time required to complete the review process.
2. If the investigator/researcher cannot provide any of the required information, the investigator/researcher shall be reminded to justify for the delay in the report, and a timetable for provision of the information. The investigator/researcher shall also submit a copy of the consent documents and procedures currently in use.

SOP # 11: Use of Data and Safety Monitoring Board (DSMB)

In larger studies or trials, the Committee may also require a DSMB be formed to keep the Committee up-to-date of the balance between risks and benefits. The primary responsibility of a DSMB is to safeguard human subjects by analysing accumulating data relevant to the risks and benefits on a regular basis. Especially in long-term trials, the DSMB reviews data periodically to assess effectiveness and toxicity, and to decide if and when the data are sufficiently favourable to one treatment that the study should be discontinued. The DSMB shall also decide whether adverse effects are serious enough to warrant termination of the study.

SOP # 12: RESPONSES TO VOLUNTEER/PATIENT REQUESTS REGARDING RIGHTS

The NHRERC shall consider its prime responsibility by assuming the protection of the rights and welfare of human subjects in a clinical investigation approved by the Committee. This SOP applies to all requests concerning the rights and well-being of the participants in the studies approved by the NHRERC. This procedure shall

provide guidelines for dealing with and accommodating requests by participants regarding their rights as participants in any approved clinical research studies. It is the responsibility of all Staff and Committee members acting on behalf of the Committee to facilitate subjects/patients' requests within the scope of their responsibilities.

Informed Consent documents reviewed by the Committee may routinely contain the statement, "Questions regarding the rights of a subject/patient" may be addressed to the Chairperson, address and/or phone number. On some occasions the first contact a subject/patient may have upon contacting Committee would be with an administrative staff member.

The NHRERC's policy shall designate the Chairperson as the person responsible for communicating with participants regarding their rights as study participants. Delegation of this responsibility to another member is acceptable as long as delegation is documented in writing. Delegation to non-Committee members is not permitted.

Handling a request

1. Upon receiving an inquiry from a study participant, the NHRERC Staff shall do the following:
 - i. Record the request and information on the Request Record Form (Form # 06)
 - ii. Communicate with the Committee about study participant rights
 - iii. Refer the inquiry to the Chairperson in writing, without providing the subject/volunteer comments/opinion as to the expected Committee's response about the inquiry
 - iv. The Administrative staff may provide assistance in contacting the Chairperson, but shall not provide comments/opinions about the inquiry.

2. The Chairperson shall document the communication for the Committee study file, request follow-up information, provide advice as required, inform the other Committee members of the inquiry, and follow-up at the next meeting and delegate these tasks to Secretariat who shall then do the following:
 - i. Record information and any actions or follow-up taken in the form (Form # 06)
 - ii. Sign and date the form
 - iii. Report to the Committee about the action taken and the outcomes
 - iv. File the request document, keep the record form in the "response" file and,
 - v. Store the file on the appropriately labelled shelf.

SOP # 13: MONITORING AND EVALUATION OF SAFETY/ADVERSE EVENTS (SAE) REPORT

The purpose of this SOP is to provide instructions on the review and follow-up reports of adverse experience and unexpected events for any active study approved by the Committee. Unanticipated risks are sometimes discovered during the course of a study. Information that may impact on the risk/benefit ratio must be promptly reported to, and reviewed by, the Committee to ensure adequate protection of the welfare of the study participants. This SOP applies to the review of SAE and unexpected events reports submitted by investigators, DSMB, Local safety monitor, IRB and any other intended parties

The primary responsibility of the Ethics Committee is to review and address SAE and unexpected events involving risks to subjects or others as well as ethics complaints. In addition, the Committee is authorized to offer mediation under appropriate circumstances. The Committee shall also make sure that researchers are aware of the policies and procedures concerning reporting and continuing review requirements. The Secretariat shall be responsible for first screening and assessment

of the reports and seeing whether they need a review of full Committee, Chairperson, other qualified Committee members or experts.

Detailed instruction

1. Before each Board Committee

The Secretariat shall review the reporter's assessment to determine whether the report requires review by full Committee, the Chairperson or other qualified Committee member(s). Criteria of the review shall be as follows:

- i. If assessment of adverse experience is unknown or unlikely, the report shall be forwarded to the Chairperson for review and determination if full Committee should review the report at the following convened meeting.
- ii. If assessment of adverse experience is possibly caused by, or probably caused by the investigational drug, full Committee should add the report to the agenda for review at the following convened meeting.
- iii. If an adverse experience/investigational new drugs safety report has previously been seen by full Committee being resubmitted by another investigator in the same study (as part of a multi- Centre study), this notification shall not require full Committee review instead be reviewed by the Chairperson or other qualified Committee members and Secretariat.

2. During the Committee meeting

After reading and reviewing the report, the Chairperson or designee shall entertain discussion on the study and similar adverse experiences or advisories. If appropriate to the discussions, the Chairperson or another Committee member may call for a consensus on whether to:

- i. Request an amendment to the protocol or consent
- ii. Request further information

- iii. Suspend or terminate the study
3. If any of the above actions are taken, the Secretariat shall notify the investigator of the action taken. If the Committee takes no action, it shall be noted in the minutes. The Secretariat shall draft a formal letter to the investigator notifying him/her the action he/she should take according to the Committee's decision. The letter shall be signed by Chairperson and date of delivery shall be recorded.

SOP # 14: NON - COMPLIANCE/VIOLATION INTERVENTION

The purpose of this SOP is to provide instructions for maintaining records that identify investigators/institutes who fail to comply with National/International guidelines for the conduct of human research or who fail to correspond to the NHRERC requests. This SOP applies to all research projects involving human participants and approved by the NHRERC. The Secretariat is responsible for collecting and recording the non-Compliance List (Form # 07).

Detailed instruction

1. Whenever non-compliance has been observed, it shall be ensured that the investigator information is placed on the agenda of each Committee meeting.
2. A file shall be maintained that identifies investigators who are found to be in non-compliance with TFDA regulations or who fail to respond to the Committee's requests.
3. The Committee may elect to suspend or terminate approval of current studies or refuse subsequent applications from the investigators cited. Such decisions shall be recorded in the minutes.
4. The Chairperson shall notify the investigator of the Committee's action in writing.
5. The Secretariat shall record the Committee's decision and draft a notification letter that shall be signed by the Chairperson and date the letter.

6. Four copies of the notification letter shall be produced. The original shall be sent to the investigator, the second copy to the relevant National Authority, the third to the sponsor or the sponsor's representative of the study and the fourth to the non-compliance file and stored on the shelf with an appropriate label.
7. The action shall be followed up after a reasonable time six months.

SOP # 15: REVIEW OF FINAL REPORTS

The purpose of this SOP is to provide instructions on the review and follow-up, appropriate, of Final Reports for any study previously approved by the NHRERC. This SOP applies to the review and follow-up the final report which is an obligatory review of each investigator's activities presented as a written report to the Committee after the last participant had completed all visits and all adverse experiences have been brought to appropriate resolution.

Although NHRERC provides a Study Report Form (Form # 08) to the investigator, any mechanism (letter format, form provided by the sponsor) may be used, provided that the information submitted is sufficient. It is the responsibility of the Secretariat to review the report for completeness before making copies for the Committee meeting.

Detailed instruction

1. Before each Committee meeting the Secretariat shall be guided by SOP# 05 (Protocol Review Procedures) for receiving and checking the report packages. The Secretariat shall read the submitted report and give a briefing to the Chairperson before making copies and distributing it to all Committee members.
2. During the Committee meeting each Committee member shall review a copy of the final report before deliberating on it. The designee shall entertain any

discussion of the study. If appropriate to the discussions, a Committee member may call for consensus on whether to request further information or to take other action with the investigator before summarizing what action to be taken. The Secretary shall note the decision in the meeting minutes.

3. After the Committee meeting, the Secretariat shall notify the investigator of the decision taken. If no action is taken, file the final report and consider the study as closed. Get a copy of the final report signed by the Chairperson or the designee, send an acknowledged letter to the investigator and archive the entire study protocol and the report.

SOP # 16: COMMUNICATION RECORDS

The purpose of this SOP is to ensure proper completion, distribution and filing of verbal and written communication and other study-related or process-related information with investigators, sponsors, volunteer participants, institutes and FDA. This SOP applies to all communicating activities related to the studies under the approval of the NHRERC.

Detailed instruction

1. Individuals may utilize different communication recording mechanisms; that may be handwritten, typed or computer-generated.
2. Written record shall contain, but not limited to, the following: date of communication, study information (e.g. sponsor, protocol number, investigator), name of person contacted, contact address, telephone number, and e-mail, summary of the communication made, notation of any follow-up necessary and signature of individual making the record.
3. Upon completion of the record, the individual shall distribute copies as appropriate for filing.

SOP # 17: SITE MONITORING VISITS

The purpose of this SOP is to provide procedures as to when and how a study site should be visited and monitored with regards to its performance or to GCP. This SOP applies to any visits and/or monitoring of any study sites as stated in the IEC/IRB approved as the place where the studies and/or laboratory tests being carried out or performed. It is the responsibility of the NHRERC to perform or designate some qualified agents to perform on its behalf on-site inspection of the research projects it has approved. The Secretariat in consultation with the Chairperson shall initiate an on- site evaluation of a study site for cause or for a routine audit.

Detailed Instruction

1. Selection of study sites

The database files of the approved protocols shall be reviewed periodically. Study sites to be monitored shall be selected based on the following criteria:

- i. If the research project has never been approved by the NHRERC, a study visit should be planned within thirty days after the study starts.
- ii. Reports of remarkable serious adverse events
- iii. Number of studies the sites handle
- iv. Frequency of submission of protocols for Committee review
- v. Cause audits
- vi. Failure to submit progress report or final report
- vii. New sites
- viii. Response to study participants request.

2. Preparing the visit

The Committee representatives shall notify the investigator within one week about plans of the visit. Meanwhile the visiting team shall make the appropriate travel arrangements, review the Committee files for the study and site, make appropriate notes, or copies some parts of the files for comparison with the site files.

3. Surprise monitoring visit

A surprise-monitoring visit will be conducted at random to researches falling under following categories:

- 3.1 Researchers who do not submit progress reports as per regulations after two reminders.
- 3.2 Researchers who prolong completion of their research beyond the approved time frame.
- 3.3 Researches that are suspected to changed their objectives and conduct as approved.
- 3.4 Any complaints that may arise from the research team about the researcher

4. During the visit

The visiting team shall:

- i. Review the informed consent document to make sure that the site is using the most recent version.
- ii. Review 25% of the participant files to ensure that participants are signing the correct randomly informed consent,
- iii. Observe the informed consent process, if possible, and
- iv. Review the Committee files for the study to ensure that documentation is filed appropriately and confidentiality.

5. After the visit

The Committee representative that made the visit shall:

- i. Write a report using the Checklist for a Monitoring Visit (form # 09) within two weeks describing the findings during the audit.
- ii. Forward a copy of the site visit to the site-monitoring file for full Committee review.
- iii. Send a copy of the report to the site for their files.
- iv. Place the report in the correct site files.
- v. Make debriefing before departure.

6. Present the inspection results to the full Committee

The presentation shall be scheduled in the meeting agenda and presented to the full Committee.

SOP # 18: SELECTION OF INDEPENDENT CONSULTANT

The Committee may further be supported in its reflections on specific protocols or requests for advice on specific ethical issues by independent advisors. The purpose of this SOP is to provide procedures for engaging the expertise of a professional as a consultant to the Committee. If the Chairperson or the Committee determines that a study shall involve procedures or information that is not within the area of expertise of the Committee members. The Chairperson or the Committee may invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to those available on the Committee. It shall be the responsibility of the Secretariat to nominate the name of the Consultant.

Detailed instruction

1. Selection of Independent consultants

The Secretariat shall choose a consultant to give study documents to review from a created roster of Consultants based on areas of expertise. The creation of the roster of experts shall involve the Secretariat conducting a qualification review of prospective consultants and making decision based on expertise, availability and independence criteria. The consultant shall provide to the Secretariat their Curriculum Vitae and sign a Professional Services Agreement (Form # 09) and a Confidentiality/Conflict of Interest Agreement (Form # 01). These documents shall be kept in a consultant file.

2. Consultation Services

The Secretariat shall provide protocol packages to appropriate consultants. The consultant may either attend the meeting to participate in the review of the study as

a non-voting member and/or may review the documents and prepare a consultant report to be reviewed by the Committee in their regular meetings or extraordinary meetings. The Consultant's report shall become a permanent part of the study file.

3. Termination of the Services

Consultation services may be terminated by either the consultants themselves or the Committee. Upon termination of the consultant's services, the Secretariat shall ensure that all the qualifying documentation and the reason for discontinuation of the services are filed with the administrative documents.

SOP # 19: MANAGEMENT OF PROTOCOL TERMINATION

This procedure describes how protocol termination is managed by the NHRERC. Protocols are usually terminated at the recommendation of the Institute Scientific Director, EIC/IRB DSMB or any other authorized body when subject enrolment and subject follow-up are discontinued before the schedule time. This SOP applies to any protocols approved by NHRERC. It is the responsibility of the Chairperson to terminate protocol in the interest of study participants' health or welfare. The Secretariat is responsible for management of the termination process.

Detailed instruction

1. Upon receiving a recommendation for protocol termination the Secretariat shall verify the contents of the package for inclusion of the following before dating:
 - i. Request for Termination Memorandum (Form # 10).
 - ii. A brief written summary of the protocol, its results, and accrual data.
 - iii. Original Continuing Review Application Form (Form # 11)
 - iv. Under "Action Recommendation" termination should be indicated.
 - v. Completeness of the remainder of the information, including accrual data since the time of the last continuing review.
 - vi. Presence of the required signatures (Institute Medical Advisor, Institute Medical and Scientific Director and Protocol Chairperson, if applicable).

2. The Secretariat shall notify the Chairperson regarding the request for protocol termination by sending a copy of the termination package to the Chairperson within one working day upon receipt of the termination request. The Chairperson shall review the results, reasons and accrual data and call an emergency meeting of the Committee.

3. The Chairperson shall sign and date the Continuing Review Application Form in acknowledgement and approval of the termination and return the form back to the Secretariat within five working days of receipt of the package who shall then do the following:

- i. Review, sign, and date the Continuing Review Application Form indicating that the termination process is complete.
- ii. Make a copy of the completed Continuing Review "Application Form and send it to the PI for their records within seven working days.
- iii. Store and inactivate the protocol documents
- iv. Keep the original version of the termination memorandum for termination and the original version of the Continuing Review Application Form in the Protocol file.
- v. Send the file to archive and store the file indefinitely.
- vi. Place the protocol and related documents into the inactive protocol folder on the LAN in the following directory: F:\documents\inactive protocols.

SOP # 20: PRERPARATION AND MAINTENANCE OF STUDY FILES

The purpose of this SOP is to provide instructions of what to keep, how to keep and maintain the study files. This SOP applies to all active study files that are maintained in the NHRERC office. It is the responsibility of the Secretariat and staff to ensure that all study files are kept securely by a proper system, facilitating

retrieval at any time and that they are stored at an appropriate place (free from dust and moisture) and for the specified period of time.

Detailed instruction

1. Storage of single-site study files

File folders shall be displayed with a blue tab to indicate the name of the sponsor company and a yellow tab to indicate the protocol number. Each folder of a single-site study shall be put into the following labelled files:

- i. Sponsor, protocol number, investigator name and title
- ii. Investigator's Brochure (drug studies)
- iii. Initial Approval
- iv. Revisions
- v. Advertisements
- vi. Adverse Experiences
- vii. Correspondence
- viii. Continuing Review, if applicable

2. Storage of multi-site study files

A Master File folder shall be displayed with a blue tab to indicate the name of the sponsor company and a yellow tab to indicate the protocol number. Each master file folder shall be put into the following labelled file:

- i. Sponsor, protocol number, project manager name
- ii. Investigator's Brochure (drug studies)
- iii. Initial Approval
- iv. Revisions
- v. Advertisements
- vi. Adverse Experiences
- vii. Correspondence

3. Storage of investigating files

Each document of investigating protocol shall be put into the following labelled files:

- i. Sponsor, protocol number, investigator name and title
- ii. Initial Approval
- iii. Revisions
- iv. Advertisements
- v. Adverse Experiences
- vi. Correspondence
- vii. Continuing Review, if applicable

4. Maintenance of study files

All study files shall be kept throughout the course of the study with the most present documentation filed on top. All closed study files shall be sent to an off-site storage facility and stored for *at least 15 years* after the study closure. Archiving of files shall only be done when the NHRERC receives a final report of the study.

SOP # 21: PROCEDURES FOR MAINTAINING CONFIDENTIALITY OF IEC/IRB DOCUMENTS

The sources of violation of confidentiality are usually found in the day-to-day use of copies of original documents. This SOP therefore describes how to handle original documents and copies of documents in order to protect confidentiality of documents. This SOP applies to all kinds of handling, distribution and storage of submitted study protocols, Committee documents, and correspondence with experts and auditors general public. It shall be mandatory to maintain confidentiality of study Committee documents, and correspondence. It is the responsibility of all members of the Committee and staff of the Secretariat to enforce confidentiality.

Detailed instruction

1. Committee members

Committee members and the Secretary who have signed a confidentiality agreement with NIMR at the beginning of their term of service to the Committee (SOP # 02) shall have access to the confidential documents.

2. Confidential documents

Confidentiality documents shall include documents reviewed by Committee members (Protocol and there related documents, case report forms, informed consent documents, diary forms, scientific documents, expert opinion or reviews). They shall also include NHRERC documents (SOPs, meeting minutes, advice and decisions) and correspondence (experts, auditors). Copies of documents, including draft and sequential versions, are considered to be confidential and are not permitted to be taken out except when a document is needed for day-to-day operations.

3. Authorization of acquisition of copies

Only members of the IEC/IRB shall be allowed to ask for copies and only staff members of the Secretariat shall be allowed to make such copies. The Secretary of the Committee may ask for help, but shall be responsible for maintaining confidentiality of all documents.

A Log of copies (Form # 12) shall be kept by the Secretariat. The log shall include: the name and signature of the individual receiving the copy; the initials of the member of the Secretariat who made the copy; the number of copies made and the date that the copies were made.

4. Copies Requested by Non-Members of the Committee

If non-members of the Committee (including the Secretary) need copies of original documents, it shall be the responsibility of one member of the Committee to request a copy and to maintain confidentiality of copied documents. Copies made for non-members of the IEC/IRB shall be recorded on the Log of Copies for the original document.

5. Filing of Log of Copies

The log of copies of an original document shall be stored with the original document. The log of copies shall not be a confidential document and can be reviewed upon request. A log of copies shall be maintained

SOP # 22: AUDITING AND INSPECTION OF THE ETHICS COMMITTEE

The purpose of this procedure is to guide how to prepare for an audit or inspection of the IEC/IRB works. This SOP applies to every unit of the NHRERC Office. It is the responsibility of the Secretariat, members, Chairperson and administrative staff of the NHRERC for performing his/her task according to the SOPs and for being well prepared and available to answer questions during evaluation, audit or inspection visits of authorities and guests.

Detailed instruction

1. Upon receiving a notice of inspection visit, the Chairperson shall inform the Secretariat and alert every unit to get ready for the visit. The Secretariat shall prepare for the visit by going through all steps in a checklist of audited and inspection (Form # 13) and note and comment on each part emphasizing on the studies with problems. Specifically the following shall be made ready for inspection:
 - i. Check if all documents are labelled and kept in the right order for easy and quick search.
 - ii. Check for any missing or miss-organized records
 - iii. Background and training records of IEC/IRB members
 - iv. Application Submission Records
 - v. Protocol Assessment Records
 - vi. Communication Records
 - vii. Amendment Approval
 - viii. Meeting Agenda, Minutes, Action letters

- ix. Active files
 - x. Continuing and Final reports
 - xi. Reserve a meeting room and all necessary facilities.
 - xii. Review the SOPs.
 - xiii. Make sure that no omission or deviation exists.
 - xiv. Make sure to have good reasons for any omission or deviation.
 - xv. Inform Committee members about the inspection date if they are able to attend the audit/inspection meeting.
2. Upon arrival of the Auditor(s)/Inspector(s), the Chairperson or the Secretariat shall welcome and accompanies the auditors/inspectors to the reserved meeting room. Members and some key staff shall also be present in the meeting room. The conversation shall start with the auditor(s)/inspector(s) stating the purpose of the visit and what kind of information and data they would need. The Chairman/designated spokesperson of the Committee shall answer questions of the auditors/inspectors clearly, politely and truthfully with confidence and straight to the points. All information and files shall be made available as requested by the auditors/inspectors.
 3. After the auditor(s)/inspector(s) have left, the Chairperson shall call for correction of any mistakes pointed out by the audit(s) and internal follow-up audit shall be carried out. A report shall be written and get approval from the Chairperson. Appropriate time for correction and improvement process shall be allowed and an outcome of the audit process shall be evaluated. The record of the report on the audit/inspection meeting shall be kept in the audit/inspection file and record of findings from the internal follow-up audit in the internal audit file.
 4. It is the responsibility of the Secretariat to remind members, the Chairperson and staff of the Committee for performing his/her task according to the SOPs

and for being well prepared and available to answer questions during evaluation, audit or inspection visits of the authorities or guests.

SOP # 23: ARCHIVING OF STANDARD OPERATING PROCEDURES

The purpose of this SOP is to provide instruments for storing inactive study files and administrative documents in a secure manner while maintaining access for review by auditors and inspectors. The files and documents are retained for at least three years after completion of the research so that the records are accessible for auditors and inspectors. Copying files and documents for or by authorized representatives of the national authority when required is allowed.

Maintenance and retrieval of archived documents

1. Maintenance and retrieval of files and documents from the archive shall be the responsibility of the Secretariat. After receiving the final report, the Committee members shall review the final report. The Secretariat shall then do the following:
 - i. Remove the contents of the entire study file from the active study filing
 - ii. Verify that all the documents are present in organized manner
 - iii. Obtain an archive number from the Archive Department and enter the number into the data base
 - iv. Place the file in a storage container
 - v. Send it to the appropriate storage facility
 - vi. Hold the files of multi-study centres, until all the study centres are closed and place in a storage container together and archive
2. To archiving administrative documents, an administrative staff of the Secretariat shall perform inventories of miscellaneous administrative documents, place the documents in an appropriate storage container, and send it to the appropriate storage facility. In retrieving documents the Secretary

shall maintain confidentiality as stipulated in SOP # 21 (Procedure for Maintaining Confidentiality of Ethical Review Committee Documents)

3. Retrieval of documents shall only be done with a Document Request Form (Form # 14) signed and dated by the Chairperson. The person requesting for the retrieval of the document/file shall also sign and date the request form. The Administrative staffs shall retrieve archived documents in accordance with approved procedures of the Archives department. The retrieved files shall be returned back to its place after completion of using it and record, sign and date when the document has been returned and kept.

SOP # 24: DISTRIBUTION OF SOPs AND GUIDELINES

This standard operating procedure describes how to distribute and to control the distribution of the NHRERC approved SOPs and Guidelines. The NHRERC works according to internal rules as described in its written SOPs. The SOPs documents are properties of the institute and shall be kept *confidential* in a safe place. They shall not be disclosed without permission from the Committee.

However, in order to maintain a transparent relationship with non-members for example the public, clients, or other interested parties; certain procedures shall form guidelines available for non-members. Guidelines shall only be disclosed after a Confidentiality Agreement for the use of a Confidentiality Agreement) has been obtained (SOP # 02).

The method applies to distribution of SOPs and Guidelines and maintaining the log of the distribution. It is the responsibility of the Secretariat or designated individuals to follow the institute's policy and methods, format, and system when distributing any SOP or Guideline of the NHRERC.

Detailed instruction

1. The Secretary shall distribute the SOP to all Committee members, archive the electronic copy and the paper original, and update the indexed list of SOPs. All requests for extra copies may be made to and fulfilled by the Secretary.
2. Two distribution logs one for SOP (Form # 15) and another for guidelines (Form # 16) shall be designed. Separate forms shall be used for recording distribution of each SOP (Form # 17) and each Guideline (Form # 18).
3. A table of information to be collected shall be made and shall include running number, name of recipients, institute that recipients belong to, code of the SOP or Guideline, number of copies taken, signature of the recipients and date taken. Sufficient copies of the forms as specified in the inventory log shall be made.
4. The Forms shall be placed in a file labelled properly (Form # 15 and Form # 16) and placed in the appropriate shelf.
5. A list of names of all Committee members and administrative staff to whom the SOP shall be given shall be listed on the distribution section of the approval cover page (Form # 19) of each master SOP. The name and all relevant SOP codes for dissemination to that person shall be filled in the distribution log form.
6. Number of each SOP to be copied shall be counted and recorded in an inventory log (Form # 17). Sufficient copies of every pages of the master SOP for everyone in the Committee shall be made and bound in a loose bound file at correct sequence for easy to locate.
7. The copies of each SOP/Guideline for each recipient shall be organized and the original copy shall be kept as a master SOP in the file labelled "Master SOPs".

The "Master SOP Files" shall be kept in a secure cabinet with a key and the key kept by the Secretariat.

8. The delivery form shall be filled in, Committee members notified and copies of the SOPs/Guidelines delivered to each recipient. The recipients shall sign on a log form (Form # 15 and 16) as proof of reception. The distribution log shall be filed and the file returned back to the shelf.
9. The name and the number of SOPs or Guidelines to be copied in the inventory log (Form # 17) shall be recorded, remaining copies and record in the 109 counted and the inventory log return back to its shelf.

SOP # 25: REVISION OF SOP

The purpose of this SOP is to address the when and how SOPs shall be reviewed. If the Committee wishes to revise or update the SOP:

1. It shall request an electronic copy of the document from the Secretary, or may request minor changes to be made directly by the Secretary.
2. The SOP shall be evaluated for accuracy and timeliness in an annual review and the Secretary shall alert the Committee of an annual review requirement.
3. The Committee, Secretary or an assigned reviewer shall ensure that the SOP reflects the most current outline of procedures. If the document does not need revision, the author shall return the document to the Secretary for recording and filing.

SOP # 26: GLOSSARY OF TERMS AND DEFINITIONS

This SOP is dedicated to collect, standardize and define terms, abbreviations, phases, titles of the National Health Research Ethics Review Committee (NHRERC) and its administrators in order to facilitate the use and understanding of the SOPs. The

definitions are divided into two sections namely the descriptions/definitions of personnel and subjects and terms, abbreviation and phases as used in the NHRERC SOPs. This SOP applies to all persons preparing and using the SOPs. It is the responsibility of the Secretariat, Members of the Committee and the Chairperson to define or determine the appropriateness of the description or definition.

Description of titles of the personnel

Titles	Description
Administrative Staff	They are IEC staff that are responsible for the day-to-day administrative functions and duties, which support the activities and responsibilities of the IEC members.
Chairperson	A member of the Committee presiding over a meeting. He/she is responsible for expedited approvals on behalf of the Committee.
Clients	As a national review Committee, NHRERC considers investigators, investigational sites, sponsors or sponsor representatives as its clients or customers. Clients requesting the services of NHRERC are asked to accept and abide by the procedures set forth in these documents.
Committee Members	Non-employee individuals serving as regular and alternate members on the NHRERC's operations. This Committee is constituted in accordance with the NHRERC membership requirements set forth in SOP # 01. Individuals qualified to vote at a duly convened NHRERC meeting (SOP # 01 - Committee Membership: Selection and Replacement)
Ethics Committee	Whose responsibility is to ensure the protection of rights, safety and well being of human participants involved in bio-medical research and to provide public assurance of that protection
Project Manager	Individual responsible for coordinating an investigational study.
Senior Administrative Staff	Titles include NHRERC Supervisor, and Administrative Coordinator.
Site Coordinator	The person at the study site who is responsible for managing the study. This person can also be referred to as a Project Manager.
SOP Committee	A selected committee of NHRERC members and administrative staff who oversee the preparation review and periodic revision of the SOPs.
The Committee	This is comprised of at least five regular members and alternate members who may serve as equals within the committee (i.e. an alternate for non-scientific to be non

	<p>scientific, MD for MD, etc.). The composition of the membership must reflect a diversity of backgrounds sufficient to assure:</p> <ol style="list-style-type: none"> i. Expertise and experience to provide adequate review of research activities consideration of race, gender, and cultural backgrounds. ii. Sensitivity to attitudes and concerns of the community and to the patient population. iii. Knowledge of applicable regulation, laws and standards of professional conduct and practice. iv. No member is participating in the initial or continuing review of any project in which he/she has a conflicting interest. v. Consideration for gender and cultural background. <p>The Committee is established to review and monitor biomedical research involving human subjects. The primary purpose of such review serves an important role in the protection of the rights and welfare of the human subjects. In accordance with applicable federal regulations, IEC has the authority to approve, require modifications to, or disapprove research.</p>
Description of Terms, abbreviations and phrases	
Active Study Files	Supporting and approved documents, records containing communications, and reports that correspond to each active (current) study approved by the NHRERC.
Addition/Correction of terms	Members are encouraged to propose any additional terms or make correction of any terms defined in this SOP at any time, if he/she feels clarification should be made, they are encouraged to write their proposal and submit to the Secretariat.
Administrative Documents	These includes official minutes of the Committee meetings as described in SOP # 04 the SOPs, historical files and Master Files as described in SOP # 20, Distribution, Implementation and File Maintenance.
Adverse Event	An adverse event is any undesirable experience associated with the use of a medical product in a patient.
Amendment protocol package	A package of the amended parts and related documents of the protocol, previously approved by the IEC/IRB, but later decided to make changes after the study had been

	carried for some time.
Clinical trial office	An institute or an office where the study takes place and where the principal investigator can be reached.
Application Assessment Form	An official record that documents the protocol review process.
Approval of the addendum	The secretariat brings the proposal to be meeting to be deliberated at the Committee meeting.
Audit	A systematic and independent examination of research trial approval activities and documents to determine whether the review and approval activities were conducted and data were recorded and accurately reported according to the SOPs, GCP, Declaration of Helsinki and applicable regulatory requirements
Committee Representatives	Many Research Ethics Review Committees (RECs) rarely find time to perform monitoring visit themselves. They may ask outside experts or Ethics Committees to perform the tasks on their behalf and later report their findings to Committee
Confidentiality	Prevention of disclosure, to other than authorized individuals, of Committee information and documents
Conflict of Interest	<p>A situation in which a person, such as a public official, an employee, or a professional, has a private or personal interest sufficient to appear to influence the objective exercise of his or her official duties. There are three key elements in this definition: financial interest; official duties; professional interest. A conflict of interest occurs when:</p> <ul style="list-style-type: none"> (i) An individual's private interest differs from his or her professional obligations to the institute. (ii) Professional actions or decisions occur that an independent observer might reasonably question. (iii) A conflict depends upon situation and not on the character or actions of the individual. (iv) Potential conflicts of interest must be disclosed and managed as per policy.
Deviation	Any instance in which the current approved by NHRERC SOP cannot be or has not been followed.
Document	Paper documents, electronic mail (e-mail), faxes, audio or video tapes.
Documents to be delivered	Any Documents, such as SOPs, Guidelines, Communication, Correspondence, Books, etc. are specified for distribution.
Expedited approval	A Committee's approval granted only by the Chairperson of the Committee or designated member for minor

	changes to current approved research activities and for research, which involves no more risk than minimal risk.
Expedited review	A review process by only a few designated Committee members who then report the decision to the full Committee meeting. An expedited review is a speedy review for minor changes to the protocol and for research that pose minimal risk to participants.
Final Report	An obligatory review of study activities presented as a written report to the Committee after the last subject has completed all visits and all adverse experiences have been brought to appropriate resolution.
Guideline	Advice or information given to perform various tasks
Inactive study files	Supporting and approved documents (protocols, protocol amendments, informed consents, advertisements, investigator and site information), records containing communications and correspondence with the investigator, and reports (including but not limited to Continuing Review Reports, IND Safety Reports, reports of injuries to participants, scientific evaluations) that correspond to each study approved by the NHRERC for which a final report has been reviewed and accepted.
Independent consultant	An expert who gives advice, comments and suggestion upon review of the study protocols with no affiliation to the institutes or investigators proposing the research protocols.
Inspection	The act by a regulatory authorities of conducting an official review of documents, facilities, records, and any other resources that are deemed by the authorities 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) facilities, Office of Ethics Committees, or at other establishments deemed appropriate by the regulatory authorities.
Investigating files	A file keeping research Protocols that are under investigating or on-going study.
Investigational Medical Device	A medical device, which, is the object of clinical research to determine its safety or effectiveness.
Investigational New Drug	Investigational new drug means a new drug, antibiotic drug, or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms "investigational drug" and "investigational new drug" are deemed to be synonymous for purposes of this part.
Master file	A file for storage of the originally signed and dated

	documents.
Master SOP files	An official collection of the institute standard operating procedures (SOP) accessible to all staff, IEC/IRB members, auditors and government inspectors as a paper copy with an official stamp on each page and the approval signatures. Photocopies made from these official paper versions of the SOP cannot be considered official.
Medical Device	A medical device is any health care product that does not achieve any of its intended purposes by chemical action or by being metabolized. Medical devices include items such as diagnostic test kits, crutches, electrodes, prescribed beds, pacemakers, arterial grafts, intraocular lenses, and orthopaedic pins. Medical devices also include diagnostic aids such as reagents and test kits for in vitro diagnosis of disease and other conditions, for example, pregnancy.
Minutes	The official record of events, activities, and actions taken on agenda items presented to a duly constituted (quorum present) independent board review meeting. The minutes identify fully each protocol and/or activity and record the outcomes of each voting action. The board votes separately on each collective set or each item submitted for review: protocol, consent form, investigator, and advertisement(s). The record notes the number for, number against, the number of abstaining votes, and the reason for the abstention(s), without identifying the individual members' names.
Monitoring visit	An action that IEC/IRB or its representatives visit study sites to assess how well the selected investigators and the institutes are conducting researches, taking care of subjects, recording data and reporting their observations, especially serious adverse events found during the studies. Normally monitoring visit shall be arranged in advance with the principal investigators.
National Health Research Ethics Review Committee	Independent Ethics Review Committee.
New Study	A study protocol including the informed consent, investigator's qualifications, information on the drug or device and advertisements (if applicable) presented to the Committee for approval for the first time and not previously approved by this Board. This includes re-application for those studies denied approval by the Committee.
Non-compliance record	A list containing the identity of investigators who are considered by the Committee to be non-compliant with

	FDA regulations or who fail to respond to the Board's requests and the incident justify the reason for the termination of the study.
Non-significant Risk Device (NSR)	A non-significant risk device is an investigational device that does not pose a significant risk.
Nutrient Supplements	Substances, which are necessary for the body's nutritional and metabolic processes.
Participants' rights	Recognition of the inherent dignity and of the equal and inalienable rights of all members of the human family is the foundation of freedom, justice and peace in the world. It is essential that Human Rights should be protected by the rule of law.
Progress Report	An ongoing review of each investigator's study activities presented as a written report to obtain extended approval for the study from the Committee. Generally, these reports are due annually with Secretariat sending a written notification reminding the investigator of this obligation. More frequent reports may be requested at the discretion of the Committee.
Protocol Amendment	A change to the study protocol during the planning or course of the trial. The amendment is a foreseen change to the study plan that requires formal approval by the sponsor.
Quorum	Attendance at any convened meeting of the board where three of the regular (or alternate) members, including at least one physician and one layperson, is maintained throughout the discussions and voting portions of the meeting.
Scientist	Professionals with either bio-medical or non-biomedical background
Serious Adverse Event (SAE)	<p>The adverse event is SERIOUS and should be reported when the patient outcome is:</p> <p><u>Death</u> - Report if the patient's death is suspected as being a direct outcome of the adverse event.</p> <p><u>Life- Threatening</u> -Report if the patient was at substantial risk of dying at the time of the adverse event or it is suspected that the use or continued use of the product would result in the patient's death. <i>Examples: Pacemaker failure; gastrointestinal haemorrhage; bone marrow suppression; infusion pump failure which permits uncontrolled free flow resulting in excessive drug dosing.</i></p> <p>Hospitalization (initial or prolonged) -Report if admission to the hospital or prolongation of a hospital stay results because of the adverse event. <i>Examples.</i></p>

		<p><i>Anaphylaxis pseudomembranous colitis or bleeding causing or prolonging hospitalisation.</i></p> <p>Disability -Report if the adverse event resulted in a significant, persistent, or permanent change, impairment, damage or disruption in the patient's body function/structure, physical activities or quality of life. <i>Examples: Cerebrovascular accident due to drug-induced hypercoagulability; toxicity,. peripheral neuropathy.</i></p> <p>Congenital Anomaly -Report if there is suspicions that exposure to a medical product prior to conception or during pregnancy resulted in an adverse outcome in the child. <i>Examples: Vaginal cancer in female off spring from diethylstilbestrol during pregnancy,' malformation in the offspring caused by thalidomide.</i></p> <p>Requires Intervention to Prevent Permanent Impairment or Damage -Report if suspect that the use of a medical product may result in a condition, which required medical or surgical intervention to preclude permanent impairment or damage to a patient. <i>Examples.. Acetaminophen overdose-induced hepatotoxicity requiring treatment with acetylcysteine to prevent permanent damage, burns from radiation equipment requiring drug therapy, breakage of a screw requiring replacement of hardware to prevent malunion of a fractured long bone.</i></p>
Significant Device (SR)	Risk	A significant risk device is an investigational device that: (1) is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of the subject, (2) is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of the subject, (3) is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impingent of human health and presents a potential for serious risk to the health, safety, or welfare of the subject, or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of the subject.
Standard Operating Procedure (SOP)		Detailed, written instructions, in a certain format, describe activities and action undertaken by an organization to achieve uniformity of the performance of a specific function.
Stipulation		Putting forward as a necessary condition
Vulnerable Participants		A vulnerable category of participants includes children, prisoners, pregnant women, handicapped or mentally

	disabled persons, and economically or educationally disadvantaged persons, who are likely to be vulnerable to coercion or undue influence.
Vulnerable subjects	A vulnerable category of subjects includes children, prisoners, pregnant women, handicapped or mentally disabled persons, and economically or educationally disadvantaged persons, who are likely to be vulnerable to coercion or undue influence.

References

1. World Health Organization, Operational Guidelines for Ethics Committees that Review Biomedical Research, 2000.
2. International Conference on Harmonization, Guidance on Good Clinical Practice (ICH GCP) 1996.
3. 45 Code of Federal Regulations 46.115 IRB Records, .108.b IRB Functions and Operations.
4. The Belmont report
5. CIOMS guidelines
6. 21CFR56.115 IRB Records
7. Ethical Guidelines for Biomedical research on Human Subjects, 2000